APPENDIX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

POLYGYNAX, vaginal capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Neomycin sulfate ..... 35 000 I.U.
Polymyxin B sulfate ..... 35 000 I.U.
Nystatin ..... 100 000 I.U.

For one vaginal capsule

Excipient with known effect: Hydrogenated soybean oil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vaginal capsule.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Local treatment of vaginitis due to sensitive germs (bacterial vaginitis, vulvo-vaginitis due to *Candida albicans* and *Candida* non-*albicans*, mixed vaginitis) and treatment of bacterial vaginosis.
The official recommendations concerning appropriate use of antibacterial products must be taken into consideration.

4.2. Posology and method of administration

Posology
FOR ADULTS ONLY
One vaginal capsule in the evening for 12 days.

Method of administration
Introduce one capsule deep in the vagina, preferably in lying down position.

Practical advices:
- The treatment should be associated with hygiene recommendations (wear cotton underwear, avoid vaginal douches, 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.
- Treatment is compatible with latex and polyisoprene male condoms (see section 4.5).

4.3. Contraindications

This medicinal product is contraindicated in the following situations:

- Hypersensitivity to the active substances or to any excipients listed in section 6.1 (or group sensitivity),
- In case of use of polyurethane male condoms, female condoms and diaphragms,
- In case of allergy to peanut or soya, due to the presence of soybean oil.

This medicinal product is generally not recommended in combination with spermicides.

4.4. Special warnings and precautions for use

Warnings:

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

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

Precautions for use:

The duration of treatment must be limited because of the risk of selecting resistant germs and superinfection by these germs.

In the absence of data on the importance of neomycin and polymyxin B fractions resorbed by the mucosa, the risk of systemic effects, especially increased with renal insufficiency, cannot be excluded.

This medicinal product contains soybean oil and may cause hypersensitivity reactions (urticaria, anaphylactic shock).

4.5. Interaction with other medicinal products and other forms of interaction

Contraindicated combinations

+ Polyurethane male condoms, female condoms and diaphragms
Risk of rupture.

Combinations not recommended:

+ Spermicide
Any local vaginal treatment is likely to inactivate a spermicidal local contraception.

4.6. Fertility, pregnancy and lactation

Pregnancy

Due to the presence of an aminoside, neomycin, causing an ototoxic risk, and the possibility of systemic absorption, the use of this medicinal product is not recommended during pregnancy.

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

Adverse reactions are classified by system organ class.

For adverse reactions reported from spontaneous notifications, their frequency is not known (cannot be estimated from the available data).

System organ class	Frequency	Adverse reactions
Immune system disorders	Not known	Hypersensitivity: rash, pruritus, urticaria and anaphylactic reaction
Reproductive system and breast disorders	Not known	Local reactions such as burning sensation, pruritus, irritation, redness and oedema

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

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 exposes to an increased risk of allergic eczema.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group:
ANTIINFECTIVES and ANTISEPTICS IN GYNECOLOGICAL USE
(G. genitourinary system and sex hormones), ATC code: G01AA51.

Combination of neomycin, polymyxin B and nystatin.
MECHANISM OF ACTION

Neomycin is an aminoside antibiotic. The target of Neomycin is the 30S ribosomal subunit, inducing inhibition of bacterial protein synthesis with the emergence of non functional proteins. Aberrant proteins penetrate the cell membrane, alter its permeability and disrupt other vital bacteria processes, leading to bactericidal activity.

Polymyxin B is a polypeptide antibiotic. Polymyxin B interacts with microorganism membrane phospholipids (Gram-negative bacterial lipopolysaccharide), leading to membrane disorganisation followed by bacterial cell destruction.

Nystatin is a polyene antifungal with an action against *Candida spp*. Nystatin binds to the cell membrane sterols of fungal strains, modifying cell permeability and causing intracellular material leakage, leading to cell death.

ANTIBACTERIAL ACTIVITY SPECTRUM OF POLYGYNAX

In vitro studies carried out in conditions recreating the vaginal environment have shown POLYGYNAX's bactericidal activity as well as its kinetics (contact time 1h and 4h) on the main bacteria responsible for bacterial vaginosis (anaerobic bacteria) and bacterial vaginitis (aerobic bacteria) using the dilution/neutralisation method. The sensitivity of various strains has been determined according to the logarithmic reduction in the bacterial load observed for each strain. The critical thresholds which differentiate sensitive strains from strains with intermediate sensitivity and resistant strains are the following: S: red log ≥ 3 and R: red log < 2.

The sensitivity of various strains to POLYGYNAX is provided in the following table:

Sensitive species	Species with intermediate sensitivity	Resistant species
Microaerobic bacterium		
Gardnerella vaginalis		
Anaerobic bacteria		
Atopobium vaginae *Mobiluncus curtisii* *Prevotella bivia*		
Aerobic bacteria		
Gram positive:		
Corynebacterium amycolatum *Methicillin-sensitive staphylococcus aureus* *Streptoccoccus agalactiae* (Group B)	*Streptococcus pyogenes* (Group A)	*Enterococcus faecalis* *Enterococcus hirae*

Gram negative:		
Branhamella catarrhalis *Escherichia coli* *Haemophilus influenzae* *Klebsiella aerogenes (Enterobacter aerogenes*) *Klebsiella pneumoniae* *Neisseria meningitidis* *Proteus hauseri (Proteus vulgaris)* *Pseudomonas aeruginosa* *Salmonella enteritidis* *Shigella flexneri* *Yersinia enterocolitica*	*Proteus mirabilis*	

Note: This table shows a non exhaustive list of bacteria which are frequently implicated in bacterial vaginosis/vaginitis. This list does not call into question the individual spectra of activity of each antibiotic active substance in POLYGYNAX on other bacterial strains.

SYNERGISTIC ACTIVITY BETWEEN POLYMYXIN B AND NEOMYCIN

An *in vitro* study has shown that the two antibiotics in POLYGYNAX have a complementary spectrum leading to a more homogeneous activity on the four main bacterial strains responsible for bacterial vaginosis/vaginitis (*Staphylococcus aureus, Escherichia coli, Streptococcus agalactiae, Gardnerella vaginalis*) and that they act at least additively.

ANTIFUNGAL ACTIVITY SPECTRUM OF POLYGYNAX

An *in vitro* study was carried out in order to assess the sensitivity of *Candida* strains through the determination of the minimum inhibitory concentrations (MIC) of nystatin. The results, shown in the below table, confirm sensitivity to nystatin remains identical, whether for *Candida albicans* or for *Candida non-albicans* strains.

Strains	**MIC_{50} (mg/l)**	**MIC_{90} (mg/l)**	**MIC value (mg/l) Minimum-Maximum**
Candida albicans (n=113)	2	4	1 - 4
Candida glabrata (n=54)	4	4	4
Candida krusei (n=11)	4	4	4
Candida tropicalis (n=11)	2	4	2 - 4
Candida parapsilosis (n=11)	4	4	2 - 4

MIC_{50}: MIC inhibiting 50% of isolates; MIC_{90}: MIC inhibiting 90% of isolates.

ACTIVITY ON LACTOBACILLI

An *in vitro* study was carried out in order to assess the impact of POLYGYNAX on the main lactobacilli found in the vaginal flora under physiological conditions (*Lactobacillus crispatus, Lactobacillus gasseri* and *Lactobacillus jensenii*). Results show that POLYGYNAX, in concentrations which may be found in the vaginal environment following the administration of the treatment in the recommended dosage, does not impact the growth of these three lactobacilli species.

5.2. Pharmacokinetic properties

There is no systemic absorption when the product is administered by vaginal route.

5.3. Preclinical safety data

Local tolerance in animals with Polygynax does not show any harmful effect on the vaginal mucosa.

Long-term studies in animals to evaluate carcinogenic or mutagenic potential have not been conducted with polymyxin B sulfate, neomycin and nystatin.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

PEG-6 stearate and glycol stearate and PEG-32 stearate (Tefose 63), hydrogenated soybean oil, dimeticone 1000.

Composition of the shell soft capsule: gelatine, glycerol, dimeticone 1000.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Capsules under blister (PVC/PVDC/aluminium): 2 years.
Capsule under blister (PVC/PE/PVDC/aluminium): 30 months.

6.4. Special precautions for storage

Capsule under blister (PVC/PVDC/aluminium): Do not store above 25°C.
Capsule under blister (PVC/PE/PVDC/aluminium): Do not store above 30°C.

6.5. Nature and contents of container

Box of 1 or 2 blisters (PVC/PVDC/Aluminium) or (PVC/PE/PVDC/aluminium) of 6 capsules.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

LABORATOIRE INNOTECH INTERNATIONAL
22 AVENUE ARISTIDE BRIAND
94110 ARCUEIL

8. MARKETING AUTHORISATION NUMBER(S)

MA093/00401

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02nd January 2007

10. DATE OF REVISION OF THE TEXT

08th January 2024

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR THE PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR SUPPLY

List I

Medicinal product subject to medical prescription.