SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

POLYGYNAX®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Vaginal capsule contains:

Neomycin sulphate……35 000IU

Polymyxin B sulphate……35 000IU

Nystatin……100 000IU

Excipient with known effect: Hydrogenated soybean oil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vaginal Soft Capsule

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Local treatment of vaginitis due to sensitive pathogens and treatment of non- specific vaginitis.

4.2. Posology and method of administration

FOR ADULTS ONLY

One vaginal capsule in the evening for 12 days.

- The **POLYGYNAX®** Vaginal capsule should be inserted, preferably at night, into the vagina as deeply as possible. This is best achieved when lying back with the legs slightly drawn up.
- The treatment should be associated with hygiene recommendations (wear cotton underwear, avoid vaginal douches, avoiding using an internal tampon during the treatment) and elimination of contributing factors, as much as possible.
- Treating the partner must be discussed on a case-by-case basis.

  Do not stop the treatment during menstruation periods.

4.3. Contraindications

POLYGYNAX® is contraindicated in:

- Patients with hypersensitivity to neomycin, nystatin, polymyxin B sulphate or any other components of the formulation ***listed in section 6.1.***
- In case of allergy to peanut or soya, due to the presence of soybean oil.
- In case of use of a diaphragm and latex condoms.

4.4. Special warnings and precautions for use

Special warnings:

Not to be taken orally.

In the event of local intolerance or allergic reaction, the treatment must be interrupted.

The sensitisation to antibiotics by local route may compromise the later use of the same antibiotic or related antibiotics when administered by the systemic route.

POLYGYNAX® contains soybean oil and may cause hypersensitivity reactions (urticaria, anaphylactic shock).

Precaution for use:

The duration of treatment by **POLYGYNAX®** must be limited because of the risk of selecting resistant bacteria leading to secondary infection by these pathogens.

Due to the possible resorption of neomycin and polymyxin B by the vaginal mucosa, the risk of systemic effects, especially in the event of renal failure cannot be excluded.

4.5. Interaction with other medicines and other forms of interaction

POLYGYNAX® may damage latex contraceptives (condoms and diaphragms) and additional contraceptive precautions may be necessary during treatment.

POLYGYNAX® may inactivate spermicidal local contraception.

4.6. Fertility, pregnancy and lactation

Pregnancy:

Due to the presence of an aminoglycoside, neomycin, which can cause an ototoxic risk, and the possibility of its systemic absorption, the use of this medicinal product is not recommended during pregnancy. Safety and/or efficacy has not been established.

Lactation:

Due to the digestive immaturity of the newborn and the pharmacokinetic properties of this medicinal product, its prescription is not recommended during lactation.

4.7. Effects on ability to drive and use machines

Not relevant.

4.8. Undesirable effects

POLYGYNAX® may have side-effects.

Information in this section is based on post-marketing data.

Immune system disorders:

POLYGYNAX® may cause local or systemic hypersensitivity reactions. Allergic skin reaction, allergic oedema.

Local reaction such as contact allergic eczema occurs more frequently with long term use and may spread far from the treated areas.

Skin and subcutaneous tissue disorders:

Urticaria, rash, pruritus, angioedema.

Reproductive system and breast disorder:

Vulvovaginal pruritus, vulvovaginal burning sensation, vulvovaginal irritation

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting**

Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9. Overdose

An excessive and prolonged administration could induce systemic effects (hearing and renal), in particular in patients with renal insufficiency. A prolonged use also entails an increased risk of allergic eczema. Treatment is systematic and supportive.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification

A 20.1.1 Broad and medium spectrum antibiotics

Anti-infectives and Antiseptics in Gynaecological use (Genitourinary system and sex hormones) ATC Code G01AA51

5.1. Pharmacodynamic properties

POLYGYNAX® is a combination of neomycin, polymyxin B and nystatin. Neomycin is an aminoglycoside antibiotic. Polymyxin B is a polypeptide antibiotic. Nystatin is a polyene antibiotic with antifungal (anticandida) activity.

Polymyxin B:

Polymyxins interact strongly with phospholipids and disrupt the structure of bacterial cell membranes. The permeability of the bacterial membrane changes immediately on contact with the drug. Sensitivity to polymyxin B apparently is related to the phospholipid content of the cell wall-membrane complex. The cell wall of certain resistant bacteria may prevent access of the drug to the cell membrane. Polymyxin B

binds to the lipid A portion of endotoxin (the lipopolysaccharide of the outer membrane of gram-negative bacteria) and inactivates this molecule.

The antimicrobial activities of Polymyxin B are restricted to gram-negative bacteria, including *E. Coli*, *Klebsiella*, *Salmonella*, *Pasteurella*, *Bordetella* and *Shigella*, which usually are sensitive to concentration of 0,05 to 2 µg/ml. Most strains of *P. Aeruginosa* are inhibited by less than 8 µg/ml in vitro. *Proteus spp*. are intrinsically resistant.

Neomycin:

Neomycin is a bactericidal antibiotic that interferes with protein synthesis in susceptible microorganisms.

Neomycin is a broad spectrum antibiotic. Gram-negative bacteria that are highly sensitive are *E. Coli*, *Enterobacter aerogenes*, *Klebsiella pneumonia* and *Proteus vulgaris*. Gram-positive microorganisms that are inhibited include *S. Aureus* and *E.faecalis*. *M. Tuberculosis* also is sensitive to Neomycin. Strains of *P.euroginosa* are resistant to neomycin.

Nystatin:

The mechanism of action of nystatin and other polyenes is based on the formation of insoluble complexes with the sterols of the cell membrane (ergosterol in fungi and cholesterol in mammals) which causes changes in the permeability that causes K and P efflux and alteration of the proton flux leading to cell death.

Nystatin is both fungistatic and fungicidal in vitro against a wide variety of yeast and yeast like fungi, including *Aspergillus fumigans*, *Candida albicans*, *Coccidiodes immitis*, *Cryptococcus neoformans* and *Histoplasma.*

ANTIBACTERIAL ACTIVITY SPECTRUM OF POLYMYXIN B AND NEOMYCIN

POLYMIXIN B

Critical concentrations separate sensitive strains from strains with intermediate sensitivity and the latter from resistant strains:

S ≤ 2 mg/l and R > 2 mg/l

The prevalence of acquired resistance may vary with geographical location and time for certain species. It is therefore useful to have information on the prevalence of local resistance, in particular when treating severe infections. These data can only be used as an orientation for the probabilities of sensitivity of a bacterial strain to this antibiotic. When the variability of the prevalence of resistance is known for a bacterial species, it is provided in the following table:

Categories	**Frequency of acquired resistance in France (> 10%) (limit values)**
SENSITIVE SPECIES	
Aerobic Gram-negative bacteria	
Acinetobacter	
Aeromonas	
Alcaligenes	
Citrobacter freundii	
Citrobacter koseri	
Enterobacter	
Escherichia coli	
Klebsiella	
Moraxella	
Pseudomonas aeruginosa	
Salmonella	
Shigella	
Stenotrophomonas maltophilia	0 – 30%

RESISTANT SPECIES **Aerobic Gram-positive bacteria** Cocci and bacilli **Aerobic Gram-negative bacteria** *Branhamella catarrhalis* *Brucella* *Burkholderia cepacia* *Burkholderia pseudomallei* *Campylobacter* *Chryseobacterium meningosepticum* *Legionella* *Morganella* *Neisseria* *Proteus* *Providencia* *Serratia* *Vibrio cholerae El Tor* **Anaerobic** Cocci and bacilli **Others** Mycobacteria	

NEOMYCIN

The prevalence of acquired resistance may vary with geographical location and time for certain species. It is therefore useful to have information on the prevalence of local resistance, in particular when treating severe infections.

These data can only be used as an orientation for the probabilities of sensitivity of a bacterial strain to this antibiotic.When the variability of the prevalence of resistance is known for a bacterial species, it is provided in the following table:

Categories	**Frequency of acquired resistance in France (> 10%) (limit values)**
SENSITIVE SPECIES	
Aerobic Gram-positive bacteria	
Corynebacterium	
Listeria monocytogenes	
Staphylococcus meti-S	
Aerobic Gram-negative bacteria	
Acinetobacter (essentially *Acinetobacter baumanii)*	50 – 75%
Branhamella catarrhalis	
Campylobacter	
Citrobacter freundii	20 – 25%
Citrobacter koseri	
Enterobacter aerogenes	
Enterobacter cloacae	10 – 20%
Escherichia coli	15 – 25 %
Haemophilus influenzae	25 – 35 %
Klebsiella	10 – 15 %
Morganella morganii	10 – 20 %
Proteus mirabilis	20 – 50 %
Proteus vulgaris	
Providencia rettgeri	
Salmonella	
Serratia	
Shigella	
Yersinia	

MODERATELY SENSITIVE SPECIES (*in vitro* of intermediate sensitivity) **Aerobic Gram-negative bacteria** *Pasteurella*	
RESISTANT SPECIES **Aerobic Gram-positive bacteria** Enterococci *Nocardia asteroides* *Staphylococcus* meti-R* *Streptococcus* **Aerobic Gram-negative bacteria** *Alcaligenes denitrificans* *Burkholderia* *Flavobacterium sp.* *Providencia stuartii* *Pseudomonas aeruginosa* *Stenotrophomonas maltophilia* **Anaerobic** Strictly anaerobic bacteria **Others** *Chlamydia* *Mycoplasmas* *Rickettsias*	

* The frequency of resistance to methicillin is approximately 30 to 50% of all staphylococci and is mainly encountered in hospitals.

Remark: these spectra correspond to those of the systemic forms of these antibiotics. With local pharmaceutical presentations, concentrations obtained in situ are much higher than plasma concentrations. There is some remaining uncertainty concerning kinetics of in situ concentrations, local physicochemical conditions which can alter the antibiotic activity and product stability in situ.

5.2. Pharmacokinetic properties

Polymyxin B:

Polymyxin B is not absorbed when given orally and is poorly absorbed from mucus membranes and the surfaces of large burns. They are excreted renally.

Neomycin:

Neomycin is poorly absorbed from the gastrointestinal tract and is excreted by the kidney as are the other aminoglycosides. About 97 % of an oral dose of neomycin is not absorbed and is eliminated unchanged in the faeces.

Nystatin:

Nystatin is not absorbed from the gastro-intestinal tract, skin or vagina. By the oral route, nystatin is practically not absorbed; most of the drug is eliminated in the faeces; during the first 24 h about one-third of nystatin is recovered in the faeces and less than 1% in urine.

5.3. Preclinical safety data

Not provided.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

PEG-6 stearate and glycol stearate

PEG-32 stearate (Tefose 63),

hydrogenated soyabean oil,

dimeticone 1 000.

Composition of the shell soft capsule:

gelatine, glycerol, dimeticone 1 000

6.2. Incompatibilities

Not applicable

6.3. Shelf life

2 years

6.4. Special precautions for storage

Store at or below 25 °C.

Keep the blister in the carton until required for use.

6.5. Nature and contents of container

Smooth, oval, pale yellow to yellow vaginal capsules.

POLYGYNAX® Vaginal capsules are packaged in PVC/PVDC/Aluminium blisters in packs of 6 or 12 capsules per blister. Blisters are placed in an outer cardboard carton.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACORP (PTY) LTD

29 Victoria Link

Route 21 Corporate Park

Irene, 0178, RSA

8. REGISTRATION NUMBER

50/20.1.1/0250

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 October 2021

10. DATE OF REVISION OF THE TEXT