Date: 16 September 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

SOFTIGYN

International non-proprietary name: live lactobacillus plantarum P 17630
Pharmaceutical form: soft vaginal capsule
Dosage strength(s): 100’000’000 CFUs
Route(s) of administration: vaginal
Marketing Authorisation Holder: Labatec Pharma SA
Marketing Authorisation No.: 68467
Decision and Decision date: approved on 26 July 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CFU	Colony-forming unit
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	U.S. Food and Drug Administration
GLP	Good Laboratory Practice
HPLC	High performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International nonproprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetic
PSP	Pediatric Study Plan (US-FDA)
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
RMP	Risk Management Plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance live lactobacillus plantarum P 17630 of the medicinal product mentioned above.

Authorisation in accordance with Art. 14 para. 1 a$^{bis-quater}$ TPA
The applicant requested a simplified authorisation in accordance with Art. 14 para. 1 a$^{bis-quater}$ TPA.

2.2 Indication and Dosage

2.2.1 Requested Indication

Local treatment of vaginitis and vulvo-vaginitis in general. Particularly vaginitis associated with ovarian deficiency, hypofollicolinic leucorrhoea, vaginitis in children, senile vaginitis, vulvar pruritus, vaginal dystrophy.

2.2.2 Approved Indication

Softigyn is used in adult women to restore and maintain the physiological vaginal flora, for example:
- in the presence of signs of vaginal inflammation (vaginitis), such as itching, burning or vaginal discharge;
- during and after local or systemic treatment with anti-infectives;
- as a preventive measure in case of recurrent vaginal mycosis.

Treatment with Softigyn is not a substitute for appropriate antibiotic or antimycotic treatment in cases where such treatment is indicated.

2.2.3 Requested Dosage

Summary of the applied standard dosage:
One vaginal capsule daily.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	8 April 2021
Formal control completed	6 May 2021
List of Questions (LoQ)	7 October 2021
Answers to LoQ	3 January 2022
Predecision	17 March 2022
Answers to Predecision	28 April 2022
Final Decision	26 July 2022
Decision	approval

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3 Quality Aspects

3.1 Drug Substance

The drug substance of Softigyn is a freeze-dried lactic bacteria, strain *Lactobacillus plantarum* P 17630. *Lactobacillus plantarum* P 17630 belongs to the *Lactobacillus* genus. It is a Gram-positive, non-spore-forming, preferential anaerobic, but also aerotolerant, bacterium.

The manufacturing process comprises *Lactobacillus plantarum* P 17630 fermentation process steps, centrifugation, addition of cryoprotectant, lyophilisation and grinding.

Master and working seed lots have been established and are adequately controlled.

The specifications include e.g. tests for appearance, water activity, identification, *Lactobacillus plantarum* P 17630 count, and microbiological contamination.

Batch analysis data from commercial scale batches were provided and indicate a consistent manufacturing process. The analytical methods established for drug substance release are described, and non-compendial methods have been validated in accordance with ICH guidelines.

The claimed shelf life for the drug substance is supported by stability data.

Intermediate Softigyn Bulk

Before formulation of the drug product, an intermediate, Softigyn Bulk, is manufactured. It is produced by mixing the drug substance with a diluent (lactose), resulting in a *Lactobacillus plantarum* P 17630 standardised powder mixture. The manufacturing process and the hold time for the intermediate are validated, and specifications are set for the intermediate.

3.2 Drug Product

Softigyn is presented as soft vaginal capsules containing a suspension of the freeze-dried *Lactobacillus plantarum* P 17630 with not less than 10^8 CFUs.

The composition of the drug product is adequately described, both qualitatively and quantitatively.

Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process.

The manufacturing process is described in sufficient detail, taking into account pharmaceutical development data. Batch manufacturing formulas and in-process controls are included.

Adequate validation data pertaining to the commercial manufacturing process are available.

For the control of the finished product, adequate tests and acceptance criteria for release and at shelf-life are established. The specification includes the parameters appearance, visual defects, average weight of capsules, average weight of fill, uniformity of mass, disintegration test, loss on drying, identification and content of sodium ethyl parahydroxybenzoate, identification and content of sodium propyl parahydroxybenzoate, identification and content of *Lactobacillus plantarum* and microbiological contamination. The corresponding test procedures are sufficiently described and validated. Batch data show consistent quality of the drug product.

The finished product is packaged in PVC/PVDC/Aluminium/Diofan blisters.

Appropriate stability data have been generated in the packaging material intended for commercial use and following the relevant international guidelines. Based on these data, a shelf-life of 24 months was established. The storage recommendation is “Store in the refrigerator at 2°C - 8°C”.

3.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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4 Nonclinical Aspects

In accordance with Art. 14 para. 1 a^{bis} TPA, Swissmedic has only reviewed the nonclinical overview for the authorisation of Softigyn, soft vaginal capsules. The approval of Softigyn, soft vaginal capsules, is based on the medicinal product Ecocillin, which contains the same active substance and has been authorised in Italy for more than 10 years.

5 Clinical and Clinical Pharmacology Aspects

Swissmedic has not assessed the primary data relating to clinical aspects of this application and is taking over the results of the assessment of the foreign reference authority of Italy.

5.1 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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7 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Softigyn, soft vaginal capsules was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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Information for healthcare professionals

Softigyn, 100’000’000 CFU soft vaginal capsules
The efficacy and safety of Softigyn have only been summarily reviewed by Swissmedic. The authorisation of Softigyn is based on Softigyn, date of revision of the text August 2020, which contains the same active substance(s) and is authorised in Italy.

Composition
Active ingredient:
Lactobacillus plantarum P 17630 live
Excipients:
- Lactose
- Sodium ethyl p-hydroxybenzoate (E215) (2.269 mg)
- Sodium propyl p-hydroxybenzoate (1.125 mg)
- Triglycerides medium chain
- Silica, colloidal anhydrous
- Gelatine
- Glycerol
- Dimeticone
- Titanium Dioxide (E171).

Each soft capsule contains 0.405 mg of sodium.

Pharmaceutical form and quantity of active ingredient per unit
Soft vaginal capsules.
Each soft vaginal capsule contains at least 100’000’000 CFU of *Lactobacillus plantarum* P 17630.

Therapeutic indications
Softigyn is used in adult women to restore and maintain the physiological vaginal flora, for example:
- in the presence of signs of vaginal inflammation (vaginitis) such as itching, burning or vaginal discharge;
- during and after local or systemic treatment with anti-infectives;
- as a preventive measure in case of recurrent vaginal mycosis.

Treatment with Softigyn is not a substitute for appropriate antibiotic or antimycotic treatment in cases where such treatment is indicated.

Posology / Method of administration

Posology
One vaginal capsule per day.
If the symptoms do not improve within a week or if they worsen, a doctor should be consulted. This applies in particular to the occurrence of fever, pain in the lower abdomen or purulent discharge. A doctor should check at regular intervals that treatment with Softigyn is appropriate.

Special dosage instructions
Pediatric population
No data are available. Softigyn is not indicated in children and adolescents.

Method of administration
Insert one vaginal capsule deeply into vagina, while lying on your back, in the evening before bedtime.

Contraindications
Hypersensitivity to the active substance or to any of the excipients.

Special warnings and precautions for use
The use of topical products, especially in prolonged use, can cause sensitive effects and adverse effects. In such case, it is necessary to interrupt the treatment.
Softigyn does not replace therapy with anti-infectives or other appropriate chemotherapies, but represents a useful complement by restoring, especially at the end of the specific treatment, the physiological conditions of the vaginal environment.
Softigyn soft vaginal capsules **contains para-hydroxybenzoates** that may cause allergic reactions (even delayed).
Softigyn contains less than 1 mmol (23 mg) of sodium per soft capsule, i.e. it is essentially "sodium-free".

Interactions
No interactions studies were performed.
Lactobacillus bacteria are sensitive to many anti-infectives. Therefore, simultaneous treatment with anti-infectives (local or systemic) may reduce the effectiveness of Softigyn.
No studies have demonstrated possible interactions between Softigyn and latex products (e.g. condoms, diaphragms, etc.). As a precautionary measure, the use of other methods of contraception should be considered during treatment with Softigyn and for the first few days after discontinuation of treatment.

Pregnancy and lactation
Lactobacillus plantarum is usual, non-pathogenic, host in vagina; therefore Softigyn can be used during pregnancy and/or breast-feeding since Lactobaccilli are not liable to systemic exposure.

Effects on ability to drive and use machines
No corresponding studies have been performed. However, Softigyn is not expected to affect the ability to drive or use machines.

Side effects
No adverse effects related to the use of the product were reported.
The data collected show the very low number of adverse events observed during post-marketing surveillance.
It is very important to report suspected side effects after registration of the drug. This allows continuous monitoring of the benefit-risk ratio of the medicine. Healthcare professionals are invited to report any suspected new or serious side effects via the online portal EIViS (Electronic Vigilance System). More information is available at www.swissmedic.ch.

Overdose
No overdosage cases were reported.

Properties

ATC code
G01AX14

Mechanism of action and Pharmacodynamic
Lactobacilli are an integral part of the ecosystem in healthy women and represent indeed the main natural defence mechanism against the development of pathogenic microorganisms.
This situation is achieved mainly by the transformation, made by lactic bacteria, of epithelial cells glycogen into lactic acid, followed by decrease in the vaginal pH to values between 3.8 and 4.4; these values are optimal for the lactobacilli growth but unfavourable for the growth of pathogenic microorganisms.
The vaginal habitat equilibrium may be altered due to some physiological or pathological conditions and for iatrogenic reasons.
Antibiotic and sulphonamides in local or general application, although essential in treatment of specific vaginitis, destroys also non-pathogenic flora, therefore it increases the risk of relapses or other infection.
The live, lyophilised, isolated from vaginal habitat, taxonomic-characterised *Lactobacillus plantarum* allows the recovery of natural bacteria flora through application of a high amount of lactic bacteria that, when introduced into the vagina, are able to adhere and multiply, in presence of Candida, and restore the pH value in acid limit.
Therefore, Softigyn offers the opportunity to restore an unfavourable habitat for the settling down and survival of pathogen germs, it reduces the number of strains and the concentration in aspecific leucorrhoea, and it represents a useful treatment in specific vaginitis, to restore the physiological conditions of the vaginal habitat.
The physiological characteristics of this therapeutic treatment is the basis for the good tolerability of the product.

Clinical efficacy
No data available.

Pharmacokinetic properties
Lactobacilli are usually hosts in the vagina so they are not subjected to systemic absorption.

Preclinical data
Being lactobacilli habitual saprophytes of the vaginal flora, the preclinical data show absence of risk for the human based on conventional pharmacology studies of safety, repeated dose toxicity, genotoxicity, potential carcinogenic, reproductive toxicity.

Pharmaceutical particulars

Incompatibilities
Not applicable.

Shelf life
24 months.

Special precautions for storage

Store in the refrigerator between + 2 °C and + 8 °C.
Keep out of the reach of children.

Marketing authorization number
68467

Presentation
Blister in PVC/PVDC/Al/Diofan - Box containing 6 soft vaginal capsules. (D)

Marketing authorization holder
Labatec Pharma SA, 1217 Meyrin (Genève)

DATE OF REVISION OF THE TEXT
Foreign reference/comparator medicinal product: August 2020
With safety-relevant additions by Swissmedic: October 2021