CLINICAL EVALUATION

D-MANNOSE

Medical Device to treat and prevent cystitis and other bacterial infections of the lower urinary tract

Rev.5 of 07/11/2018

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REVISION TABLE		
REV.	**DATE**	**DESCRIPTION**
0	**02/04/2015**	**First release**
1	19/05/2015	**Changes introduced with reference to the evaluation report n. 31697/15-MM (ITALCERT) on 11/05/2015**
2	28/03/2016	**The Manufacturer revised the clinical evaluation after the introduction of a new formulation without cranberry extract.**
3	26/09/2016	**Changes introduced with reference to the integration to evaluation report n. 1019/16-MM (ITALCERT) on 25/07/2016 for the clinical evaluation: report n°1114/16-MM**
4	01/09/2018	•Partially rewritten in order to be in better compliance with MEDDEV 2.7/1 Rev.4 •Bibliographic update September 2016 – September 2018
5	*07/11/2018*	*Changes introduced with reference to Italcert report n°9255/18-MM/Iz*

CONTROLLED RELEASE	
Yes	No

RELEASE AND APPROVAL				
Issue	**Date**	**Dr.** [redacted] **(New Project Development Manager)**	**Dr.** [redacted] **(Scientific consultant)**	**Dr** [redacted] **MD PhD Specialist in Human Nutrition**
0	02/04/2015	[redacted]	[redacted]	[redacted]
1	19/05/2015	[redacted]	[redacted]	[redacted]
2	28/03/2016	[redacted]	[redacted]	[redacted]
3	26/09/2016	[redacted]	[redacted]	[redacted]
4	01/09/2018	[redacted]	[redacted]	[redacted]
5	*07/11/2018*	[redacted]	[redacted]	[redacted]

Summary

1. Identification of medical device

Proprietary name of the Medical device: **D-MANNOSE**

Manufacturer: **SIIT S.R.L.**

Medical devices based on D-mannose					
Risk class	**Classification rule**	**CE MARK**	**Technical file**	**Dir. 93/42 EEC**	**First immission on the market**
IIa	Rule 5	Annex V	FT026	Annex IX	**2016**

Stage 0

2. Definition of the scope of the Clinical Evaluation Report (MedDev 2.7/1 Rev.4, Section 7)

For the approval of medical device according to provisions of MDD93/42/EEC as amended by MDD 2007/47EC –Annex X, the confirmation of conformity with the requirements concerning the characteristics and performances referred to in Section 1 and 3 of Annex I under the normal conditions of use of the device and the evaluation of the undesirable effects, that must constitute an acceptable risk when weighed against the performances intended, is based on the satisfaction of the device Essential Requirements that need to be addressed from a clinical perspective (ref. to Table below).

No.	*Essential Requirements requiring clinical data support*
I.1[1]	*The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their intended use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and:* *— reducing, as far as possible, the risk of use error due to the ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety), and* *— consideration of the technical knowledge, experience, education and training and where applicable the medical and physical conditions of intended users (design for lay, professional, disabled or other users).*
I.3[2]	*The devices must achieve the performances intended by the manufacturer and be designed, manufactured and packaged in such a way that they are suitable for one or more of the functions referred to in Article 1 (2) (a), as specified by the manufacturer.*
I.6[3]	*Any undesirable side-effect must constitute an acceptable risk when weighed against the performances intended.* ***I.6.1*** *Demonstration of conformity with the essential requirements must be included a clinical evaluation in accordance with Annex X*

The clinical evaluation shall include also:

- *any design features or target treatment population that require specific attention,*
- *the clinical claims made about the MD,*
- *data related to equivalent devices,*
- *any design features related to its safety,*
- *evaluation of its performance in relation to the disease to be treated,*
- *the adequacy of its labelling and product information (particularly claims, contraindications, precautions/warnings), and the suitability of instructions for use*
- *Risk management documents of the device.*

[1] *Annex I point 1*
[2] *Annex I point 3*
[3] *Annex I point 6*

2.1. Definition of the medical device

2.1.1. Device description

The device is described in detail in the following paragraphs 2.2, 2.3, 2.4, 2.5 and 2.6.

2.1.2. Relevant changes with respect to previous versions of this CER

●This revision includes a bibliographic update and a partial rewriting for being in better compliance with the latest regulations.
With respect to the previous documents, no changes involved the galenic form or the posology, which remained identical.
Any reference to a formulation including extract of cranberry, present in previous revisions, has been eliminated, as this substance is no more allowed in medical devices.

2.1.3. Design features of the device, or indications or target populations that require specific attention.

No design features of the device require specific attention: the efficace dose is identical or smaller to that in equivalent devices already on the market (see § 5.1 and 5.2).
Indications or populations that require specific attention to the substance contained in the device are considered in the paragraphs 2.4, 7.2.2.5, 8.2.1, 8.2.2 and 8.3.

2.1.4. Current knowledge/ state of the art in the corresponding medical field and about the active components of the device

The current knowledge/state of the art in the corresponding medical field and about the active components of the device is resumed in paragraphs 3.1, 3.2, 3.3 and in chapters 7 and 8, with recent bibliographic references.

2.1.5. Data source(s) and type(s) of data to be used in the clinical evaluation.

Search criteria, selection criteria and summary of data are resumed in Chapter 5.
Clinical and preclinical data held by the producer would be included in the paragraph 4.1. However, no clinical data generated by the manufacturer were available for inclusion in this CER.

2.1.6. Information needed for evaluation of equivalence

The criteria followed for evaluation of equivalence are resumed in the paragraph 5.1 and 6.1.
Equivalent medical devices (manufactured by the same producer or other producers) are listed in the paragraphs 5.1, and 5.2.

2.1.7. Risk management documents of the device

These aspects are considered in the Chapters 8 and 9.

2.1.8. Specific clinical concerns that have newly emerged and need to be addressed.

No specific clinical concerns have newly emerged in this update of the CER.

2.1.9. PMS aspects that have been checked for update in this CER

The following PMS aspects have been checked for update in this CER:

-new clinical data available for the device under evaluation: **clinical updates added**;

-new clinical data available for the equivalent device (if equivalence is claimed): **see the attached documents;**

-new knowledge about known and potential hazards, risks, performance, benefits and claims, including

--data on clinical hazards seen in other products (hazard due to substances and technologies): **no new data**;

--changes concerning current knowledge/ the state of the art, such as changes to applicable standards and guidance documents, new information relating to the medical condition managed with the device and its natural course, medical alternatives available to the target population: **see the attached file;**

--other aspects identified during PMS as reactive vigilance data: **no other aspected worth of note were identified**

2.1.10. Needs for planning PMS activities.

The PMS Plan for this device is discussed in chapter 9.

2.2. Scope of the medical device

The medical device object of the present document, containing D-mannose, is intended for the treatment of cystitis and other lower urinary tract infections. These infections are caused mainly by gram-negative bacteria of the type Escherichia coli, more rarely by Staphylococci or other gram-positive strains. The use of natural products having proven efficacy is advisable, since they ar effective, have much fewer side effects than drugs and do not induce antibiotic resistance.

The device is formulated in sachets for oral administration, and is intended for use in adult patients of both sexes and in children over 14 years of age.

2.3 Composition of the medical device "Mannose MD"

The medical device "D-mannose" is formulated in sachets of 4 g each, with the following composition:

D-MANNOSE	
Active components	**g/sachet**
D-mannose	2,000
Excipients Fructose (sweetener), Sucralose (sweetener), Citric acid (acidifying agent), Flavour, Red beet powder (coloring agent), Silicon dioxide (anticaking agent), Magnesium stearate (anticaking agent)	

2.4 Destination and use of the medical devices and rationale followed for the development

2.4.1. Destination and use of the medical device "Mannose MD"

The present medical device is intended to the use of D-mannose to treat and prevent cystitis and other bacterial infections of the lower urinary tract (UTI) in patients of both sexes, and reducing associated symptoms (fdysuria, frequent urination, urine or milky odor, pelvic pain, etc).
The formulation has been chosen by combining relevant clinical data taken from scientific literature, which together give evidence of the effectiveness at the prescribed dosages, and of the safety for the intended purpose.

D-MANNOSE is a natural sugar that has the peculiarity to be absorbed in the intestine but not metabolically transformed. When it is excreted with the urine, D-mannose significantly inhibits the capacity of the pathogens to adhere to the epithelium of the urinary tract, making possible to avoid the attachment and at the same time to dislodge microbes that were already attached to the cell lining.
The product, in powder form, is formulated in sachets of 4 grams each. The pharmaceutical form chosen has been designed to guarantee the activity of the functional ingredients tested during the development of MD, to guarantee the efficacy of the formulation.

The functional component and the excipients are already marketed in medical devices and medicinal substances.

2.4.2. Claims of the medical device "Mannose MD"

The medical device has the following claims:
• Treatment of cystitis and other bacterial infections of lower urinar tract, and relief of related symptoms.
• Prevention of cystitis and other bacterial infections of lower urinar tract.

The MD "Mannose MD" is for use in adults and children ≥ 14 year of age, following the posology reported below.

For its mechanism of action (inhibition of capacity of attachment of pathogenic bacteria to the cells of uroepithelial lining without interaction with host's body), the functional component can be included in medical devices (see §3.3).

2.4.3. Rationale followed during the development of the product

●Our scope was to obtain a medical device that could be effective in treating lower urinary tract infections of bacterial nature and, after prolonged use, limit their subsequent possibility of recurrence. In this way, the necessity of using of antibiotics will be reduced, contributing to control the problem of resistance.

●To this scope, we have evaluated the action that is possible to achieve by using D-Mannose. Mannose is an epimer of glucose that has a sum of very unique characteristics: **it exerts a direct anti-adhesive action on pathogens in the urinary epithelium, allowing they are flushed-away during urination.**

●Scientific data evidence the effectiveness of the active component: D-mannose, at doses around 6 g/day, is useful to treat ongoing infections, whereas at lower doses (1.5-2 g/day) it may prevent the occurrence of future episodes.

●According to the clinical evidences listed in the next chapters, the use of D-mannose, may be as effective as antibiotics **in reducing virulence of uropathogenic bacteria**, with the advantage of being better tolerated and having no side effects or specific contraindications. **It may also be used as an adjunct to antibiotic treatment, as there is no interference in the mechanisms of activity.**

● We claim that D-mannose may be included in medical devices, as pharmacokinetic studies have shown that mannose, after the ingestion, is efficiently absorbed in the upper intestine but not virtually metabolized in humans, and is excreted unconverted into the urine (which means the absence of metabolic or immunostimulant acitvities). During the transit in the urinary apparatus, it exerts its potent anti-adhesive action. Therefore, this sugar – differently from glucose or fructose - does not significantly enter the carbohydrate metabolism when taken orally, and thus it does not have any metabolic effect.
In December 2017 it was published version 1.18 of theMANUAL ON BORDERLINE AND CLASSIFICATION IN THE COMMUNITY REGULATORY FRAMEWORK FOR MEDICAL DEVICES updated in the light of the outcomes of the discussions of the working party on borderline and classification issues.
In version 1.18 of the document, d-mannose used for the prevention of urinary tract infections was interpreted as a substance exerting a "pharmacological action". In other words, d-mannose would not act by a mechanical or physical action, would not meet the definition of a medical device and should not be qualified as such. The Manufacturer, S.I.I.T. Srl, has edited a detailed position paper providing an overview of D-mannose and its role in the prevention of urinary tract infection, an overview of the medical device regulatory framework and classification issues, and a discussion of the scientific evidence regarding the mode of action.
The position paper is attached as addendum (Addendum_D-Mannose position paper) in Annex 19 – Valutazione Clinica of the current technical file.
In addition, ad hoc in vitro tests performed by the manufacturer (see attached document) confirm a non-pharmacological, non-metabolical, non-bacteriostatic and non-bactericidal mechanism of action: in 2018 S.I.I.T. Srl, in cooperation with the Department of Public Health and Infectious Diseases of Sapienza University (Rome), carried out an in vitro study to provide original data to prove that the preventive activity of D-mannose against UTIs is based on its mechanical and physical interaction with FimH without any pharmacological effects on shape, viability, ability to grow in culture, motility and/or metabolic activity of E. coli, as well as on viability and proliferation of eukaryotic cells.
The scientific assessment reporting the first results of this study is reported as Addendum (Addendum_Final Sapienza Report on D-mannose) in Annex 19 – Valutazione Clinica of the current technical file.The outcomes of an in-vitro study have been resumed above (§ 3.3.5), and are detailed in the attached document.

So, for its mechanism of action (inhibition of the adhesive capacity of the bacterium in the presence of the sugar), D-mannose can be included in medical devices (see §3.3).

●The functional ingredient and its quantity have been chosen by combining relevant clinical data taken from scientific literature, which together give evidence of its evident activity at the prescribed dosages and its safety for the intended purpose.

●The galenical form chosen has been designed to guarantee the optimal release of the functional ingredient and good taste and efficacy of the formulation.

Altogether, a sufficient amount of clinical data taken from scientific literature gives evidence of the effectiveness of the component for the intended purpose, of the main mechanic nature of the activity at the prescribed dosages, as well as of the safety of the product for the intended purpose.

With this aim, the development of the product has followed these steps:

- ✓ Biocompatibility studies in vitro and in vivo (Chapter 8.1).
  An additional battery of in vitro test sponsored by the manufacturer (see attached document), in orded to confirm the "mechanic" mode of action of D-mannose towards the bacterium: in 2018 S.I.I.T. Srl, in cooperation with the Department of Public Health and Infectious Diseases of Sapienza University (Rome), carried out an in vitro study to provide original data to prove that the preventive activity of D-mannose against UTIs is based on its mechanical and physical interaction with FimH without any pharmacological effects on shape, viability, ability to grow in culture, motility and/or metabolic activity of E. coli, as well as on viability and proliferation of eukaryotic cells.
  The scientific assessment reporting the first results of this study is reported as Addendum (Addendum_Final Sapienza Report on D-mannose) in Annex 19 – Valutazione Clinica of the current technical file.The outcomes of an in-vitro study have been resumed above (§ 3.3.5), and are detailed in the attached document.
- ✓ A complete survey of published and unpublished clinical studies and patent literature involving the raw materials included in the present MD (Chapters 4, 5 and 6).
- ✓ Safety and tolerability of the components.

However, the producer ensures that an adequate postmarketing control will be performed, in order to monitor occurrence of any side effect.

2.5. Suggested posology

The medical device "D-mannose" is formulated in powder form for oral administration, in sachets of 4,000 mg, each containing 2,000 mg of the active component, and has the following suggested posology:

Acute treatment of cystitis

Day	N° of sachets per day
1st, 2nd and 3rd day	3 sachets
4th and 5th day	2 sachets

The sachets should be given spread over the day.
If possible, take the sachet just after an urination, in order to retain mannose in your bladder as long as possible.

Prevention of recurrences

Total duration of the treatment	N° of sachets per day
6 months. After one month of continuative use it is suggested to break the prophylaxis, and take 3-5 days of "washout" before beginning a new 1-month cycle.	1 sachet

Dissolve the sachet in a glass of water. It is advisable to drink at least 2 liters of water per day to facilitate diuresis.

The product should begin to relieve symptoms within a day or two. If after three days of use you have not achieved an appreciable improvement of the symptoms, it is better to consult a physician.

Before beginning to use the product it is suggested to take medical advice.
The product is indicated from the age of 14 years. Do not use this medical device under 14 years.
Use the product from 14 to 18 years only under medical advice and the strict supervision of a physician.

2.6. Intended application of the device in reference to the Directive 93/42 EC

Single use / Reusable	Invasive / Non invasive	Duration of use or contact with the body	Organs, tissues or body fluids contacted by the device
Single use	Invasive Non implantable	Less than 24 hours in the entire digestive tract.	Gatrointestinal tract

The MD does not include any medicinal substance, tissue, or blood product; it does not include software or accessories and is not sterile. It is a single use invasive, short term contact MD, whose intended application is for the treatment and prevention of cystitis and related symptoms in adults and children over 14 years of age.

3. Intended therapeutic and/or diagnostic indications and claims

3.1. Urinary tract infections and the growing risk of pathogenic bacteria becoming resistant to antibiotic

3.1.1. Urinary tract infections and their causative factors

Urinary tract infections (often abbreviated as UTI), both acute and chronicized, are microbial diseases that can affect any part of the urinary tract. However, the term is primarily used to designate the infections of the lower urinary tract, namely the bladder and the urethra. These types of microbial threats are particularly common in young women, during pregnancy, and during the peri-and post-menopausal periods. It has been estimated that at least one out of five women suffers from this problem at some point in his life. In most cases, these infections are due to the invasion of non-pathogenic bacteria resident in the microflora in the lower gastrointestinal tract or vagina, if they find conditions that allow attachment and growth in the otherwise sterile urinary tract.
The symptoms of urinary tract infections are variable according to the main organ concerned. In the case of urethritis, the only symptom is dysuria (burning sensation during urination). When the infection affects the bladder (cystitis), in addition to dysuria, the most frequent problems are a frequent need to urinate and milky or smells urine. More severe symptoms may include inability to pass urine, hematuria, pelvic pain, and fever. UTIs are potentially more dangerous than those of the upper urinary tract or interesting kidneys (pyelonephritis). Females are more likely than males to develop infections of the lower urinary tract because they have a shorter urethra, closer to the anus, and at the same time because they lack the prostate gland, which produces secretions with antibacterial properties. This makes easier migration, adhesion to tissues and colonization by microorganisms. However, in older men with prostatic hypertrophy or with gallstones, the occurrence of UTI becomes as frequent as in women. Other major causes of urinary tract infections are sexual activity and the use of catheters, which can cause physical damage to the protective coating of the mucosa, allowing bacteria to invade and colonize the underlying epithelium. On the other hand, genetic predisposition, anatomical malformations of the urinary tract, especially prostate enlargement, as well as some primary diseases, are all factors that can facilitate the development of infections. Pyelonephritis, however, is often caused by bloodborne pathogens [see, for example: 1,A1,A2,A3,A4,A5,A6,A7].

The most common etiologic agents implicated in infections of the lower urinary tract are Escherichia coli (which alone accounts for nearly 90% of registered cases) and other gram-negative bacteria such as *Klebsiella, Proteus, Neisseria*, and *Chlamydia* [A8]. Other cases are related to the presence of gram-positive staphylococci, especially *S. aureus* and *S. saprophyticus.* All of these microorganisms have a high ability to form biofilms, i.e. bacterial communities compact and firmly anchored to the tissues, thanks to the production of polysaccharidic adhesive substances, which makes them more resistant to the removal during urination, as well as less attackable by the immune defenses and by antibiotic treatments. Some forms of urinary tract infections, much less frequent, are caused by mycopathogens such as Mycoplasma.

3.1.2. Antibiotics as therapy in urinary tract infections and the development of resistance

The urinary tract infections are usually treated with a short course of antibiotics, and antibiotics are generally recommended as default treatment for acute uncomplicated urinary tract infections [A9]. The "International Clinical Practice Guideline" recommends the four antibiotics nitrofurantoin, cotrimoxazol (trimethoprim-sulfamethoxazole; at resistance rates of <20% and if not used in the three preceding months), fosfomycin-trometamol and pivmecillinam (s. decision-making tree for diagnosis and treatment in fig. **1**) [2].

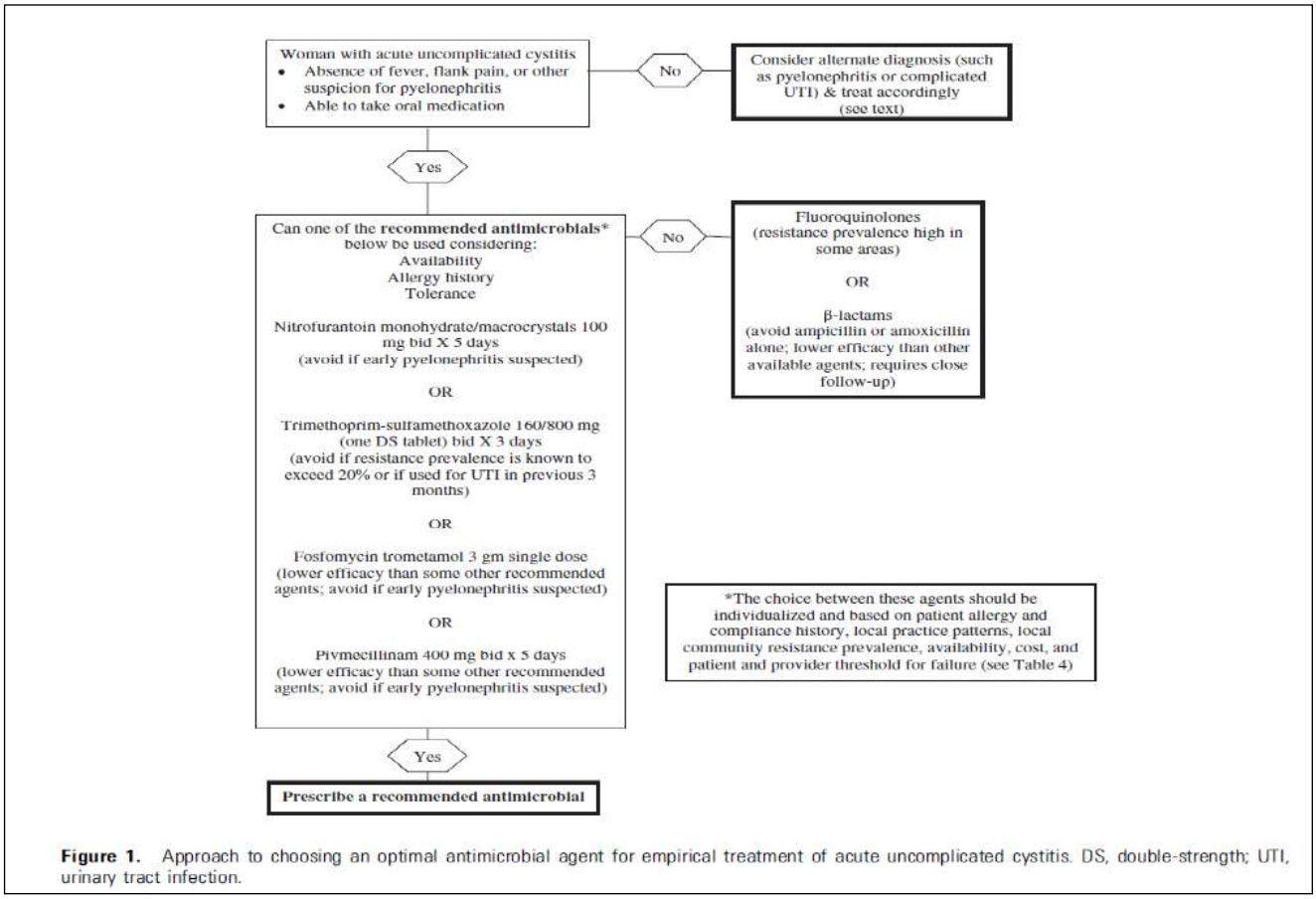

Figure 1. Approach to choosing the optimal antimicrobial product for empirical treatment of acute uncomplicated bladder infection (DS, double-strength; UTI, urinary tract infection). Taken from the IDSA Guideline (from: Gupta et al. [2]).

However, in addition to the high ability to form resistant bacterial biofilms, factor that makes such drugs not too effective against UTI, in at least 20% of the cases treated with antibiotics, the infection becomes recurrent, since the antibiotic makes microbes more prone to develop resistant phenotypes [A10,A11,A12,A13,A84]. So, since uncomplicated urinary tract infections are primarily caused by uropathogenic *E. coli*, the significant increases of *E.-coli*-resistance as described above are a big problem.

Significant resistance rate increases for *E. coli* and reduction of pathogen sensitivities, e.g. to cephalosporins of the 3rd generation (β-Lactam broadband antibiotics) and combinations of these cephalosporins with fluoroquinolones or amino-glycosides are described [A14]. For other β-Lactam antibiotics such as ampicillin or amoxicillin (both also broadband antibiotics) for which there is a lower pathogen sensitivity to begin with in *E. coli*, clearly increasing resistance rates can be found as well. For cotrimoxazol, the combination of trimethoprim and sulfamethoxazole put on the list of vital medicines by the WHO in 1977, pathogen sensitivity has remained mostly consistent for the period of 2008-2015, but sensitivity of *E. coli* continues to be very low at 77.4%.

This suggests the clinical evaluation of agents of different types, not associated with the emergence of resistance and not having the well-known side effects of antibiotics [3,14,A15,A4,A5].
A recently published paper on alternative treatment of acute uncomplicated cystitis with D-mannose explicitly also emphasizes the relevance of *E.-coli*-resistance to reserve antibiotics [15]: "The increased prevalence of uropathogenic *E. coli* resistance to reserve antibiotics and recently to carbapenem and colistin, makes urinary tract infections a top example of the antibiotic resistance crisis and highlights the necessity to find new approaches to treat and prevent bacterial infections". Other authors have underlined the utility of using natural agents such as cranberry or D-mannose or probiotics to increase time of respite of infections [A18,A19].
Unlike antibiotics, there is no low risk of developing resistance to D-mannose [see, for example: 4,A20]. We recall here that the onset of resistance occurs under selective pressure in the presence of an "environmental" threat, like the presence of antibiotics: mutant phenotypes with better survival to the antibiotics will spread at the expenses of the drug-sensitive strains [see, for example: A21,A22,A23,A24]. The activity of D-mannose, not linked to bacteriostatic or bactericidal effects, does not trigger this selective mechanism.

3.2 Active components of the medical device and related mechanisms of activity

3.2.1. D-mannose

D-Mannose is a naturally occurring aldohexose sugar, but is differs from glucose by inversion of one of the four chiral centers of the molecule, precisely that on the carbon atom in the 2 position (Figure **2**); in other words, mannose is considered to be the "C-2 epimer" of glucose. This sugar is normally present in human metabolism and has an important biological role, especially because it is involved in the glycosylation of many proteins [A25].

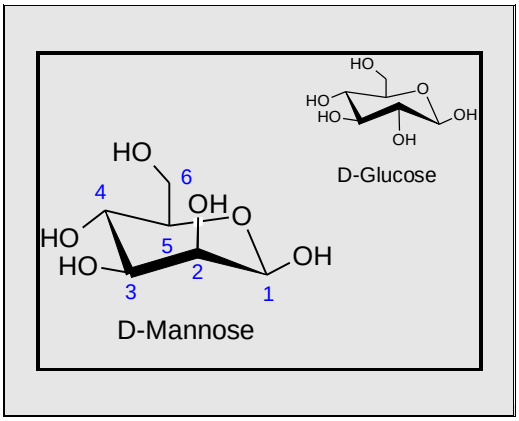

Figure 2. Spatial configuration of D-Mannose, as compared to that of glucose

The peculiarity of D-Mannose, is that - although it is a simple sugar – the substance is not virtually metabolized in humans [see, for example, the pharmacokinetic data by 5,6,A26,A27,A28,A29,A30,A20]. It is assumed that the mannose present in the organism, required for *N*-glycosylation and glycophospholipid anchor synthesis, derives primarily or exclusively from enzymatic stereospecific interconversion of the glucose. Pharmacokinetic studies have shown that at least **90% of mannose ingested is efficiently absorbed in the upper intestine, but it is also rapidly removed from the bloodstream** (clearance half-time $T_{1/2}$ varies from 30 minutes to some hours, depending on dose), **and excreted unconverted into the urine within 30-60 minutes; the remainder is excreted within the following 8 hours** (Figure **3**). No significant increase in blood-glucose levels occur during this time, and mannose was detectable in the tissues only in trace level.

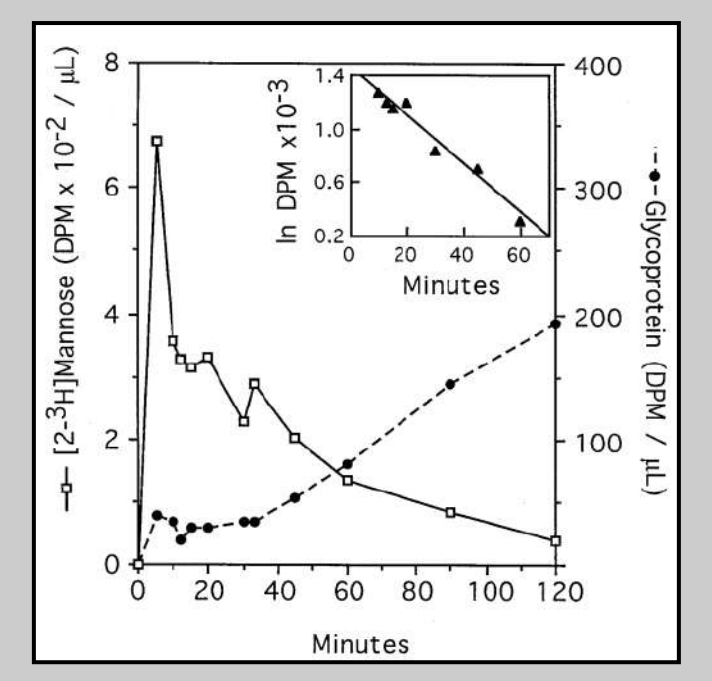

Figure 3. Kinetics of mannose appearance and clearance of radiolabeled glycoproteins in rat serum after injection in the circulation of rats.

Therefore, this sugar – differently from glucose or fructose - does not significantly enter the carbohydrate metabolism when taken orally, and thus it does not have any metabolic effect.

3.2.2. Mechanisms of antibacterial activity of D-mannose in the urinary tract

Together with such peculiar pharmacokinetic behavior, **the other suggestion about a potential effectiveness of supplementations with mannose to prevent *E. Coli*-specific urinary tract infections (that, as quoted above, are the most common among the UTIs) dates back to the end of the 70s, when it was observed that the most important attachment mechanism of this bacteria to the bladder wall is the protrusion of thread-like appendixes called "pili" or "fimbriae".** The fimbriae are of bacterial membrane at the end of which hang out mannose-specific glycoproteins termed "adhesins", which have a strong affinity for the terminal mannose units of uroplakin Ia (UPIa), a membrane glycoprotein that is highly expressed on superficial epithelial umbrella cells of urinary tract. The expression of P-fimbriae is one (but not the only) of the factors determining the degree of virulence of the strains. The mechanism of action of D-mannose is the competitive inhibition of bacterial adherence to urothelial cells, because of its similarity in structure to the binding site of urothelial glycoprotein receptors adherence. It has been shown that this sugar binds and blocks specifically the FimH adhesin, which is positioned at the tip of the type 1 fimbria of enteric bacteria and, during bacterial colonization, binds to carbohydrate-containing glycoprotein receptors on the epithelium of the urinary tract. **Starting from these observations, it was hypothesized that the transit of urine containing sufficiently high levels of free mannose could saturate the *E. coli*'s mannose-binding FimH lectins, and thereby make the bacterium unable to grapple onto the cells of the urinary tract, and most easily displaced and flushed away** [7,8,9,10,11,12,13,A31,A32,A33,A34,A35,A16,A17,A36,A37,A38,A39,A40,A41,A85]. The fimbriae plays the key role also in extraintestinal pathogenic Escherichia coli invasion and translocation through the intestinal epithelium [16].

A similar anti-adhesive effect mechanism has been suggested for the adhesion of the bacterium to other kinds of host's cells [A42,A43], and for the reduction of the adherence of other pathogens to epithelial tissues, including Pseudomonas and Streptococci to endometrial epithelial cells [see, for example: A44,A45]. It is also important to point out that the anti-adhesive effect of mannose strictly depends on the configuration of the molecule. Only the D-isomer and the α-anomer (α-D-mannose) can bind and block the bacterial adhesin. Other carbohydrates have little or no anti-adhesive effect [A46]. However, for completeness, at least two objections concerning the use of mannose should be mentioned:
1. with the exception of *Proteus*, all the other uropathogenic bacteria, including some strains of *E. coli* with mannose-resistant adhesins, do not have mannose-sensitive pili at all [A47,A48,A49], and thus the use of this sugar can be effective only when targeted towards mannose-sensitive *E. coli* and towards *Proteus*-sustained infections;
2. mannose-sensitive pili are also one of the ways by which the blood cells of immune system recognize, tag and subsequently destroy *E. coli* [A50]. When these pili are saturated by mannose, the macrophages could become less effective in engulfing the bacteria [A51,A52]. These questions, still unsolved, will have to be specifically addressed in future laboratory and clinical studies.

3.2.3. Results of *in vitro* studies with D-mannose in UTIs

The potential effectiveness of mannose against urinary infections is currently substantiated by the results of some *in vitro* and animal studies.
In vitro, the oldest studies reported that the capacity of adherence of *E. coli* to kidney cell monolayers [A53] and buccal mucosal cells [7,8] was strongly reduced by the presence of D-mannose (Table **1**), but not by other kind of sugars.

Saccharide	Concentration required for 50% inhibition
	μM
α-CH_3-D-mannoside	0.5
Yeast mannan	10
D-Mannose	50
D-Fructose	3,000
α-CH_3-D-glucoside	18,750
D-Mannitol	37,500
D-Glucose	37,500
L-Mannose	>100,000*
D-Fucose	>100,000
L-Fucose	>100,000
Sucrose	>100,000
D-Galactose	>100,000
Lactose	>100,000
Maltose	>100,000

* No inhibition detectable at 100,000 μM.

Table 1. Inhibition of binding of mannose-sensitive *E. coli* by different sugars at 37°C [from: 7].

Schaeffer [10] studied the complex factors influencing adherence of different strains of [^{3}H]-labeled *Escherichia coli* to human uroepithelial cells obtained from midstream urine specimens of healthy women. **When a 2.5% (wt/vol) solution of D-mannose was added to the culture broth, the adherence was markedly inhibited for all the strains tested** (Table **2**). Interestingly, **the adherence was significantly inhibited even after prolonged incubation time, when large numbers of bacteria were attached to the epithelial cells.**

Strain	Growth conditions	Bacteria/cell[a]	Mannose inhibition[a] (%)
4454	6-h YNB	10.5 ± 5.7[b]	94 ± 8.4
4476	6-h YNB	8.8 ± 9.9[b]	100 ± 0
AC	6-h YNB	7.29 ± 10.6[b]	95 ± 7.9
AC	18-h YNB	3.16 ± 0.02[b]	76 ± 12.0
AC	6-h YNB	42[c]	100
AC	18-h YNB	96.2[c]	100

[a] Mean ± standard deviation.
[b] 18-h MacConkey agar prior to YNB.
[c] 72-h brain heart infusion broth prior to YNB.

Table 2. Inhibition of E. coli adherence (two different strains) to uroepithelial cells by D-mannose (2.5%) (YNB = Yeast nitrogen base) [from: 10].

In subsequent tests [11], **2.5% (wt/vol) concentrations of D-mannose completely inhibited *E. coli* (O18 strain) adherence** (Figure **6**).

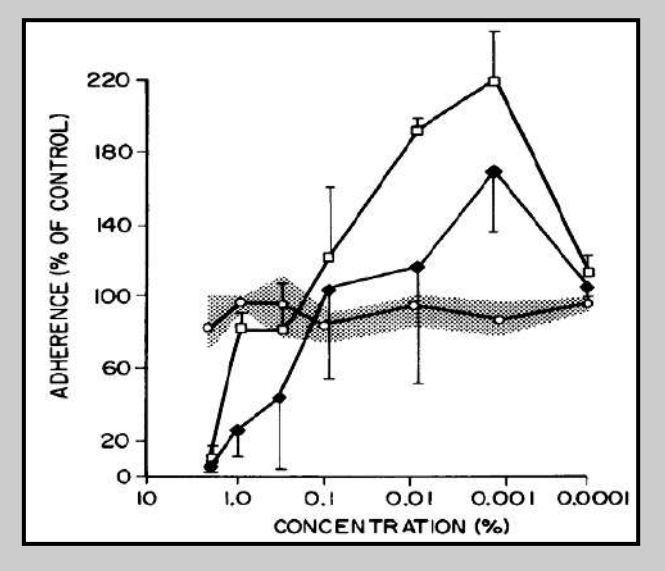

Figure 4. Effect of various concentrations of D -mannose (♦), D -fructose (□), and D -glucose (o) on adherence of E. coli to uroepithelial cells [from: 11].

Mannitol or alpha-methyl-D-mannoside (all sugars bearing a hydroxyl group in the C-2 position) showed IC_{50} concentrations comparable with that of D-mannose, whereas D-lyxose, D-arabinose, D-fructose, and D-glyceraldehyde were much less effective (Table **3**). A variety of other carbohydrates had no effect on the adherence of E. coli to the uroepithelial cells.

Compound	Concn required for 50% inhibition (mM)
Six-carbon	
D-Mannose	27.8
D-Mannitol	27.4
α-Methyl-D-mannoside	77.0
D-Fructose	83.0
Five-carbon	
D-Arabinose	166.0
D-Lyxose	166.0
Three-carbon	
L-Glyceraldehyde	350.0
Yeast mannan	0.05%[a]
ConA	0.0093

[a] Molecular weight not determined.

Table 3. Inhibition of *E. coli* adherence to uroepithelial cells by carbohydrates or the specific adhesion blocker concanavalin A (ConA) [from: 11].

Reducing the concentration of D-mannose in the culture broth to too low levels, between 1.0 and 0.1%, resulted in a progressive growth in the adhesion of the bacteria, and a further reduction in the concentration, to levels between 0.01 and 0.001%, caused an enhancement of bacterial adherence up to 160% of the control level. Preincubation of the epithelial cells in 2.5% D-mannose for 1 min before bacteria were added had no significant effect on the adhesiveness.
The same investigators [A54] then tested the effect of D-mannose on adherence of a large panel of *E. coli* strains to vaginal and buccal epithelial cells of women with recurrent urinary tract infections, and on agglutination of human and guinea pig erythrocytes. Urinary, vaginal or anal isolates from women with such infections were used. 66 strains out of 73 (90%) demonstrated adherence to epithelial cells. Of these sensitive bacteria, D-mannose inhibited completely the adherence of 25 strains (42 per cent) that adhered to vaginal cells and inhibited an additional 11 strains (18 per cent) by at least 50 per cent. Similar results were obtained with buccal cells. The inhibitory effect of D-mannose was similar regardless of the origin of the strains. **These results suggest that, likely, the use of mannose will be helpful in the majority of urinary infections involving the presence of *E. coli*.** No consistent association between hemagglutination, and epithelial cell adherence and the effect of D-mannose was observed.
Previously, less positive results had been reported [A55,A56], who demonstrated mannose-sensitive *E. coli* hemagglutination but mannose-insensitive adherence to uroepithelial cells. The reasons for these discrepancies remain unclear, but they were perhaps due to the use of different experimental conditions.

3.3. Compliance of "Mannose MD" with the current definitions of medical device

3.3.1. The anti-adhesive effect of D-mannose is not a consequence of a metabolic or an immunostimulant effect on host's organism.

D-mannose when given by oral route is not virtually metabolized in humans. Pharmacokinetic studies have shown that although at least 90% of D-mannose ingested is efficiently absorbed in the upper intestine, the sugar is rapidly removed from the bloodstream with a half-time of about 30 minutes. Within next 30 to 60 minutes D-mannose is excreted unconverted into the urine and the remaining fraction is excreted within the following 8 hours. No significant increase in blood-glucose levels occurs during this time and only trace levels of D-mannose are detectable in the tissues. D-mannose – differently from other sugars (such as glucose or fructose) – does not significantly enter the carbohydrate metabolism or other metabolic routes when taken orally, and thus its activity is not mediated by metabolic effects [5,A27,A28,A29,A30,A57,A20]. There is also no evidence that might suggest an immunological effect of D-mannose. Indeed, no immunostimulat effects of D-mannose have been observed. D-mannose does not elicit an antibody response, recruitment of lymphocytes or cytokines production, hallmarks of immune response. These observations rule out the possibility of a metabolic or an immunostimulant effect on host's organism.

3.3.2. The anti-adhesive effect of D-mannose is not a consequence of a pharmacological effect on host's organism.

It has been demonstrated that a pre-incubation of human epithelial cells with active concentrations of D-mannose, prior to their exposure to the bacteria, did not significantly impact the bacteria adhesive capabilities [see, for example: 11]. Thus, this clearly demonstrates that the ability of D-mannose to prevent UTIs relies on its impact on the bacteria present in the urinary tract and not on the host's organism.

3.3.3. The anti-adhesive activity of D-mannose is not mediated by a pharmacological effect on the microorganism.

According to the current scientific concepts, any pharmacological action must comprise a pharmacokinetical and a pharmacodynamical phase, the latter being related to the so-called "receptor concept". Such understanding of a pharmacological action is in line with a definition provided by the MEDDEV Guidance. The pharmacological action consists of the three steps: (1) an active ingredient-receptor interaction (= primary reaction), (2) signal transduction and (3) a subsequent or secondary reaction (that includes also the blocking of a reaction). When applied to a specific example of beta-lactam antibiotics, an antimicrobial drug active against *E. coli* strains, the following steps can be distinguished: after resorption and distribution within the body (pharmacokinetical phase), beta-lactam antibiotics come in contact with microbial cells (pharmacodynamical phase), where they act as antagonists for D-alanyl-D-alanyl transpeptidase enzymes (= step 1), inhibiting the transpeptidation reaction and peptidoglycan synthesis (= step 2). In the next steps (= step 3), inhibitor of autolytic enzymes in the cell wall is inactivated, ultimately resulting in a lysis (*i.e.* a breakdown) of the cell membrane [see, for example: A58, A59]. As discussed below, the interaction of D-mannose with the bacterium neither causes a signal transduction and a subsequent biochemical reaction, nor blocks it, which would be necessary to postulate a pharmacological mode of action. The formation of the D-mannose-bacteria complex simply allows the washout of microorganisms by the urinary flow -- a simple physical mode of action not comparable to the above described three-steps pharmacological mode of action carried out by the antimicrobial drug taken as an example. In addition, the absence of

the risk of developing resistance to D-mannose is another supporting evidence that – unlike antibiotics – D-mannose does not affect metabolic pathways or changes phenotypes of the bacterium (see also the paragraphs below).

The mechanism of action of D-mannose is explained by a competitive inhibition, leading to a decrease of the capacity of the microorganism to adhere to urothelial cells, upon coming into contact with D-mannose. It is nowadays well-established that the transit of urine contains sufficiently high levels of free mannose to saturate the *E. coli*'s mannose-binding FimH lectins. Consequently, the bacterium is unable to grapple onto the cells of the urinary tract and can be more easily displaced and flushed away by shear forces during micturition. This effect occurs because of the similarity in structure of D-mannose to the binding site of urothelial glycoprotein receptors. It has been clearly shown that the presence of this sugar specifically blocks the FimH adhesin, which is positioned at the tip of the type 1 fimbria of bacteria and, during bacterial colonization, binds to mannosylated glycoprotein receptors on the epithelium of the urinary tract [7,8,9,10,11,12,13,A31,A60,A32,A61,A33,A34,A35,A16,A36,A62,A37,A38,A39,A40,A41,A63]. A similar anti-adhesive mechanism has been also suggested for the adhesion of the bacterium to other types of host's cells [A42,A43], as well as for the reduction of the adherence of other pathogens to epithelial tissues, including that of *Pseudomonas* and *Streptococci* to endometrial epithelial cells [A44,A45]. However, the Commission Working Group has not considered at all the mode of action as it applies to other bacterial strains that are implicated in UTIs.

When studied in greater detail using as a basis the current model of interaction between *E. coli* and its host, termed a "catch-bond mechanism", it can be demonstrated that **the presence of the sugar does not trigger any receptor-mediated pharmacological mechanism**, **and so is in compliance with the specification given in the MEDDEV 2. 1/3 rev 3, page 6.** The evidences are the following:

3.3.3.1. The capacity to entrap D-mannose molecules is not a consequence of the presence of the sugar itself, but of conformational changes caused by the presence of dynamic (flow) conditions. It has been observed that, in the lower urinary tract under shear force, the Fim adhesins undergo a transition from a "swimming" conformation of the pili to a conformation that makes their tips highly affine to mannose or mannosylated proteins [see, for example: 12,A64,A61,A33,A65,A46,A66,A12,A13,A67]. **However, such conformational changes occur independently of the presence of D-mannose.** Free mannose just "deceives" the receptors of the bacterium that are already in the adhesion-ready form, saturating the binding site (or, alternatively, causing a steric hindrance) that prevents the interactions with host's mannosylated proteins of the urinary epithelium.

3.3.3.2. Studies at the molecular level have shown that the "coverage" of the binding sites by D-mannose occurs by means of reversible hydrogen bond, Van der Waals forces, formation of networks and hydrophobic/hydrophilic interactions, but not of stable covalent binding, which would change the molecular conformation of the protein(s) [13, A68, A46]. In particular, it has been reported that the D-mannose ring forms 12 direct hydrogen bonds with main and side-chains of amino acid residues of the FimH protein [A63]. Also, the alpha-anomeric hydroxyl group O1 of D-mannose is involved in a hydrogen-bonding through a water molecule that is conserved between the two structures. The positions of other water molecules participating in this network depend on the crystal packing of the protein (Figure **6**).

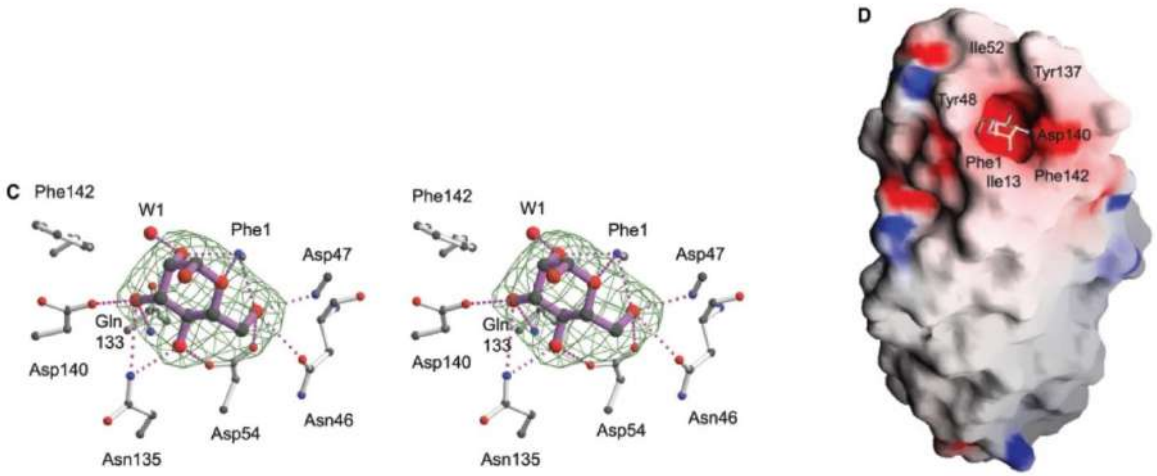

Figure 6. Schematic depictions of hydrogen-bonding and other physical interactions between D-mannose and FimH adhesin. (**C**) Stereo presentation of omit electron density for the α-D-mannoside bound in the pocket of FimH. The interacting amino acids are shown in ball-and-stick, hydrogen bonds are highlighted in purple. (**D**) Receptor binding domain of FimH displaying the electrostatic potential surface, with positively charged residues shown in blue, negatively charged residues in red, and neutral and hydrophobic residues in white. The residues of the hydrophobic ridge around the mannose-binding pocket are labelled [from: 13].

These data show that the saturation of the binding pocket by free D-mannose is mediated through physical forces, and does not trigger specific intracellular signalling pathways, as it would be in the case of "pharmacological" mode of action.

3.3.3.3. Another supporting evidence that the interaction is physical is the fact that the binding of the lectins with mannose residues is promptly reversible, and leaves the bacterium intact. Once exogenous D-mannose is washed away from the culture, the microbe regains its full ability to adhere to host's cells [8]. **This reversibility further supports the conclusion that the interaction between *E. coli* and D-mannose is physical, not pharmacological and neither biocidal, as the viability of the microorganisms is not affected.**

3.3.4. Negative evidences about a pharmacological mechanism of action

Finally, we add that the hypothesis of a purported pharmacological mechanism cannot be logically supported by experimental quantitative data:

3.3.4.1. Unlike antibiotics and other antimicrobial drugs, D-mannose does not affect bacterial viability or bacterial metabolism and does not target cell membranes. Likewise, D-mannose is recovered intact after the "contact" with the bacteria, evidencing that the microbe does not transform this simple molecule, as occurs with pharmaceutical substances, and neither has the capacity to metabolize it.

3.3.4.2. The threshold concentration of D-mannose necessary for triggering such purported pharmacological effects is not defined in literature. In other words, even if a pharmacological mechanism would be possible, there is no evidence that the concentration attainable *in vivo* in the urine after giving the established active doses (1.5-2 grams) would exceed the minimum effective dose for achieving pharmacological effects. Therefore, the dose-response effect required by the definition of "pharmacological means" is, at least, unclear.

3.3.4.3. There are no laboratory or clinical studies showing the existence of a risk of developing resistance to D-mannose, also after a long-term use [see, for example: 4,A20]. This strongly supports the conclusion of the absence of a significant modification of metabolic pathway of the bacterium, or of a pharmacological or biocidal mechanism. We recall here briefly that the onset of resistance occurs under selective pressure in the presence of an "environmental" threat, like the presence of antibiotics. Mutant phenotypes with better survival to the antibiotics will spread at the expenses of the drug-sensitive strains [see, for example: A21,A22,A23,A24]. The fact that the presence of D-mannose does not promote resistance, evidences the absence of competition against normal ("wild-type") strains. In other words, D-mannose does not affect growth rate (*i.e.* there is no interference with metabolic pathways), and does not modify structural integrity of bacterial cell (*i.e.* there are no bactericidal or pharmacological effects), as these activities would trigger a struggle for the "survival of the most apt" ending with the acquisition of resistance.

3.3.5. Summary of the conclusion of the experimental procedure carried out on D-mannose at the University of Rome by Prof. Palamara

This set of experiments is explained and detailed in the document attached to the FT026.
In short, the research team concluded the document with the following considerations, which strengthen our claims:
-"D-mannose at concentrations of ≤10% *[note: a concentration much greater than the urinary dilution of D-mannose in our product, as it is given at maximal dose of 2-6 g/day]* does not impair *E. coli* strain CFT073 viability. Higher concentrations of D-mannose as well as other selected sugars impair bacterial viability due to osmotic pressure effects".

↓

No bacteriostatic or bactericidal (biocidal) effects

-"D-mannose does not interfere with the activity of distinct classes of antibiotics on strain CFT073, at any tested concentrations, indicating its safe use in association with antibiotic for UTI treatment".

-"D-mannose is the less preferred carbon source to support *E. coli* growth in comparison with other sugars tested. We assessed a sugar preference gradient in *E. coli* being D-glucose > L-arabinose > D-fructose > D-mannose".

↓

No activities of D-mannose on the metabolism of the bacteria. In any case, we underline that a pro-metabolic activity would be unfavourable to the proposed mechanism (reduction of the number of adhering microbes), and so it can not be responsible for the antiadhesive action.

-"D-mannose significatively interfers with the adhesion of strain CFT073 to HTB-9 bladder cells. This is due to D-mannose saturation of the FimH adhesin expressed by strain CFT073".

↓

This confirms the mechanism we have elucidated above.

-D-mannose exposed HTB-9 monolayers do not show any morphological changes, indicating that D-mannose does not affect basic cellular processes.

↓

A further proof that the action of D-mannose does not activate receptor-mediated signaling, as it would be in case of pharmacological actions.

Overall these data demonstrate that D-mannose is the less preferred metabolizable sugar in *E. coli*. It does not show bacteriastatic or bactericidal activity. D-mannose at concentrations ≤ 10% does not have any dose-response effect, indicating that it does not act pharmacologically on *E. coli* viability and growth. The dose-response effect shown by D-mannose at concentrations above 10% is exclusively related to the osmotic pressure exerted by all sugars on the bacterial cell wall.

3.3.6. Conclusions

Prior to placing the product on the market as a medical device, S.I.I.T in conjunction with its notified body fully considered what the most appropriate regulatory classification for the product should be. The conclusion was that D-mannose should properly be classified as a medical device given that the scientific evidence demonstrates clearly that the mode of action of D-mannose against *Escherichia coli (E. coli)* or other uropathogens sharing the same mode of attachment is physical and not pharmacological, metabolic or immunological in any sense.

By considering the mechanism detailed above and the definitions of medical device according to the current EU regulation (see the discussion in the attached position paper), we make the following conclusions:

- D-mannose has a medical purpose in that it has a role to play in preventing UTIs.
- D-mannose is intended for the use in humans.
- D-mannose does not achieve its effect by metabolic means. D-mannose given by oral route is not metabolized by human organism. The primary intended purpose, *i.e.* the anti-adhesive action of D-mannose on pathogens in the urethra, depends upon not being metabolized after intestinal absorption [5,A29,A30,A57,A20].
- D-mannose does not achieve its effect by immunological means. Currently, there is no evidence that the action of this simple sugar against urinary tract pathogens occurs through the stimulation of immune reactions such as antibody response, recruitment of lymphocytes, production of cytokines, *etc.*
- D-mannose does not achieve its effect by pharmacological means elicited on cells of host's body, as this substance is excreted intact in the urine, without undergoing any process of biotransformation, as it would if there were interactions with cellular receptors [11,A39,A40].
- D-mannose does not achieve its effect by pharmacological means elicited on pathogen cells, as it "covers" and blocks the active site of FimH adhesion proteins by transient and reversible physical interactions (Van der Waals forces, H-bonds and hydrophobic/hydrophilic interactions), not by stable covalent links with the receptor and/or the induction of structural changes in the protein(s) which would trigger modifications in a signal pathway (conditions that are required to fall under the definition of "pharmacological means" as given by the European Commission in the MEDDEV 2. 1/3 rev 3, page 6). Thus, the presence of the molecules of D-mannose creates a steric hindrance that "conceals" the adhesins, preventing the binding of the microorganism to the mannosylated proteins on urothelial uroplakins [7,8,9,10,11,12,13,A31,A60,A64,A68,A32,A61,A33,A34,A65,A35,A16,A46,A69,A36,A66,A62,A37,A38,A39,A40, A41,A12,A13,A63]. The existence of a dose-response effect required by the Commission's definition of "pharmacological means" is unclear and, in any event, not a robust criterion.
- D-mannose is neither biocidal, as it do not diminish viability or vitality of the bacteria. *In vitro*, once the sugar is removed from the culture broth, the pathogen regains full ability to adhere to epithelial cells [8].
- There is no qualitative nor quantitative evidence of the purported pharmacological effects in the literature.
- D-mannose does not induce resistance, as it would in the presence of drug-like pharmacological mechanisms [A21,A22,A23,A24].

Taking all these facts into consideration, we claim that – at best of our knowledge - **D-mannose promotes the reduction of the adhesion and consequent colonization of the invasive pathogens in the lower urinary tract with means that**

are in accordance with all the current definitions of "medical device" as that definition is interpreted under MEDDEV Guidance and Court of Justice case law. This substance does not act pharmacologically, immunologically, or metabolically. Its action, as described and portrayed in the literature, falls squarely under the definitions of a medical device such as given by EU.

For the reasons detailed above, in compliance with the present European legislation, we claim that the medical device "Mannose MD", shoud be classified in the Class IIa, as it complies with the following criterion:
-non surgical, non implantable invasive device, for short-term use, not intended for use in connection to an active medical device.

Stage 1

4. Identification of pertinent data

(← MedDev 2.7.1 rev.4: Section 8, p.17 and following; Appendix 4, p.36 and ff.; Appendix 5, p.37 and ff.)

4.1. Data generated and held by the manufacturer

There are no clinical or post clinical data held by the manufacturer.
In 2018 S.I.I.T. Srl, in cooperation with the Department of Public Health and Infectious Diseases of Sapienza University (Rome), carried out an in vitro study to provide original data to prove that the preventive activity of D-mannose against UTIs is based on its mechanical and physical interaction with FimH without any pharmacological effects on shape, viability, ability to grow in culture, motility and/or metabolic activity of E. coli, as well as on viability and proliferation of eukaryotic cells.
The scientific assessment reporting the first results of this study is reported as Addendum (Addendum_Final Sapienza Report on D-mannose) in Annex 19 – Valutazione Clinica of the current technical file.The outcomes of an in-vitro study have been resumed above (§ 3.3.5), and are detailed in the attached document.

4.2. Data retrieved from literature

The sources of data used in the Clinical evaluation are taken from official National Institute of Health Pubmed and Cochrane Database of Systematic Reviews, by selecting scientific literature data based on clinical relevant evidence which together can guarantee the safety and the performance of the ingredients of MD, in its final formulation.

Name of person undertaking the search: [redacted] (literature and patent search expert)

4.2.1. PICO search strategy

4.2.1.1. Definition of the question

Patient/Problem	Adults and children suffering from lower urinary tract infections of bacterial origin
Intervention	D-mannose as medical device preventing the attachment of pathogens to the urinary epithelium
Comparison	Placebo or non-pharmacological or pharmacological antimicrobial agents
Outcome	Treatment and prevention of cystitis and related symptoms (dysuria, frequent urination, milky malodorous urine, pelvic pain, etc.)

Writing out the question:

In adults and children suffering from lower urinary tract infections of bacterial origin, is D-mannose as medical device preventing the attachment of pathogens to the urinary epithelium, compared to placebo or non-pharmacological or pharmacological antimicrobial agents, effective in treating and preventing cystitis and related symptoms (dysuria, frequent urination, milky malodorous urine, pelvic pain, etc.)?

4.2.1.2. Type of question/problem

Underline one of these: **Therapy** / **Prevention** / Diagnosis / Etiology / Prognosis

4.2.1.3. Type of studies/publications to include in the search

Check all that apply:

☑ Meta-analysis
☑ Systematic review
☑ Clinical practice guidelines
☑ Randomized controlled trial
☑ Research studies or articles
☑ Case report or series

4.2.1.4. List of searched databases

●Medline
●Cochrane Library

4.2.1.5. List of main topics and alternate terms from PICO question that were used for the search:

Identification of the keywords:
D-mannose; Cystitis; Urinary tract infections; UTI.

4.2.1.6. Search strategy in PubMed

The search was performed using the criteria outlined in the NCBI Manual, using the Boolean operators (AND, OR, NOT) and, if necessary, "nested" concepts and truncation symbol (*).

- Logical criteria of the search query
  - "(D-mannose OR mannose) AND ((urinary AND tract AND infection*) OR UTI OR cystitis)"
- The database yielded the following Search Detail:

- "(("mannose"[MeSH Terms] OR "mannose"[All Fields] OR "d mannose"[All Fields]) OR ("mannose"[MeSH Terms] OR "mannose"[All Fields])) AND ((("urinary tract"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields]) OR "urinary tract"[All Fields] OR "urinary"[All Fields]) AND tract[All Fields] AND (infection[All Fields] OR infection'[All Fields] OR infection'epid'emique[All Fields] OR infection'larda[All Fields] OR infection's[All Fields] OR infection,[All Fields] OR infection1[All Fields] OR infection100[All Fields] OR infection118[All Fields] OR infection13[All Fields] OR infection17[All Fields] OR infection2016[All Fields] OR infection21[All Fields] OR infection3[All Fields] OR infection36[All Fields] OR infectiona[All Fields] OR infectional[All Fields] OR infectionally[All Fields] OR infectionand[All Fields] OR infectionary[All Fields] OR infectionassociated[All Fields] OR infectionat[All Fields] OR infectionaustralian[All Fields] OR infectionbiology[All Fields] OR infectionbokutoh[All Fields] OR infectionbut[All Fields] OR infectionby[All Fields] OR infectioncausing[All Fields] OR infectioncomprises[All Fields] OR infectionconfirmed[All Fields] OR infectioncongenital[All Fields] OR infectioncongenitale[All Fields] OR infectioncontrol[All Fields] OR infectiondagger[All Fields] OR infectiondaggermicrobiologydouble[All Fields] OR infectiondiagnosis[All Fields] OR infectiondouble[All Fields] OR infectioned[All Fields] OR infectionem[All Fields] OR infectionen[All Fields] OR infectioner[All Fields] OR infectiones[All Fields] OR infectionform[All Fields] OR infectioni[All Fields] OR infectionimmunity[All Fields] OR infectionin[All Fields] OR infectionincomplete[All Fields] OR infectioninduced[All Fields] OR infectioning[All Fields] OR infectioninternational[All Fields] OR infectionintimo[All Fields] OR infectionirg1[All Fields] OR infectionirrigation[All Fields] OR infectionis[All Fields] OR infectionist[All Fields] OR infectionists[All Fields] OR infectionit[All Fields] OR infectionity[All Fields] OR infectionized[All Fields] OR infectionizing[All Fields] OR infectionl[All Fields] OR infectionless[All Fields] OR infectionlondon[All Fields] OR infectionmalthough[All Fields] OR infectionman[All Fields] OR infectionmanager[All Fields] OR infectionmarseille[All Fields] OR infectionmthe[All Fields] OR infectionoccurred[All Fields] OR infectionof[All Fields] OR infectionplus[All Fields] OR infectionprevention[All Fields] OR infectionpublished[All Fields] OR infectionqimr[All Fields] OR infectionrate[All Fields] OR infectionreconstruction[All Fields] OR infectionrelated[All Fields] OR infectionresponse[All Fields] OR infections[All Fields] OR infections'[All Fields] OR infections"[All Fields] OR infections'21[All Fields] OR infections'illnesses[All Fields] OR infections's[All Fields] OR infections1[All Fields] OR infections2[All Fields] OR infections3[All Fields] OR infections9[All Fields] OR infectionsa[All Fields] OR infectionsaging[All Fields] OR infectionsanaemiens[All Fields] OR infectionsand[All Fields] OR infectionsanitation[All Fields] OR infectionsare[All Fields] OR infectionscan[All Fields] OR infectionscaused[All Fields] OR infectionschildren[All Fields] OR infectionsconclusion[All Fields] OR infectionsdagger[All Fields] OR infectionsdo[All Fields] OR infectionsicddr[All Fields] OR infectionsin[All Fields] OR infectionsity[All Fields] OR infectionskrankheiten[All Fields] OR infectionsness[All Fields] OR infectionsnonthaburi[All Fields] OR infectionsor[All Fields] OR infectionsoxford[All Fields] OR infectionsparis[All Fields] OR infectionspooled[All Fields] OR infectionsprogram[All Fields] OR infectionss[All Fields] OR infectionssiafter[All Fields] OR infectionssygdomme[All Fields] OR infectionst[All Fields] OR infectionstitle[All Fields] OR infectionstreating[All Fields] OR infectionsuganda[All Fields] OR infectionsveje[All Fields] OR infectionswas[All Fields] OR infectionswere[All Fields] OR infectiontwo[All Fields] OR infectiontypes[All Fields] OR infectionunderwent[All Fields] OR infectionuniversity[All Fields] OR infectionus[All Fields] OR infectionw[All Fields] OR infectionwas[All Fields] OR infectionwere[All Fields] OR infectionwith[All Fields] OR infectionworldwide[All Fields] OR infectionx[All Fields] OR infectionxbroiler[All Fields] OR infectionxdiet[All Fields] OR infectionyy1[All Fields] OR infectionzika[All Fields])) OR UTI[All Fields] OR ("cystitis"[MeSH Terms] OR "cystitis"[All Fields]))"

4.2.1.7. List any limits that may apply to your search:

Gender: No gender limit
Age limit: 14 years to adults
Condition to treat: No limits
Language(s): English, French, German, Italian, Spanish
Date of search: September 19th April 2018
Period covered: January 1st 1960 – September 19th 2018

4.2.2. Search in complementary sources of information

A complementary research was performed using the following sources:

- **BIBLIOGRAPHIC REFERENCES INCLUDED IN THE FULL-TEXT ARTICLES** (the screen was aimed to find the existence of works not mentioned in other sources)
- **COCHRANE DATABASE OF SYSTEMATIC REVIEWS**
- **SEARCH IN AUTHORITY OPINIONS** (EMA, FDA, WHO, etc.)
- **PATENT SEARCH USING THE DATABASES "ESPACENET", "WIPO PATENTSCOPE" AND "USPTO"** (Keywords: D-mannose; Urinary tract infections)

Furthermore, a selection of recent studies and books of pharmacology / medicine, etc., on causes and treatments of lower urinary tract infections, was taken into consideration. They have been included in the first Table of paragraph 6.1.

4.2.3. Criteria used in the selection of works relevant to this CER

For D-MANNOSE, the search evidenced 398 publications, publications, documents and patents.

- **270** of them were discarded directly.

These publications were discarded because of:

-old studies which were deemed as pertinent, but without abstract, and appeared on old journals no longer existing;
-old studies on animal models of urinary tract infections;
-genomic studies on identification of different strains of uropathogens;
-studies on virulence of different strains;
-studies on in vitro colture of strains of uropathogens;
-studies on immunological response to infections;
-studies on physiological aspects that predispose to invasion;
-studies on E. coli in extraurinary infections;
-studies published in more than one paper;
-studies pertinent to the matter, but without abstract and written in language different from English, Italian, French, German or Spanish.

128 publications remaining

- **54** of them, after having been included and read in abstract form, were considered not pertinent and discarded (**underlined in blue, with reference NP**);

The publications deemed as not relevant after having been read in abstract were discarded because of:

-in vitro studies performed before the 90's (as there is plenty of recent literature);
-studies on blinding specificities of different uropathogens;
-studies with alkylated forms of D-mannose and other D-mannose derivatives;
-studies on activities of agents different from D-mannose
-old reviews no more updated;

74 publications remaining

- **63** of them have been included and read in abstract form to verify if data supported evidences found in full-text papers (**underlined in black, with an "A" followed by n° of reference**);

These publications include:

-in vitro and in vivo studies, with the exception of recent studies resuming the "state of the art" of the knowledge.
-clinical studies with formulations containing D-mannose in association with other agents;
-

- **11 of them, underlined in red, with n° of reference, have been included and read in full-text. These studies included also two studies using D-mannose.**

4.2.4. List of references

The following tables summarizes all scientific literature object of evaluation to verify evidence of effectiveness of functional components, therapeutic dosage-and safety dosage in adults and children, and check for adverse effects on patients.

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NP	**In vitro adherence of type 1-fimbriated uropathogenic Escherichia coli to human ureteral mucosa.** PubMed 2568346 Fujita K. et al.	*Infect Immun.* 57(8):2574-9.	1989
NP	**Persistence of Escherichia coli bacteriuria is not determined by bacterial adherence.** PubMed 1879917 Andersson P. et al.	*Infect Immun.* 59(9):2915-21.	1991
NP	**Virulence factors of Escherichia coli in urinary isolates.** PubMed 1823249 Vidotto M.C. et al.	*Braz J Med Biol Res.* 24(4):365-73.	1991
NP	**[The role of E. coli adhesiveness in the pathogenesis and clinical course of urinary tract infections].** PubMed 1362812. Krzeska I. et al.	*Pol Tyg Lek.* 47(31-33):706-9.	1992
NP	**Virulence characteristics of Escherichia coli in nosocomial urinary tract infection.** PubMed 7687152 Ikäheimo R. et al.	*Clin Infect Dis.* 16(6):785-91.	1993
NP	**Characterization of fimbriae produced by enteropathogenic Escherichia coli.** PubMed 7901197 Girón J.A. et al.	*J Bacteriol.* 175(22):7391-403.	1993
NP	**Virulence-associated characteristics of Escherichia coli in urinary tract infection: a statistical analysis with special attention to type 1C fimbriation.** PubMed 7692211 Siitonen A. et al.	*Microb Pathog.* 15(1):65-75.	1993
NP	**Fimbriation, surface hydrophobicity and serum resistance in uropathogenic strains of Escherichia coli.** PubMed 7812269 Puzová H. et al.	*FEMS Immunol Med Microbiol.* 9(3):223-9.	1994
NP	**Assessment of the significance of virulence factors of uropathogenic Escherichia coli in experimental urinary tract infection in mice.** PubMed 8908603. Yamamoto S. et al.	*Microbiol Immunol.* 40(9):607-10.	1996
NP	**The expression of nonagglutinating fimbriae and its role in Proteus mirabilis adherence to epithelial cells.** PubMed 9304781 Tolson D.L. et al.	*Can J Microbiol.* 43(8):709-17.	1997
NP	**Virulence factors in uropathogenic E. coli.** PubMed 10862292 Shrikhande S.N. et al.	*Indian J Pathol Microbiol.* 42(3):321-5.	1999
NP	**Association between antibiotic resistance and the expression of Dr adhesin among uropathogenic Escherichia coli.** PubMed 11173810 Kachroo B.B.	*Chemotherapy.* 47(2):97-103.	2001
NP	**Virulence factors of Escherichia coli isolated from urine of diabetic women with asymptomatic bacteriuria: correlation with clinical characteristics**. PubMed 11759045 Geerlings SE. Et al	*Antonie Van Leeuwenhoek.* 80(2):119-27.	2001
NP	**Occurrence and characterisation of uropathogenic Escherichia coli in urinary tract infections.** PubMed 17642991 Raksha R. et al.	*Indian J Med Microbiol.* 21(2):102-7.	2003
NP	**Infections and SLE.** PubMed 16373252 Zandman-Goddard G., Shoenfeld Y.	Autoimmunity. 38(7):473-85.	2005
NP	**Fimbriae of uropathogenic Proteus mirabilis.** PubMed 17640292 Rocha S.P. et al.	*FEMS Immunol Med Microbiol.* 51(1):1-7.	2007
NP	**Molecular variations in Klebsiella pneumoniae and Escherichia coli FimH affect function and pathogenesis in the urinary tract.** PubMed 18474655 Rosen D.A. et al.	*Infect Immun.* 76(7):3346-56.	2008
NP	**Mannose-binding lectin in pre-menopausal women with recurrent urinary tract infections.** PubMed 19886899 Colodner R. et al.	*Clin Microbiol Infect.* 16(9):1394-8.	2010
NP	**An approach to uropathogenic Escherichia coli in urinary tract infections**. PubMed 21346899 Ranjan K.P. et al.	*J Lab Physicians.* 2(2):70-3.	2010
NP	**Rational design strategies for FimH antagonists: new drugs on the horizon for urinary tract infection and Crohn's disease.** PMID: 28506090 Mydock-McGrane L.K. et al.	*Expert Opin Drug Discov.* 2017; 12(7):711-731.	2017
NP	**The association of mannose-binding lectin 2 polymorphisms with outcome in very low birth weight infants.** PMID: 28558032 Hartz A. et al.	*PLoS One.* 12(5):e0178032.	2017
NP	**Selective depletion of uropathogenic E. coli from the gut by a FimH antagonist.** PMID: 28614296 Spaulding C.N. et al.	*Nature.* 546(7659):528-532.	2017
NP	**Mannose-Binding Lectin-Deficient Donors Increase the Risk of Bacterial Infection and Bacterial Infection-Related Mortality After Liver Transplantation.** PMID: 28649744 Lombardo-Quezada J. et al.	*Am J Transplant.* 18(1):197-206.	2018
NP	**Evaluation of CpxRA as a Therapeutic Target for Uropathogenic Escherichia coli Infections.** PMID: 29311237 Dbeibo L. et al.	*Infect Immun.* 86(3). pii: e00798-17.	2018
NP	**Epithelial C5aR1 Signaling Enhances Uropathogenic Escherichia coli Adhesion to Human Renal Tubular Epithelial Cells.** PMID: 29765378 Song Y. et al.	*Front Immunol.* 9:949.	2018

Stage 2

5. Appraisal of pertinent data (Section 9, Appendix 6)

5.1. *Equivalence with medical devices of the same producer*

From many years, SIIT has produced medical devices containing D-mannose as functional component and same function of those object of this evaluation, although in association with other functional components (extracts of cranberry or pomegranate).
These formulations are marketed under various brand names.

No report of relevant adverse events or other incidents was recorded from these products.
The equivalences of the medical device object of this technical file – "Mannose MD", are showed in the Table **4** and **5** at the following pages. D-mannose is formulated in various pharmaceutical forms. The Tables resume technical features and the prescriptions in the IFU of the most common of these products on the EC market. Green boxes indicate equivalence with the product object of this CER; red boxes indicate non-equivalence.

	CLINICAL EQUIVALENCES					BIOL. EQUIV.	TECHNICAL EQUIVALENCES			MANUFACTURING PROCESS	
PRODUCT	CLAIMS	Q.TY	POSOLOGY	TARGET POPULATION	DURATION OF ADMIN.		FORM OF ADMIN.	FUNCTIONAL COMPONENTS	EXCIPIENTS	TECHNICAL SPECIFICATIONS	PRODUCTION
LACTOFLORENE CISTITE	Support of intestinal bacterial flora eaquilibrium	Lactobacillus paracasei 1 mld UFC D-Mannose 1000 mg/sachet	1 sachet/day, which could be increase up to 3 sachets/day	**Adults (no further information)**	**No information**	**Same body apparatus**	**Sachet**	Mannose is the same of that in the present technical file.	Quali- quantitative difference in the excipients	Mannose used in Lactoflorene cistite formulation is identical to the one used in the present technical file.	The productive process of the two medical devices are different
	Support of urinary tract functionality	Cranberry 126,316 mg/sachet				**Different functional substance (except D-mannose)**					

Table 4. Equivalent products containing D-mannose manufactured by SIIT

5.2. Benchmark medical devices of other producers

There are on the market since long time medical devices of other producers equivalent to the functional components of "Mannose MD".

	CLINICAL EQUIVALENCES					BIOLOGICAL EQUIV.	TECHNICAL EQUIVALENCES			MANUFACTURING PROCESS	
PRODUCT	CLAIMS	Q.TY (mg/capsule)	POSOLOGY	TARGET POPULATION	DURATION OF ADMIN.		FORM OF ADMIN.	FUNCTIONAL COMPONENTS	EXCIPIENTS	TECHNICAL SPECIFICATIONS	PRODUCTION
XANACIST	Prevention and treatment of cystitis	No information	1-2 tablets/day	Adults (no further information)	No information	Same body apparatus Same functional substance (except for Arctostaphylos uva ursi, Cranberry amd beta-glucans)	Tablets	The product contains the functional ingredient having the same contact with the body, anatomical site and mechanism of action.	Quali- quantitative difference in the excipients	Finished product specifications are not identical to the ones of the MD object of this technical file.	Not specified
MONURELLE PLUS	Treatment of cystitis Prevention of cystitis	No information	2 tablets/day 1 tablet/day	Adults (no further information)	5 days At least 15 days	Same functional substance in contact with the body	Capsules	The product contains the functional ingredient having the same contact with the body, anatomical site and mechanism of action.	Quali- quantitative difference in the excipients	Finished product specifications are not identical to the ones of the MD object of this technical file.	Not specified
MANNOSIO KOS	Increased mannose requirement	500 mg/tablet	2-4 tablets/day	Adults (no further information)	No information	Same functional substance in contact with the body	Tablets	The product contains the functional ingredient having the same contact with the body, anatomical site and mechanism of action.	Quali- quantitative difference in the excipients	Finished product specifications are not identical to the ones of the MD object of this technical file.	Not specified

D-MANNOSE LONGLIFE	**Support urinary tract functionality and body fluid drainage**	1000 mg/capsule	2 tablets/day	Adults (no further information)	**No information**	**Same functional substance in contact with the body (except for Arctostaphylos uva ursi)**	**Capsules**	**The product contains the functional ingredient having the same contact with the body, anatomical site and mechanism of action.**	Quali- quantitative difference in the excipients	**Finished product specifications are not identical to the ones of the MD object of this technical file.**	Not specified
MANNOCIST-D KRYMI	**Acute urinary infections** **Prevention of cystitis after an acute episode**	1500 mg/sachet	2 sachets/day 1 sachet/day	Adults (no further information)	**3 days** **Until symptoms resolve**	**Same functional substance in contact with the body**	**Sachets**	**The product contains the functional ingredient having the same contact with the body, anatomical site and mechanism of action.**	Quali- quantitative difference in the excipients	**Finished product specifications are not identical to the ones of the MD object of this technical file.**	Not specified
MANNOSIO-D LABORATORI BIO LINE	**Reduced intake of mannose or increased mannore requirement**	900 mg	2 tablets/day	Adults and children over 12 year of age	**No information**	**Same functional substance in contact with the body**	**Tablets**	**The product contains the functional ingredient having the same contact with the body, anatomical site and mechanism of action.**	Quali- quantitative difference in the excipients	**Finished product specifications are not identical to the ones of the MD object of this technical file.**	Not specified

Table 5. Examples of equivalent products containing D-mannose manufactured by other producers

6. Performance in clinical trials of equivalent devices

6.1. Analysis of scientific literature

The most relevant clinical data obtained from the analysis of scientific literature about equivalent products are grouped in a table intended to evidence:

Study rating

- Calculated through the "Jadad scale", modified to account for single blinding because double blinding is not always logistically possible in bowel preparation studies.
  - Green labels in correspondence of "**Rating**", indicate randomized **high-quality study** (score ≥ 3).
  - Yellow labels in correspondence of "**Rating**" indicate randomized **low-quality study** (score ≤ 2)
  - Red labels in correspondence of "**Rating**" indicate **non-randomized study**
- Ethics Committee
  - Green labels in correspondence of "**EC?**", indicate a study approved by an Ethics Committee
  - Red labels in correspondence of "**EC?**", indicate a study not approved by an Ethics Committee

Clinical equivalences

- The **total quantity of D-mannose and fluids (water or clear drink)** administered in the clinical study
  - Green labels in correspondence of "**Quantity**", indicate **clinical dosage of D-mannose equivalent** to the MDs object of this CER.
  - Red labels in correspondence of "**Quantity**", indicate **higher clinical dosage of D-mannose** with respect to the MDs object of this CER.
  - Yellow labels in correspondence of "**Quantity**", indicate **lower clinical dosage of D-mannose** with respect to the MDs object of this CER.

  The **posology**
  - Green labels in correspondence of "**Posology**", indicate **posology identical** to the MDs object of this CER.
  - Red labels in correspondence of **Posology**", indicate **posology different** to the MDs object of this CER.

- **Number of subjects** participating to the study. **Enr** indicated the number of patients initially enrolled. **ITT** (Intention-to-treat analysis) is a comparison of the treatment groups that includes all patients as originally allocated after randomization. This is the recommended method in superiority trials to avoid any bias. For missing observations, "last value carried forward" is the recommended method. **PP** (Per-protocol analysis) is a comparison of treatment groups that includes only those patients who completed the treatment originally allocated. If done alone, this analysis leads to bias.
- **Clinical conditions** (category and pathology of participants) and study design
  - Green labels in correspondence of the column "**Category of subjects**", indicate **clinical conditions equivalent** to those intended for the use of the present MD.
- **Age**
  - Green labels in correspondence of the column "**Age**", indicate **age of the participants equivalent** to that intended to use the present MD.
- **Duration of the study** (time of continuative administration)
  - Green labels in correspondence of "**Duration of the study**" indicate **a period of continuative administration identical** to that allowed for the MDs object of this CER.
  - Red labels in correspondence of "**Duration of the study**" indicate **a period of continuative administration different** from that allowed for the MDs object of this CER.

Biological equivalences

- **Material** in contact with the organism

Technical equivalences

- **Form of administration**
  - Green labels in correspondence of the column "Form of administration", indicate scientific evidence of same pharmaceutical form of administration of the present MD.
- **CE certification**
  - Green labels in correspondence of "**CE Marks?**", indicate that the product under investigation has the CE certification
  - Red labels in correspondence of "**CE Marks?**", indicate that the product under investigation does not have the CE certification
- **Ingredient function** and **primary endpoints of the study** (main activity expected for the ingredient during the study)
  - Green labels in correspondence of this column indicate **equivalent endpoints and study conditions** of present MD.

Outcomes and safety

- Green / Red / Yellow labels in correspondence of the column "Effective / Not effective" indicate scientific evidence of effectiveness (**E**) / no effectiveness (**NE**) / lesser effectiveness (**LE**) with respect to placebo or comparator.
- Green / Red / Yellow labels in correspondence of the column "Side effects" indicate scientific evidence of lack of side effects / presence of severe side effects, / presence of moderate and transient side effects, respectively.

With this subdivision, it is possible to summarize the importance of the clinical studies in establishing the safety and the performance of the device.

6.2. Inclusion of animal studies

- Green labels in correspondence of the box "Equivalent daily dose in humans", indicate allometric calculation which gives scientific evidence of same clinical dosage of present MD.
- Red labels in correspondence of of the box "Equivalent daily dose in humans", indicate allometric calculation which gives scientific evidence of clinical dosage exceeding dosage of present MD.
- Yellow labels in correspondence of of the box "Equivalent daily dose in humans", indicate allometric calculation which gives scientific evidence of lower clinical dosage of present MD.

The conversions values are calculated using the tables below (FDA/CDER draft guidance 3814, Dec 2002; Nair and Jacob, *J Basic Clin Pharma* 7:27, 2016), generally used to estimate the safe starting dose in clinical trials for therapeutics in adult healthy volunteers.

Table 1: Conversion of Animal Doses to Human Equivalent Doses (HED) Based on Body Surface Area

Species	To convert animal dose in mg/kg to dose in mg/m², multiply by km below:	To convert animal dose in mg/kg to HED[a] in mg/kg, either:	
		Divide animal dose by:	Multiply Animal dose by:
Human	37	---	---
Child (20 kg)[b]	25	---	---
Mouse	3	12.3	0.08
Hamster	5	7.4	0.13
Rat	6	6.2	0.16
Ferret	7	5.3	0.19
Guinea pig	8	4.6	0.22
Rabbit	12	3.1	0.32
Dog	20	1.8	0.54
Primates:			
Monkeys[c]	12	3.1	0.32
Marmoset	6	6.2	0.16
Squirrel monkey	7	5.3	0.19
Baboon	20	1.8	0.54
Micro-pig	27	1.4	0.73
Mini-pig	35	1.1	0.95

[a] Assumes 60 kg human. For species not listed or for weights outside the standard ranges, human equivalent dose can be calculated from the formula:

HED = animal dose in mg/kg x (animal weight in kg/human weight in kg)$^{0.33}$.

[b] This km is provided for reference only since healthy children will rarely be volunteers for phase 1 trials.

[c] For example, cynomolgus, rhesus, stumptail.

Table 1: Human equivalent dose calculation based on body surface area*

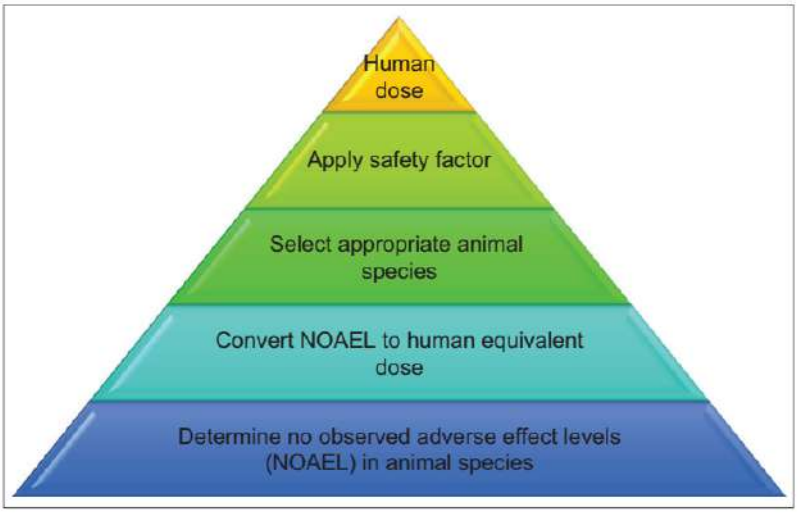
Species	Reference body weight (kg)	Working weight range (kg)	Body surface area (m^2)	To convert dose in mg/kg to dose in mg/m^2, multiply by K_m	To convert animal dose in mg/kg to HED in mg/kg, either	
					Divide animal dose by	Multiply animal dose by
Human	60	-	1.62	37	-	-
Mouse	0.02	0.011-0.034	0.007	3	12.3	0.081
Hamster	0.08	0.047-0.157	0.016	5	7.4	0.135
Rat	0.15	0.08-0.27	0.025	6	6.2	0.162
Ferret	0.30	0.16-0.54	0.043	7	5.3	0.189
Guinea pig	0.40	0.208-0.700	0.05	8	4.6	0.216
Rabbit	1.8	0.90-3.0	0.15	12	3.1	0.324
Dog	10	5-17	0.50	20	1.8	0.541
Monkeys (rhesus)	3	1.4-4.9	0.25	12	3.1	0.324
Marmoset	0.35	0.14-0.72	0.06	6	6.2	0.162
Squirrel monkey	0.60	0.29-0.97	0.09	7	5.3	0.189
Baboon	12	7-23	0.60	20	1.8	0.541
Micro pig	20	10-33	0.74	27	1.4	0.730
Mini pig	40	25-64	1.14	35	1.1	0.946

*Data obtained from FDA draft guidelines.[7] FDA: Food and Drug Administration, HED: Human equivalent dose

The human equivalent dose (HED) is determined by the equation:

HED (mg/kg) = Animal dose (mg/kg) × (Animal K_m / Human K_m)

Concerning the calculation of the No Adverse Effect Levels (NOAEL), the steps to estimate starting dose in human studies are depicted in this scheme:



In the Step 4, the HED is divided by a factor value of at least 10, to increase safety of human dose.

For example, in the following exemplificative table, data of safety performed on animals (rat NOAEL) are added of an additional safety factor "21", to extrapolate a safe correspondent dosage in man:

		NOAEL (mg/kg/day)	factor to obtain mg/m^2 (kg/m^2)	NOAEL* factor (mg/m^2)	humans m^2/ 60 kg	Human equivalent dose (mg)	assumed starting dose for Phase I (mg)	safety margin
4-wk tox	Rat	67	6	402	1,54	619	30	**21**

Animal studies were included only if the amount of clinical data available was deemed to be insufficient.

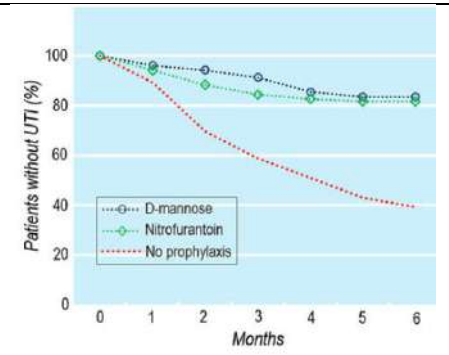
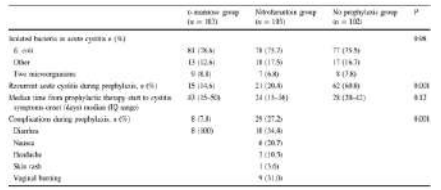
Stage 3

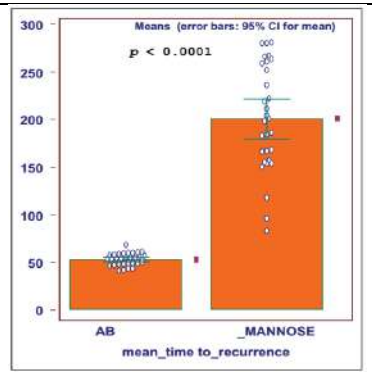
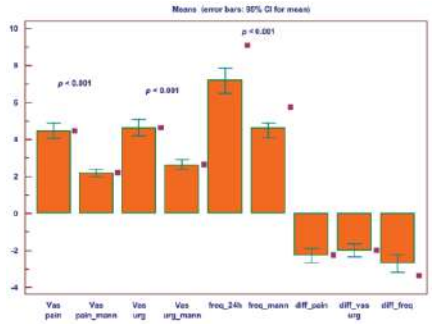
7. Analysis of clinical data

(← MedDev 2.7.1 rev.4: Section 10, p.27 and following; Appendix 7, p.41 and ff.)

7.1. D-mannose - Results of studies with equivalent products in prevention of lower urinary tract infections

			CLINICAL EQUIVALENCES						BIOLOGICAL EQUIV.	TECHNICAL EQUIVALENCES		OUTCOMES / SAFETY		
Author	**YEAR**	**RATING** **EC?**	**Q.TY (g/d)**	**POSOLOGY**	**N° OF SUBJ.**	**CATEGORY OF SUBJECTS AND STUDY DESIGN**	**AGE (Y)**	**DURATION OF ADMIN.**		**FORM OF ADMIN.** **CE MARKS?**	**INGREDIENT FUNCTION AND PRIMARY ENDPOINTS**	**EFF. / NOT EFF.**	**RESULTS**	**SIDE EFFECTS**
17 Also publ. in 18	2014 2014	3 Yes	2 g/day in a glass of water	Once a day	Enr. 689 ITT 308 PP 308	Randomized nonblinded study. After initial antibiotic treatment of acute cystitis, non-pregnant women with history of recurrent uncomplicated UTI, received either prophylaxis with D-mannose, or the antibiotic nitrofurantoin, or no prophylaxis.	20-79 years	6 months		U-Tract® Powder No (product approved in the USA)	Prevention of recurrence. Number of episodes of recurrence; time to first symptoms onset. Safety.	**E / NE**	At the end of the study, 15 patients out of 103 (14.6%) in the D-mannose group had recurrent UTI, vs. 21/103 (20.4%) in nitrofurantoin group, and 62/102 (60.8%) in the no prophylaxis group. The data in the two active groups were statistically comparable, whereas the rate was significantly higher in no prophylaxis group compared to the two active groups (p<0.001).	Significantly lower risk of side effects compared to nitrofurantoin (see the table in the box aside). In patients taking D-mannose, episodes of diarrhoea were the only side effect (8% of patients), but they did not require discontinuation of the prophylaxis.

													 Conversely, there were no statistically significant differences between groups in the time to the first return of symptoms. 	
19	2014	3 Yes	3 g/day Then 2 g/day	t.i.d. Then b.i.d.	60 Enr 60 ITT 60 PP	Randomized nonblinded cross-over pilot trial. After initial antibiotic treatment, non-pregnant women with recurrent uncomplicated UTIs received antibiotic treatment with Bactrim (trimethoprim + sulfamethoxazole) or D-mannose.	22-54	2 weeks + 22 weeks		Powder Not specif. ?	Prevention of recurrence. Time to recurrence of bacteriuria.	**E**	At the end of the study, mean time to UTI recurrence was 52.7 days with antibiotic treatment, and 200 days with oral D-mannose (p<0.0001).	No significant side effects were reported

													 Also secondary outcomes (symptom scores and average numbers of 24-hour voidings, assessed by VAS) decreased significantly. 	
20	2016	3 Yes	1.5 g/day	Once a day for one week every month	43 ITT 43 PP	Randomized controlled non-blinded pilot study in two phases (treatment (see §7.3) and follow-up prophylaxis). Non-pregnant women with symptoms of acute cystitis (dysuria, frequency, urgency, supra-pubic pain, nicturia, and haematuria) or asymptomatic with diagnosis of UTI.	18-65 years	6 months		Mannocist® Powder Yes	Prevention of recurrence. Number of episodes of recurrence; time to first symptoms onset.	**E**	As prophylactic agent administered for 6 months, it showed positive results (4.5% vs. 33.3% recurrences in treated and untreated patients respectively; $p < 0.05$). The mean time to UTIs onset was 43 days in the group undergoing prophylaxis and 28 in the other one ($p < 0.0001$).	Treatment did not present any side effect also in a long-term schedule.

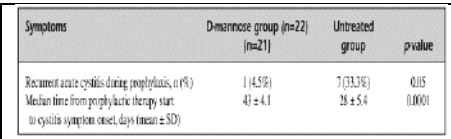
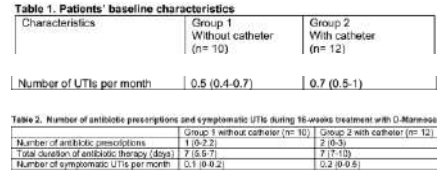
														
21	2017	- Yes	3 g/day	t.i.d.	22 Enr (4 M / 18 F) 22 ITT 22 PP	Single-center, open-label, feasibility study. Adult patients with multiple sclerosis (MS) reporting recurrent urinary tract infections, using and not using urinary catheters.	41.7-59.5 years	16 weeks		Powder Not specif. ?	Prevention of recurrence. Number of antibiotic prescription during the trial; episodes of recurrence; time to first symptoms onset.	**E**	At the end of the study, the number of monthly proven UTIs decreased both in catheter users and non-users ($p < 0.01$). 	No adverse effects were reported.

Table 7. Results of clinical trials with D-mannose in the prevention of lower urinary tract infections

7.2. Comments about the outcomes of trials with equivalent devices against lower urinary tract infections. Finding optimal dosage and duration of treatment with D-mannose

7.2.1. Eligibility criteria and general considerations about the outcomes of the included studies

7.2.1.1. Eligibility criteria

Three clinical trials of different duration, unblinded for practical reasons (antibiotic tablets were used as comparator), were performed in adult women suffering from recurrent urinary tract infections (defined as ≥ 2 episodes of acute cystitis in the last 6 months and/or ≥ 3 episodes of acute cystitis in the last year) [17,19,20]. All were selected for inclusion and read in full-text [Table **7**].
One feasibility, open-label clinical trial was performed in adults of both sexes with multiple sclerosis [21]. **This study was read in full-text but was discarded, as this subcategory of patients is not included in the IFU.** In addition, the study was performed in a small number of participants, and at dose larger than that recommended for the medical device object of this CER [Table **7**].

One of three residual trials compared D-mannose with nitrofurantoin, an antibiotic used specifically against the UTIs, or with control [17]. Another [19] compared D-mannose with Bactrim (combination therapy trimethoprim + sulfamethoxazole). The last was an compared D-mannose prophylaxis with no treatment [20].

Concerning the quality of the 3 studies read in full-text, one [17] was performed with a product that is authorized in the US but is not marketed in the EU. Another [19] did not specify any brand for the substance used. Only the last used a product registered in the EU [20].
The studies used **randomization** but were not blinded (due to the differences between D-mannose and antibiotics) or non-treated control. However, they were of **acceptable methodological quality** (Jadad score = 3) and **were approved by Ethics Committees or Internal Boards**.

One study included a large number of participants (308, ITT) [17], the other two were pilot studies enrolling a small number of patients (60, ITT; 43, ITT) [19,20].
No studies would met criteria for being considered "pivotal" in this assessment, as two of them administered D-mannose for continuative periods longer than the maximum admitted for our medical device (one month), [17,19]**.**
The third **study adopted a non-continuative administration (one week / month) as the prescribed for our product, but the dose was smaller than that included in our product, and the study enrolled a too small number of participants** [20]**.**

7.2.1.2. Effectiveness of D-mannose

All studies had statistically significant outcomes, consistent with the main claims of our product.
The first study [17] showed **statistically significant reduction of the number of episodes with respect to control ($p < 0.001$), and non-inferiority to antibiotic prophylaxis**. However, the other primary endpoint (time to the return of symptoms) did not differ between treatments and control.
Conversely, the second study [19] **showed statistically significant increase in the mean time to first recurrence with respect to the use of antibiotic** ($p < 0.0001$).
The third study [20] showed **statistically significant reduction of the number of episodes with respect to untreated control ($p < 0.05$), and longer mean time to UTI onset** ($p < 0.0001$)**.**

Taken altogether, these studies have confirmed that D-mannose is effective **in improving the primary outcome of reducing the mean number of episodes in the long-term (there were no shorter timepoints).**
Two studies out of three have shown [19,20]**, with high statistical significancy** ($p < 0.0001$ for both)**, that, in cases of recurrence, the time to the first episodes is longer when taking D-mannose**.
No follow-up after discontinuation of D-mannose were performed.

Positive results have been reported also using D-mannose in association with other antimicrobial agents of various nature. These studies have not been included in those eligible for detailed analysis in Table **7**, as the effectiveness for any single component of the mixture was not arguable:
-"Proantinox/UTI-Stat®", a product associating a concentrated liquid cranberry extract and mannose, on the market in the United States. The formulation was administered orally at different doses (from 15 to 75 mL daily) for 12 weeks to 28 pre- and postmenopausal women (average age 46.5 y) with a history of 2-3 UTIs in <6 months. At the end of the study, only 2 (9.1%) of participants had reported a recurrence. Also the quality of life scores, with regard to the physical functioning domain and role limitations from physical health domain, were significantly improved. The product showed a good safety profile and tolerability. The recommended dose was set at 60 mL/d, and the maximal tolerated dose was 75 mL/d [A70].
More complex mixtures were used in the following trials:
-"Manosar®", an association of prolonged-release D-mannose (2 g), Proanthocyanidins, ursolic acid, A, C, and D vitamins and zinc [A71].
-"Kistinox® Forte sachets", containing D-mannose, cranberry, and propolis extract in in perimenopausal women [A72].
-An association of D-mannose, N-acetylcysteine and Morinda citrifolia extract, when associated to antibiotic therapy [A73,A74]
-an association of D-mannose, berberine, arbutin, birch and forskolin [A75].
-an association of D-mannose, Hibiscus sabdariffa, and Lactobacillus plantarum in the prevention of infectious events following invasive urodynamic examination [A76,A83].

7.2.2. Finding the optimal dosage and therapeutic regime of D-mannose against lower urinary tract infections

7.2.2.1. Studies using dosage equivalent to that suggested for the device "Mannose MD"

The studies used doses ranging from 1.5 to 3 g/day. One study used dose and schedule equivalent to that included in our medical device (2 grams once a day for all the duration of the treatment) [17]. **The minimal effective daily dose of this substance, taken as powder for oral intake, was 1.5 g/day** [20]**.** The product UTI-Stat® provides 500 mg per day of D-mannose®, but it is a combination of D-mannose and cranberry extract.

By considering these evidence, we recommend the following "average" prophylactic dosage of D-mannose in adults:
●2 g daily (one sachet) in one single intake.

7.2.2.2. Studies using treatment duration equivalent to that suggested for the device "Mannose MD"

In the clinical studies eligible for the analysis, the treatments had similar total duration (24 weeks to 6 months). **One study** [17] **used an intermediate timepoint of one month (the maximal continuative duration allowed for our MD), showing that there was already a difference with respect to placebo group, but no statistical analysis was performed at this point.**

Another study [20] **used a non-continuative schedule of administration, showing it may be as effective as continuative administration.**

Therefore, we recommend the following duration of prophylaxis:

●one month of continuative administration, followed by some days of interruption (washout), before a new one-month cycle of treatment, up to five non-consecutive treatments, for a total duration of about six months.

7.2.2.3. Studies in patients of age equivalent to that allowed for "Mannose MD"

The age of participants ranged from 18 [20] **to 79 years** [17].

There are no data in adolescents. However, the substance is safe and does not interfere with human metabolism. So, we deem that the product can be safely administered also to girls suffering from cystitis from the age of 14, on physician's opinion.

Therefore, we indicate the following age for use of the product:

●adults and adolescents over 14 years.

7.2.2.4. Mode of administration

All studies used D-mannose in form of powder for dissolution in a glass of water, as the formulation used in the medical device object of this CER.

7.2.2.5. Safety

At doses of 2-3 g/day, and administered for a duration up to 6 months, studies show good tolerance and no side effects of D-mannose (see also § 8.2.1).

7.2.2.6. Conclusions of systematic reviews and meta-analyses on D-mannose

Though D-mannose is widely available and used for UTI prevention in humans, the clinical studies on the topic were lacking until recently [22,A15,A4,A5,A6]. Four narrative reviews have been published in the last two years [3,23,A18,A19]. No systematic reviews and meta-analyses exist.

The narrative review of Beerepoot [3] on non-antibiotic prophylaxis of urinary tract infections concluded that "initial findings are promising, but further clinical trials [with D-mannose] are needed".

Another narrative review [A18] concluded that "Food supplements such as cranberry or D-mannose can also interfere with the recurrence of cystisis, by preventing the bacteria sticking to urinary tract epithelia. Their efficency is relative and seems to be dose-dependent. Better tolerated than prophylactic antibiotic treatments, they can increase times of respite".

Finally, Stompro [23] included the studies [17] and [19]. She concluded that "there is significant evidence to argue for D-mannose to be used as a prophylactic agent in those who suffer from recurrent urinary tract infections. Both TMP/SMX and nitrofurantoin are common antibiotics prescribed for prevention of recurrent urinary tract infections and the data

presented from each study demonstrates that D-mannose, when taken regularly, is comparably effective for decreasing recurrence or limiting side-effects from the treatment".

7.2.2.7. Existing guidelines about the use of D-mannose in prophylaxis of UTIs

The only existing guideline including D-mannose has been published by UK NICE [24]. It considered only one study [17]. The study by Porru [19] was considered as having a lower grade of evidence, and was discarded.
The grading of evidences, ranging from high (effectiveness vs. no treatment; safety) to low (effectiveness vs. antibiotic treatment) is resumed in the following Table.

Table 17: GRADE profile – D-mannose versus no treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	D-mannose	No treatment	Relative (95% CI)	Absolute		
Participants with recurrent urinary tract infection												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	15/103 (14.6%)	62/102 (60.8%)	RR 0.24 (0.15 to 0.39)[2]	462 fewer per 1000 (from 517 fewer to 371 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

Abbreviations: CI, Confidence interval; N/A, Not applicable; RR, Relative risk
[1] Kranjcec et al. 2014
[2] 95% confidence interval not stated; intervals calculated by NICE

Table 18: GRADE profile – D-mannose versus antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	D-mannose	Antibiotics	Relative (95% CI)	Absolute		
Participants with recurrent urinary tract infection												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[2]	none	15/103 (14.6%)	21/103 (20.4%)	RR 0.71 (0.39 to 1.31)[3]	59 fewer per 1000 (from 124 fewer to 63 more)	⊕⊕OO LOW	CRITICAL
Adverse events												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	8/103 (7.8%)	29/103 (28.2%)	RR 0.28 (0.13 to 0.57)[3]	203 fewer per 1000 (from 245 fewer to 121 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

Abbreviations: CI, Confidence interval; N/A, Not applicable; RR, Relative risk
[1] Kranjcec et al. 2014
[2] Downgraded 2 levels - at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[3] 95% confidence interval not stated; calculated by NICE

Table 8. Grading of the evidence about effectiveness and safety of D-mannose in prophylaxis of cystitis recurrence [from: 24].

7.2.3. Inclusion of animal studies

There were no animal studies with D-mannose in prophylaxis of UTIs.

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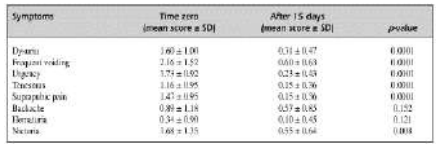
7.3. D-mannose - Results of studies with equivalent products in treatment of lower urinary tract infections

			CLINICAL EQUIVALENCES						BIOLOGICAL EQUIV.	TECHNICAL EQUIVALENCES		OUTCOMES / SAFETY		
Author	YEAR	RATING EC?	Q.TY (g/d)	POSOLOGY	N° OF SUBJ.	CATEGORY OF SUBJECTS AND STUDY DESIGN	AGE (Y)	DURATION OF ADMIN.		FORM OF ADMIN. CE MARKS?	INGREDIENT FUNCTION AND PRIMARY ENDPOINTS	EFF. / NOT EFF.	RESULTS	SIDE EFFECTS
20	2016	3 Yes	3 g/day Then 1.5 g/day	b.i.d. Then once in a day	43 Enr 43 ITT 43 PP	Randomized controlled non-blinded pilot study in two phases (treatment and follow-up prophylaxis (see §7.3)). Non-pregnant women with symptoms of acute cystitis (dysuria, frequency, urgency, supra-pubic pain, nicturia, and haematuria) or asymptomatic with diagnosis of UTI.	18-65 years	13 days (3 days + 10 days)		Mannocist® Powder Yes	Treatment of UTI. Symptoms (assessed by UTISA score).	**E**	UTISA scores recorded after completing the treatment, compared with baseline scores, showed a significant improvement in the most common symptoms ($p < 0.0001$) and on quality of life ($p = 0.0001$). 	Treatment did not present any side effect.

Symptoms	Time zero (mean score ± SD)	After 15 days (mean score ± SD)	p-value
Dysuria	1.60 ± 1.00	0.31 ± 0.47	0.0001
Frequent voiding	2.16 ± 1.52	0.60 ± 0.63	0.0001
Urgency	1.74 ± 0.92	0.23 ± 0.53	0.0001
Tenesmus	1.16 ± 0.95	0.35 ± 0.76	0.0001
Suprapubic pain	1.47 ± 0.95	0.15 ± 0.36	0.0001
Backache	0.89 ± 1.18	0.59 ± 0.85	0.152
Hematuria	0.34 ± 0.90	0.10 ± 0.45	0.121
Nicturia	1.68 ± 1.35	0.55 ± 0.64	0.001

Table 8. Results of clinical trials with D-mannose in the treatment of lower urinary tract infections

7.4. Comments about the outcomes of trials with equivalent devices against lower urinary tract infections. Finding optimal dosage and duration of treatment with D-mannose

7.4.1. Eligibility criteria and general considerations about the outcomes of the included studies

7.4.1.1. Eligibility criteria

A randomized nonblinded clinical trial with non-treated control group was performed in adult women (of age ranging to fertile to menopausal, without subgroup analyses) suffering from acute urinary tract infection [Domenici, 2016]. It was selected for inclusion and read in full-text [Table **8**].

Concerning the quality of the study, it was performed with a product registered in the EU.
Although it did not used blinding, the study was of **acceptable methodological quality** (Jadad score = 3), and **was approved by Internal Board**.

However, this study did not met criteria for being considered "pivotal" in this assessment, as the dose was smaller than that included in our product, and the study enrolled a too small number of participants.

7.4.1.2. Effectiveness of D-mannose in treatment of lower urinary tract infections

After 15 days of administration, the study [20] showed **statistically significant reduction in all the symptoms present in the UTISA Assessment Questionaire,** with the exception of backache and hematuria**.**

This study shows that D-mannose is effective **in improving the primary outcome of reducing the symptoms of acute urinary tract infection with high statistical significancy** ($p < 0.0001$ for the majority of symptoms).

Positive results have been reported also using D-mannose in association with other antimicrobial agents of various nature. This study have not been included in those eligible for detailed analysis in Table **8**, as the effectiveness for any single component of the mixture was not arguable:
The product "Cystostop Rapid®", containing 1000 mg D-Mannose + extracts of birch leaves and cranberry was compared to antibiotic therapy in 158 female subjects with acute uncomplicated urinary bladder infections [A77,A78]. 2 tablets of Cystostop Rapid were taken every 2-3 hours for a total of 6 intakes, 2 tablets each. A tablet contained 1000 mg *D*-mannose, 50 mg standardized dry extract of cranberry and 50 mg standardized dry extract of birch leaves. The participants received either Cystostop Rapid, or ciprofloxacin 500 mg twice daily, for 3 days. The effectiveness of Cystostop Rapid was superior to that of ciprofloxacin, providing a two-fold more rapid improvement of cystitis symptoms (mean time to

improvement of 24 hours versus 46 hours for ciprofloxacin; $p<0.02$). Clinical improvement within 48 hours of Cystostop Rapid regimen occurred in 97% ($p<0.02$) of patients, vs. 65.3% of patients on ciprofloxacin. Improvement of symptoms within 12 hours was reported in 36% of patients on Cystostop Rapid vs. 5.5% of patients in the ciprofloxacin group ($p<0.02$). No adverse events or intolerability to the therapy were reported throughout the course of the study.

7.4.2. Finding the optimal dosage and therapeutic regime of D-mannose against lower urinary tract infections

7.4.2.1. Studies using dosage equivalent to that suggested for the device "Mannose MD"

The study [20] used a dose of 3 g/day for the first three days, then reduced to 1.5 g/day for the rest of the trial. The effectiveness of this dosage schedule was evident after 15 days. However, in the study mentioned above [A77], using a higher dose of 6 g/day was safe and provided clinical improvement in 24-48 hours.

By considering all these evidence, we recommend the following treatment dosage of D-mannose in adults:
- **6 g daily (three sachet) divided in three intake for the first three days ("attack dose").**
- **4 g daily (two sachet) divided in two intake for the subsequent two days.**

7.4.2.2. Studies using treatment duration equivalent to that suggested for the device "Mannose MD"

In the only clinical study eligible for the analysis, using a dose lower than in our MD, the treatments had a duration of 13 days (3 + 10) (no intermediate timepoints were used). However, the comparison with the study of Panchev [A77] providing higher doses suggests that the time to improve the symptomatology could be proportional to the dose.

Therefore, we recommend the following duration of treatment for the medical device object of this CER that includes high dosage with respect to the study of Domenici [2016]:
- **five days. If the symptoms do not have an improvement after this time, it is suggested to stop treatment and consult a doctor.**

7.4.2.3. Studies in patients of age equivalent to that allowed for "Mannose MD"

The age of participants ranged from 18 to 65 years [20].

There are no data in adolescents. However, the substance is safe and does not interfere with human metabolism. So, we deem that the product can be safely administered also to girls suffering from cystitis from the age of 14, on physician's opinion.

Therefore, we indicate the following age for use of the product:
●**adults and adolescents over 14 years.**

7.4.2.4. Mode of administration

All studies used D-mannose in form of powder for dissolution in a glass of water, as the formulation used in the medical device object of this CER.

7.4.2.5. Safety

All the studies, both on short and long term, show good tolerance and no side effects of D-mannose at doses up to 6 g/day (see also § 8.2.1).

7.4.2.6. Conclusions of systematic reviews and meta-analyses on D-mannose

Currently, there are no narrative reviews, systematic reviews or meta-analyses including the option of D-mannose for treating UTIs.

7.4.2.7. Existing guidelines about the use of D-mannose in prophylaxis of UTIs

Currently, there are no guidelines on the use of D-mannose for treating UTIs.

7.4.3. Inclusion of animal studies

As the clinical data are poor, to support the claims on effectiveness and safety of D-mannose, we have included a meaningful *in vivo* results in treatment of animal models of UTIs (Table **9**).

N°	YEAR	Q.TY	POSOLOGY	DURATION	FUNCTION OF INGREDIENT	ANIMAL MODEL	AGE	TIME OF ADMIN.	FORM OF ADMIN.	EFF. / NOT EFF.	RESULTS	SIDE EFF.
A79	1983	0.1 ml of 2.5% or 10% D-mannose	Acute	9-day follow-up	Effect of D-mannose and D-glucose on bacteriuria due to E. coli	Adult male Sprague-Dawley rats inoculated with 10^5, 10^7, or 10^8 bacteria.	-	-	Intra-vesical injection	**E**	Levels of bacteriuria on days 1 and 5 were significantly lower in rats inoculated with 10^5 E coli and 10% D-mannose than in controls ($p < 0.05$ and 0.01 resp.) and the percentages of rats with less than 100 bacteria/ml were higher on days 1 and 3 ($p = 0.05$ and 0.02 respectively). Bacteriuria was significantly lower in rats inoculated with 10^7 bacteria and 10% D-mannose than in controls on days 5 and 7 ($p < 0.01$ for each day) and the percentage of rats with less than 100 bacteria/ml was higher on day 7 ($p = 0.01$). D-Mannose was effective against a wide panel of uropathogens, not only against E. coli.	-

Table 9. Results of animal studies with D-mannose in the treatment of lower urinary tract infections

This result indicates that, ***in vivo,* although** a high dose not reached in human use **the use of D-mannose was significantly effective in reducing bacteriuria already within 1 day, and that the efficacy is dependent upon the concentration of both saccharide and bacteria.**. **The presence of a higher number of bacteria required a longer time to reach a significant effect, but D-mannose was effective also in this case.** D-glucose reduced bacteriuria to some extent only with a concentration of 10% after instillation of 10^5 *E. coli*.

Interestingly, Wellens and others [12] have demonstrated that ***alpha*-D-mannose** and some of its alkylated derivatives **not only dose-dependently block the adhesion of sensitive strains of *E. coli* to a human bladder cell line** (Figure **7**), **but also, in an animal model of cystitis, significantly prevented adhesion and invasion into bladder cells, as well as the subsequent formation of biofilms.**

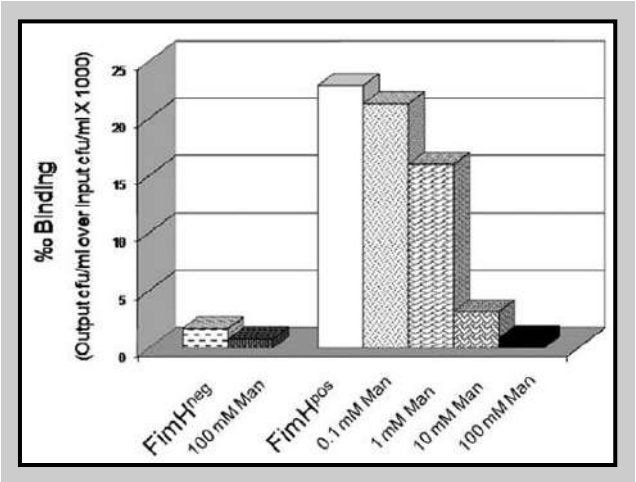


Figure 7. Inhibition of type 1 (FimH) pili-expressing *E. coli* adhesion to human bladder cell line 5637 by different concentrations of D-mannose. FimHneg = isogenic fimH-negative strain, serving as a negative control [from: 12].

7.5. Final considerations about the analysis of equivalent medical devices and the clinical literature

7.5.1. Considerations about equivalent products on the market

By considering the following observations on equivalent products already on the bench (see Tables in the § 5.1 and 5.2):

●D-mannose has an increasing use for treatment or prevention of lower urinary tract infections, as it is reputed a safer alternative to drugs, which may reduce the consumption of antibiotic. For the same reason, it may be also used as an adjunct of antibiotic therapy in the treatment of urinary tract infections.

●there are already on the market various over-the-counter products, manufactured by SIIT or others, containing the same functional component (**D-Mannose**), alone **and also in association with other antimicrobial natural substances, particularly cranberry extracts**.

●D-mannose has approved claims for the same indications as the medical device object of this CER (**treatment and prevention of lower urinary tract infections)**.

●the products on the market provide **comparable daily amounts of the functional component** as the medical device object of this CER;

●the duration of administration, when indicated in the IFU, **is similar to that prescribed for our product**;

●the majority of the formulations using D-mannose alone are in **powder for dissolution in water**, as the medical device object of this CER.

●D-mannose containing medical devices **have been classified in Class IIa**

We conclude that there are already on the market products equivalent to the medical device object of this CER in all the critical aspects.

7.5.2. Considerations about studies using equivalent products

After the systematic analysis of the clinical literature about equivalent products (see § 7.1, 7.2, 7.3 and 7.4), no studies were selected as "pivotal" for drawing conclusion on the functional component included in the medical device object of this CER.

However, these papers, as well as observations taken from other studies, allow making the following observations on clinical studies with equivalent products:

-The are few studies on D-mannose in prevention or treatment of UTIs. Their results were positive with regard to the claims of reducing number and time of recurrence (both with respect to controls and antibiotic drugs), as well as to treat acute symptomatology (with respect to controls). All the studies are recent and have sufficient methodological quality (randomization and statistical analysys, no blinding), but - with the exception of one - they were "pilot" studies not enrolling a sufficient number of participants.

-In the clinical literature, we found equivalences with the product object of this CER in the following aspects:

--comparable daily dosage;
--suggested posology;
--claims for use (condition to treat);
--duration of administration;
--form of administration (the studies were always performed with powder formulations for dissolution in water and oral intake);
--feasibility of use also in male cathetherized patients.

In addition, preclinical studies demonstrate that there is no interference with the activity of antibiotics.

-In the clinical literature, we found no equivalences with the product object of this CER in the following aspects:

--recommendation for age of user under 18 years;

We conclude that the literature confirms effectiveness and safety of the component of our medical device, at dosage comparable, for the prescribed length of administration, administered in adult patients, to treat or prevent the same conditions claimed in the IFU, alone or in association with antibiotic therapy.

7.6. Differences that could affect performance and safety of the device

●Although the functional component are already sold on the market (§ 5.1 and 5.2), there are still few published studies, and no studies enrolling a large number of participants. For some claims (effectiveness vs. antibiotics in prevention of recurrences; effectiveness in treatment of acute episodes), the current overall level of evidence is “low” (§ 7.2.2.6, 7.2.2.7, 7.4.2.6, 7.4.2.7).

●there is insufficient clinical documentation in prophylaxis, and no evidence in treatment of male patients with UTIs, catheterized or not.

●Due to the peculiar mechanism of activity of D-mannose, there is a wide margin of safety in all the subcategories of patients. Nonetheless, there are no clinical data in children, in males, as well as in pregnant or lactating women. So, in these cases it is recommended to take the product under strict medical supervision.

7.7. Declaration of equivalent effectiveness and safety

●**There are sufficient evidences to declare equivalence with medical devices already sold on the market**, at comparable daily doses (1 to 3 sachets per day, each containing 2 grams of D-mannose, and for the prescribed durations of treatment (from some days for treatment, to one month for prevention), for the claim of treating or preventing urinary tract infections and their recurrences.

●**There are direct clinical evidences to declare that equivalent formulations containing the active component of the device object of this CER, at equivalent daily doses and for the prescribed duration of treatment, have shown effectiveness in treating lower urinary tract infections.**

●**The clinical trials prove that the active substance, at the prescribed dosages, is safe and without significant side effects. In addition, it is sold on the market of the OTC from many years. Because there is no difference in the functional components, and the excipients used in the device object of this CER are all accepted as safe, we declare that the safety of "D-Mannose" may be deduced from the safety of equivalent products.**

8. Safety and residual risks for the medical device

8.1. Compliance with points E1 of Annex E

To be in compliance with point E1 of Annex E, *in vitro* and *in vivo* safety tests have been performed by the manufacturer on samples of a product containing mannose + cranberry extract, in [redacted] laboratory. This product also contains cranberry in addition to D-mannose, and therefore these test may be considered as a "worst condition" with respect to our product, that contains only D-mannose. The results were commented upon by the research and development department of the manufacturer.

The following tests were performed:

Biocompatibility tests The tests were performed by [redacted], on a product containing D-mannose (same dosage than in the present MD) + cranberry (a worst condition) and are below reported:
- Cytotoxicity for elution [redacted]
- Acute ORAL Toxicity [redacted]
- Test for delayed hypersensitivity [redacted]

The following results have been obtained.

- ✓ The **cytoxicity test** was performed by elution, according to ISO 10993-5, using a cell culture of mammals fibroblasts BalbC 3T3 cells.
  1 g of product sample was dissolved in culture medium and incubated 6 hours and then applied on monolayer on the cells. After 24 hours the cells were observed under microscope, showing complete lysis of the cellular layer and reduction of cell vitality was 0,4%. The cytotoxicity test was evaluated– Elution test. The extract of the test was performed by immersing 1 sachet of the test item in 1000 ml of culture medium for 4 hours, then the test item was incubate for 4 hours at temperature of 37°C ± 1°C.
  On the basis of the results the test item "CRANBERRY + D-MANNOSE" must be considered NOT CYTOTOXIC.

- ✓ The **acute oral toxicity** was evaluated according to OECD N° 420. The test substance was administered at the dose of 2000 mg/kg to a group of 5 female rats through a stomach tube for 4 hours. The animals have been observed for 14 days for evidence of toxic symptoms. At the end of study animals were sacrified and autopsy was performed. No case of mortality, toxic symptoms or abnormalities have been evidenced during the study.
  On the basis of obtained results, the test item "CRANBERRY + D-MANNOSE" has a LD_{50} >2000 mg/kg and can be included in class 5/NC of GSH classification.
  This is very important and confirms that our Medical Device is a compound with NO ACUTE TOXICITY.

- ✓ The **delayed hypersensitivity test** (GMPT test) was evaluated according to ISO 10993-10:2010.
  The test has been performed to 15 Guinea pigs (10 test and 5 control), according to ISO 10993-10:2010. The treatment has been performed with an induction phase, during which 3 intradermal injections of 0,1 ml of emulsions/test solutions have been administered for 6 days to prepare animals. At day 7 treated animals were applied of 0,5 g of product sample to the skin for 48 hours. Control group was treated with sodium chloride injection.
  The test was followed by challenge phase at day 21 by application on left skin of animals 1 ml of sodium chloride and right back side of 0,5 g of test sample. The contact time was 24 hours. No abnormalities were evidenced after 48 and 72 hours of challenge test on all pigs (visible changes=0).
  On the basis of these results, the test item "CRANBERRY + D-MANNOSE" must be considered NOT SENSITIZING.

Taken altogether, these data show that the association of the active ingredient included in "Mannose MD" contributes to formulate a safe Medical device, in compliance with the Point E1 of the Annex E.

8.2. Compliance with points E2 of Annex E

8.2.1. Evidences from literature and Health Autority Databases on safety, toxicity and interactions of D-mannose

8.2.1.1. Evidence of safety of D-mannose in the clinical literature

D-mannose has a safe history of use. This sugar, at the doses required to achieve a therapeutic effect (in the order of few grams/day), is safe and without specific side effects, also on long-term use, except for very rare cases of individual intolerance, in which it caused loose stools, bloating or nausea [A29,A80]. This substance is absorbed in the upper intestine, and therefore does not interfere with the gut microflora or with the hepatic metabolism of drugs taken concomitantly.
No major adverse events were reported during the clinical studies with D-mannose summarized in the paragraphs 7.1 and 7.3: except cases of mild and transitory diarrhea [17], the compound was always well tolerated, even after long-term administration (up to 6 months) [17,20].
As the substance does not interfere with glucose production and does not accumulate into tissues, it is thought to be safe also during pregnancy or lactation, but these suppositions are not currently substantiated by positive or negative clinical evidences. For this reason, during pregnancy and lactation is always recommendable to take the substance after consulting a physician.

D-mannose supplements should be used under medical control by diabetics, as there are anedoctal reports that they increase the levels of glycosylated haemoglobin (HbA1C) and hypothetically might worsen glucose control [A81,A82].

Taking too high doses of D-mannose (however, higher than current recommended dose) may cause kidney damage, as it increases serum and urinary creatinine in the urine [A57].

8.2.1.2. Evidence of safety of D-mannose in Public Health Databases or other sources

No severe adverse reactions clearly attributable to D-mannose, recall, incidents or missing incidents were found in public databases analyzed (updated to September 2018):
http://www.agenziafarmaco.gov.it
http://www.fda.gov
http://www.salute.gov.it
https://ec.europa.eu/commission
http://www.adrreports.eu/en/search_subst.html

8.2.1.3. Evidence of toxicity or mutagenicity of D-mannose in the literature

D-mannose is not absorbed by the intestine, and exreted intact in the urine, where it elicits a direct action on the adhesive capacity of bacteria (see §3.3). This explains the safety and the absence of acute/subacute/subchronic toxicity of the compound [ToxNet Database]. Being regarded as biologically inert and not exhibiting toxic properties, the substance has not been the subject of specific animal toxicity studies.
NOAEL and LD_{50} dose are not established [ToxNet Database].
D-mannose is not considered teratogenic or mutagenic in humans [Natural Medicines Comprehensive Database] .

8.2.1.4. Potential interactions of D-mannose

No interaction of D-mannose with drugs, food components or dietary supplements was never reported.
However, as a general rule, all drugs (especially life-saving drugs) and nutritional supplements, including vitamins, nutrients, herbal and homeopathic remedies, should be ingested at least two hours before or two hours after the use of "Mannose MD".

8.2.2. Presence of medicinal, human, or animal components in the device

The device does not include medicinal, human or animal components.

8.2.3. Pharmacokinetic, excretion and time of retention of D-mannose in the digestive tract

There pharmacokinetic data on D-mannose have been already resumed in § 3.2.1**.** This sugar is absorbed in the intestine by means of different mechanisms not entirely elucidated, but once transported into the enterocytes, it is stored in the cytoplasm, but not substantially metabolized, and gradually pass intact into the bloodstream; thence, it is excreted with the urine. Only a few percent is incorporated into glycoproteins: in the body, the majority of mannose for glycosylation does not comes from dietary sources, but from glucose, through an enzymatic isomerization [5,6,A26,A27,A28,A29,A30,A20]. Only in glucose deficient subjects, the body uses directly mannose from dietary sources.
This substance is absorbed in the upper tract of intestine, and therefore does not interfere with the gut microflora or with the hepatic metabolism of drugs taken concomitantly.

8.2.4. Safety of the excipients included in "Mannose MD"

The excipients included in the sachets form are widely used in food supplements and / or pharmaceuticals and, with the exception of cases of individual intolerance; they are safe and usually well tolerated.

8.3. Instructions for use (IFU)

●The literature analysis about the safety of the components of the medical device leads to the conclusions stated below. Accordingly, the manufacturer believes that the evidences reported in the evaluated scientific literature, are exhaustive in demonstrating the efficacy and safety of the functional components present in the Medical Device, at the dosages of the designed formulation. Therefore, the manufacturer deems that no additional clinical trials are necessary to confirm the efficacy of the Medical Device.

●Labeling and instructions for use have been revised, to manifest consistency with clinical data and cover all the hazards emerged from literature and from risk analysis, which may affect the use of the device. They have been revised, approved and attached to the Technical File FT026, Attachments 11 e 12.

●There is sufficient demonstration that the formulation of "Mannose MD" is in line with the definition of medical device (see §3.3).
The active ingredient exerts its primary activities in a mechanical way. There are no demonstrated immunostimulant, metabolic or pharmacologic effects. However, these would be secondary and not related to the expected mechanic effects intended for the product.

●The IFU lists the following potential gastrointestinal side effects:
- nausea, bloating, or loose stool. No other side effects of some relevance are known on short to long term administration.

●"Mannose MD" has no specific contraindications, except in patients with allergies or hypersensibility to the ingredient;

●The IFU contain the following warnings:

- Use the product only after consultation with your doctor or a pharmacist.
- Do not use in case of known hypersensitivity to components of the product;
- During pregnancy and lactation assume the product only after taking medical advice;
- Keep the device at temperature under 25°C;
- Keep out of reach of children;
- Do not use the device after the expiration date on the box;
- Do not use if package is damaged;
- Do not exceed the recommended dose, in case of adverse effects suspend use and consult your doctor,
- Although D-mannose does not modify the bioavailability and is not metabolized in the liver, it is appropriate that the intake of the product occurs at least 2 hours before or after the administration of drugs taken orally or any other medications or food supplements: the presence of the functional component of the device could adversely affect their efficacy. Consult your physician before taking the product in case of concomitant drug therapies.
- the product has not to be intended as an alternative to antibiotics, but rather as an adjunct to antibiotic therapy.

●Concerning the IFU of products containing D-mannose manufactured by SIIT, the Manufacturer never received incidents reports from the market related to unclear or unclomplete instructions that may give rise to misuse mistake that may omit the appeareance side effects, controindications or interactions with other substances. Until today, the lack of accidents from consumers suggests that the instructions of use provided by the Manufacturer are suitable and sufficiently clear to be used by a "lay person", otherwise an individual who does not have formal education in a relevant field of healthcare or medical discipline.

8.4. Conformity assessment with requirement on safety (MDD ER1 / AIMDD ER1)

The information materials supplied by the manufacturer (including label, IFU, available promotional materials including accompanying documents possibly foreseen by the manufacturer), should be reviewed to ensure they are consistent with the relevant clinical data appraised in stage 2 and that all the hazards, information on risk mitigation and other clinically relevant information have been identified appropriately.
Input from the risk management and the use of standards:

● *Risk management documents should determine if all identified hazards are fully covered by harmonised standards or other relevant standards or if there are gaps needed to be covered by clinical data.*

- ✓ **Risk evaluation for risk analysis and management has been conducted in accordance with UNI CEI EN ISO 14971 "Application of risk management MDs". Any potential risk that could cause assessable damage were identified.**

● *Risk management documents should determine if all identified risks relating to patient treatment, method of operation of the device or risks relating to usability have been minimised or if there are question regarding clinical risks that need to be solved.*

- ✓ **Risk management has been conducted in accordance with UNI CEI EN ISO 14971 "Application of risk management MDs". Total residual risk value of the medical device of the present study is acceptable (all RPN values are in the acceptable region).**

● *Harmonised standards are generally expected to be applied in full in order to confer a presumption of conformity.*

- ✓ **Harmonised standards on usability (EN 62366 and if applicable EN 60601-1-6) have been applied to ensure that usability aspects are taken into consideration during the device development. However, they do not give guidance on a detailed level of design, while usability aspects are known to cause or contribute to a large portion of incidents. Therefore, post market data may be needed to prove that the risk of use error, due to the ergonomic features of the device and the environment in which the device is intended to be used, has been reduced as far as possible.**

8.5. Conformity assessment with requirement on acceptable benefit/risk profile (MDD ER1 / AIMDD ER1)

It is expected,
• that the clinical evaluation demonstrates that any risks which may be associated with the intended purpose are minimised and acceptable when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety; and
• that the IFU correctly describe the intended purpose of the device as supported by sufficient clinical evidence; and
• that the IFU contain correct information to reduce the risk of use error, information on residual risks and their management as supported by sufficient clinical evidence (e.g. handling instructions, description of risks, warnings, precautions, contraindications, instructions for managing foreseeable unwanted situations).

a. Evaluation of the description of the intended purpose of the device
The information materials supplied by the manufacturer (including label, IFU, available promotional materials including accompanying documents possibly foreseen by the manufacturer) should be reviewed. The evaluators should evaluate if the description provided by the manufacturer correctly identifies those medical conditions and target groups for which conformity with the relevant Essential Requirements has been demonstrated through sufficient clinical evidence. When reading the IFU, there should be no uncertainty for

users as to when a given medical condition or medical indication or target population is covered by the CE marking or when it falls entirely under the user's own responsibility (off label use).

- ✓ **Currently, no promotional material have been developed by SIIT and its existing distributors for the formulation. Indeed, the original master texts, shared with distributors for artworks develepment, were realized following the main criteria of UNI CEI EN IS0 980:2009, UNI CEI EN 1041:2009 and EN 62366 aimed to supply all necessary info for a correct use, storage and interpretation of the medical device characteristics. The IFU clearly identifies the target group of users, the age range of application and the intended therapeutic purpose.**

b. Evaluation of the device's benefits to the patient

Positive impacts of a device on the health of an individual should be meaningful (relevant for the patient) and measurable. The nature, extent, probability and duration of benefits should be considered. Benefits may include:

• positive impact on clinical outcome (such as reduced probability of adverse outcomes, e.g. mortality, morbidity; or improvement of impaired body function),

• the patient's quality of life (significant improvements, including by simplifying care or improving the clinical management of patients, improving body functions, providing relief from symptoms),

The use of equivalent products has a positive impact on selected outcomes (i.e., corresponding to the claims of the product: treatment of acute urinary infections and prevention of recurrences, and on general QOL of patients, as evidenced in the paragraphs 7.1, 7.2.1.2, 7.2.2.6, 7.3, 7.4.1.2 and 7.5 of this CER.

c. Quantification of benefit(s) to the patients

Defining specified endpoints is indispensable for setting up clinical investigations and properly performing the identification, appraisal, and analysis of the clinical data.

• Benefit(s) are often evaluated along a scale or according to specific endpoints or criteria (types of benefits), or by evaluating whether a pre-identified health threshold was achieved. The change in subjects' condition or clinical management as measured on that scale, or as determined by an improvement or worsening of the endpoint, determines the magnitude of the benefit(s) in subjects. Variation in the magnitude of the benefit across a population may also be considered.

• The clinical relevance of these changes should be discussed and justified.

• Ideally, these parameters should be directly clinically relevant.

- ✓ **The eligible clinical studies of adequate methodological quality with equivalent products containing D-mannose (although no studies were selected as "pivotals" because of too small number of participants) have shown a statistically significant impact benefits on the following endpoints** (§ 7.1 and 7.3)**:**

  -tratment of acute episodes, with a significant reduction of total symptom score (*p* < 0.0001) and improvement of quality of life (*p* < 0.0001) [20]**;**

  -reduction of number of episodes of recurrences during long-term treatment versus untreated women (*p* < 0.001) and versus no treatment (*p* < 0.05) [17,20];

  -longer time to return of cystitis during long-term treatment versus antibiotic treatment (*p* < 0.0001) [19];

  -another recent study had insufficient methodological quality [21]**. However, it showed that D-mannose may be useful to prevent recurrence also in other categories of sufferers (for example, patients with multiple sclerosis, catheterized or not) (*p* < 0.01).**

  The studies with equivalent products containing D-mannose, just discussed, confirm that D-mannose appears in general to be effective to a statistically significant extent in improving the primary outcomes of treating acute episodes and preventing / retarding recurrences. In the prevention, it may be as effective as antibiotics.

- ✓ **However, there are some topics that are not clear:**
  -to confirm these results, studies with a larger number of participants will be necessary, especially to substantiate effectiveness in treatment. In addition, no studies have been performed in specific subcategories of patients (adolescents; pregnant or lactating women).
  -the extent to which the use of D-mannose could support the action of the antibiotic therapy (currently the universal first-line treatment). In other word, efficacy studies comparing antibiotic alone and antibiotic + D-mannose would be of critical importance.

• Based on the current state of medical knowledge, the evaluators shall justify and document the clinical relevance of endpoints used for the clinical evaluation of a device and demonstrate the validity of all surrogate endpoints (if surrogate endpoints have been used).

- ✓ **There is no need for using surrogate endpoints, as the overall outcomes of the included studies meet the claims of our product. As a whole, the studies with D-mannose show that the product object of this CER is effective against all the symptoms claimed in the IFU.**

The probability of the patient experiencing one or more benefit(s) is another important aspect of evaluating benefits and the clinical performance of a device.
• Based on the clinical data provided and on a sound statistical approach, a reasonable prediction of the proportion of "responders" out of the target group or subgroups should be made.
• The data may show that a benefit may be experienced only by a small proportion of patients in the target population, or, on the other hand, that a benefit may occur frequently in patients throughout the target population. It is also possible that the data will show that different patient subgroups are likely to experience different benefits or different levels of the same benefit.
• If the subgroups can be identified, the device may be indicated for those subgroups only.
• In some cases, however, the subgroups may not be identifiable. Magnitude and probability of clinical benefits will have to be put together when weighing benefits against risks.
• A large benefit experienced by a small proportion of subjects may raise different considerations than does a small benefit experienced by a large proportion of subjects. For example, a large benefit, even if experienced by a small population, may be significant enough to outweigh risks, whereas a small benefit may not, unless experienced by a large population of subjects.

- ✓ **All the studies eligible for analysis, except one, were performed in nonpregnant women of different age, from fertile age to menopause. No studies identified subgroups in the target populations. For this reason, it is not possible to establish whether there are subcategories (fertile / menopausal; pregnant / nonpregnant, severe / moderate symptomatology etc.) that have different benefit from D-mannose**
- ✓ **Another study** [21] **was performed in patients of both sexes with multiple sclerosis, catheterized or not catheterized. No difference in effectiveness was observed between these subgroups.**

The duration of effect(s) (i.e. how long the benefit can be expected to last for the patient, if applicable to the device).
• The duration should be characterised (for example as a statistical distribution) on the basis of sound clinical data and appropriate statistical approaches.
• PMCF will be decisive to refine and corroborate reasonable predictions over time.
• The mode of action may play an important role: Some treatments are curative, whereas, some may need to be repeated frequently over the patient's lifetime.
• To the extent that it is known, the duration of a treatment's effect may directly influence how its benefit is defined. Treatments that must be repeated over time may introduce greater risk, or the benefit experienced may diminish each time the treatment is repeated.
• The evaluation of the duration of effect should take into consideration current knowledge/the state of the art and available alternatives.

In people suffering from acute or chronic cystitis, reviews and official recommendations do not specify indications of treatment times necessary to achieve benefits. A time between some days and one month, as generically indicated in the IFU, seems effective. This is evidenced by clinical studies included in this CER (paragraphs 7.1 and 7.3), as well as from evidence-based analyses (paragraph 7.2.2.6 in this CER), and from the consolidated use of D-mannose in the conditions indicated in the IFU (paragraphs 5.1 and 5.2 in this CER).

d. Evaluation of the clinical risks of devices.
The risk management documents are expected to identify the risks associated with the device and how such risks have been addressed. The clinical evaluation is expected to address the significance of any risks that remain after design risk mitigation strategies have been employed by the manufacturer. PMS reports are compiled by the manufacturer and often include details of the device's regulatory status (countries in which the device is marketed and date of commencement of supply), regulatory actions undertaken during the reporting period (e.g. recalls, notifications), a tabulation of incidents (particularly serious adverse events/ incidents, including deaths, stratified into whether the manufacturer considers them to be device-related or not) and estimates of the incidence of incidents. Post-marketing data about incidents are generally more meaningful when related to usage but caution is needed. The extent of user reporting in the medical devices vigilance system may vary considerably between countries, users, and type of incident. Considerable under-reporting by users is expected. However, the analyses of data within these reports may, for some devices, provide reasonable assurance of both clinical safety and performance. It may be helpful to provide a table summarising device-related incidents, paying particular attention to serious adverse events/ incidents, with comments on whether observed device related incidents are predictable on the basis of the mode of action of the device. To demonstrate the extent of the probable risk(s)/ harm(s), the following factors – individually and in the aggregate - should be addressed:
• Nature severity, number and rates of harmful events associated with the use of the device:
- Device-related serious adverse events/ incidents: Those events that may have been or were attributed to the use of the device and produce an injury or illness that is life threatening, results in permanent impairment or damage to the body, or requires medical or surgical intervention to prevent permanent harm to the body.
- Device-related non-serious/ non-reportable harmful events: Those events that may have been or were attributed to the use of the device and that do not meet the criteria for classification as a device-related serious adverse events/ incidents.
- Procedure-related incidents: Harm to the patient that results from use of the device but is not caused by the device itself. For example, anaesthetic-related complications associated with the implantation of a device.

- ✓ **The results of an analysis of severe or less severe adverse reactions or side effects potentially related to the use of the device are resumed in the paragraphs 8.2.1, 8.2.2., 8.2.3, and 8.2.4 of this CER. All potential side effects or the factors of risk for life-threatening adverse reactions are adequately mentioned in the IFU. Further data will be collected from the PMS.**

• Probability of a harmful event: The proportion of the intended population that would be expected to experience a harmful event; whether an event occurs once or repeatedly may be factored into the measurement of probability.
• Duration of harmful events (i.e., how long the adverse consequences last): Some devices can cause temporary, minor harm; some devices can cause repeated but reversible harm; and other devices can cause permanent, debilitating injury. The severity of the harm should be considered along with its duration.
• It is also important to look at the totality of the harmful events associated with the device. The number of different types of harmful events that can potentially result from using the device and the severity of their aggregate effect has to be considered. When multiple harmful events occur at once, they have a greater aggregate effect.

• Comment specifically on any clinical data that identifies hazards not previously considered in the risk management documentation, outlining any additional mitigation required (e.g. design modification, amendment of information materials supplied by the manufacturer such as inclusion of contraindications in the IFU).

- ✓ **Because of the extremely limited incidence of adverse events, no analysis of probability / duration of adverse events has been performed. The types of harmful events are summarized in the above-mentioned paragraphs. No other potential hazards to be considered in the risk management documentation have been identified.**

e. Evaluation of acceptability of the benefit/risk profile

• Evaluate if the clinical data on benefits and risks are acceptable for all medical conditions and target populations covered by the intended purpose when compared with the current state of the art in the corresponding medical field and whether limitations need to be considered for some populations and/or medical conditions.
• The current knowledge/ state of the art therefore needs to be identified and defined, possibly also relevant benchmark devices and medical alternatives available to the target population. Typically, documentation of the clinical background shall include the following information:
- clinical background
- information on the clinical condition(s) to be treated, managed, or diagnosed
- prevalence of the condition(s) - natural course of the condition(s) - other devices, medical alternatives available to the target population, including evidence of clinical performance and safety - historical treatments - medical options available to the target population (including conservative, surgical and medicinal) - existing devices, benchmark devices.
• Sufficient detail of the clinical background is needed so that the state of the art can be accurately characterised in terms of clinical performance, and clinical safety profile. The selection of clinical data that characterises the state of the art should be objective and not selective of data on the basis of being favourable for the device under evaluation. Information should be provided on alternative approaches that have been used or considered and their benefits and drawbacks. Deficiencies in current therapies should be identified from a critical and comprehensive review of relevant published literature. The literature review should demonstrate if the device addresses a significant gap in healthcare provision. Where there is no such clinical need, the design solution needs to show an improved or at least equivalent benefit/risk profile compared to existing products or therapies.

- ✓ **Details of the clinical background, information on the condition and therapeutic alternatives are detailed above (see chapter 3 of this CER). D-mannose is effective and safe, being virtually devoid of side effects.**
- ✓ **There is evidence about the high benefit/risk ratio of using a substance like D-mannose with respect to antibiotic drugs (for details, see the literature quoted in Chapter 3, and the § 7.1, 7.2, 7.3, 7.4, 7.5, 7.6 and 8.2).**
- ✓ **On the side of the efficacy, the few clinical studies published to this date suggest that mannose could be as effective as antibiotics in prevention of recurrence. Conversely, no comparisons were attempted on the side of treatment of acute UTIs.**
- ✓ **Importantly, this natural sugar is far safer than antibiotics. We underline two relevant aspects:**
  -unlike antiobiotics, it has no side effects worth of note, and may be used also for long continuative periods;
  -using a substance such as D-mannose could be helpful in reducing the onset of antibiotic resistance in microbes, that is becoming a major pharmacological problem.

- ✓ **So, we claim that the benefit/risk ratio of D-mannose in lower urinary tract infections, is higher or non-inferior to that of antimicrobial drugs.**

- ✓ **The selection of clinical data was performed objectively, including all available data without exclusions.**

• If or when treatment comparability versus accepted therapy is not available at the time of placing on the market, this should be clearly described in the device IFU.
• Even if a device cannot compete with an agreed first-line treatment or the best in class, it may add to the portfolio of acceptable treatments, as even a first-line treatment will likely have contraindications or non-responders.
• Devices, that might not be best-in-class, might provide sufficient clinical evidence for an acceptable benefit/risk-profile for specific, defined subgroups or even superior clinical performance under specific conditions (e.g. emergency outdoor conditions).

- ✓ **Concerning D-mannose, no comparative data with other devices are available in the literature.**
- ✓ **With respect to pharmacological agents, the data in §3.1, 7.1, 7.3 and 7.5 show that D-mannose, although can not be considered as best-in-class, due to a still limited clinical evidence, may be considered at least as an useful and cheap adjunct to antibiotic therapy in treatment or prevention of UTIs, in order to reduce the amount of antibiotic consumed, limiting the risks of side effects and onset of resistance.**

• The position within the treatment portfolio has to be specified properly in the clinical evaluation report and other relevant documentation.

- ✓ **Scope of these medical devices and the rationale followed in the development of the products, aimed to improve the performances of equivalent medical devices already on the market, is detailed in Chapter 2 of this CER.**

8.6. Conformity assessment with requirement on performance (MDD ER3 / AIMDD ER2) (Appendix 7)

The devices must achieve the performances intended by the manufacturer. The ability of a medical device to achieve its intended purpose as claimed by the manufacturer needs to be demonstrated, including any direct or indirect medical effects on humans as well as the clinical benefit on patients resulting from the technical or functional, including diagnostic characteristics of a device, when used as intended by the manufacturer.
Clinical performance includes any claims about clinical properties and safety of the device that the manufacturer intends to use. It is expected:
• that the devices achieve their intended performances during normal conditions of use, and
• that the intended performances are supported by sufficient clinical evidence.

- ✓ **The device fulfills all these conditions**

8.7. Conformity assessment with requirement on acceptability of undesirable side-effects (MDD ER6 / AIMDD ER5) (Appendix 7)

Any undesirable side-effect must constitute an acceptable risk when weighed against the performances intended. In order to evaluate the acceptability of the side-effects of a device:
• there needs to be clinical data for the evaluation of the nature, severity and frequency of potential undesirable side-effects;
• the clinical data should contain an adequate number of observations (e.g. from clinical investigations or PMS) to guarantee the scientific validity of the conclusions relating to undesirable side-effects and the performance of the device;
• in order to evaluate if undesirable side-effects are acceptable, consideration has to be given to the state of the art, including properties of benchmark devices and medical alternatives that are currently available to the patients, and reference to objective performance criteria from applicable standards and guidance documents.
If there is lack of clinical data or an insufficient number of observations, conformity with the requirement on acceptability of undesirable side-effects is not fulfilled.

- ✓ **Although many studies are old and of limited significance, there is a sufficient amount of clinical data about the efficacy and the safety of D-mannose in the treatment and prevention of lower urinary tract infections (see the paragraphs 7.1, 7.2, 7.3, 7.4, 7.5 and 7.6 in this CER).**

Conclusions:

●Taken altogether, all these data show that the active ingredient in the Medical Device is effective and safe.
●The functional components of the product is absorbed in the upper intestinal tract, but not metabolized. The product is likely safe also in childhood, pregnancy and breastfeeding. However, in this case it suggested to consult a physician.
●Taken altogether, besides possible intolerances (uncommon), and purported contraindications in diabetics and in people with some inherited metabolic diseases (contraindincations not confirmed in the practical use), all the available data show that the active ingredients and the excipients included in the medical devices “Mannose MD” are safe. The side effects are always mild and transitory. At prescribed dosage and for a duration not exceeding the recommended time of administration, no severe adverse reactions are expected.
People with known intolerance to active component or excipients should avoid using the product. In general, at first signs of intolerance or allergy, the patient should immediately stop taking the product and consult a physician. In case of any doubt, report the active components of the product to your physician, so he can suggest if you can take or not the device. To improve its effectiveness, the product should be taken with an adequate quantity of water (at least 2 liters per day).

●The active component is not degraded during transit through the digestive tract and after the absorption, excreted intact in a short time, not absorbed and not retained in the body, and not fermented in the colon.
●The formulation “Mannose MD” is in line with the definition of medical device.
●The producer commits to include in the clinical evaluation the data acquired in §6.2.2 any time significant data will emerge.

9. Clinical Evaluation Report, including PMF/PMS Plan (Stage 4)

The post marketing surveillance is performed every year on each Medical Device designed and produced to assess its safety and to keep under control the occurrence of incidents or indirect harms.
Besided to Reactive Surveillance and Vigilance the Manufacturer will carry out the following post-marketing assessments:

- **Review of the relevant Scientific Literature available relating to the safety, performance, design characteristics and intended purpose of the device (Eu Dir 93/42/CE, Annex X point 1.1.1) every 12 months. The review will be performed by our Scientific Consultant ([redacted]) following the below described criteria and reporting the results of the search to Clinical Evaluation Manager.**

The criteria for selection of published clinical data are determined on the basis of:
- 1.1 choosing an appropriate level of "Impact Factor Criteria" (IFS) of the sources considered (http://www.ncbi.nlm.nih.gov/pubmed);
- 1.2 Scientific publications or alert reports concerning the MD and equivalent (refer to the search for web sites such as European and Italian sites www.ec.europa.eu, www.salute.gov.it, Health Technology Assessment, Eudamed, etc)
- 1.3 Type of methodology followed for the published data (for example studies blinded simple, only double-blind, randomized, only triple-blind, placebo, no placebo etc.)
- 1.4 Publications that relate to investigations carried out on at least a minimum number of subjects;
- 1.5 Publications highlighting also negative aspects related to DM or its components;

- **Actively update of the clinical assessment (by the Scientific Consultant and the Regulatory team) with data from Post Market Reactive Surveillance every 12 months or whenever significant new information affecting risks and benefits become available.**

- **The Manufacturer will implement a Questionnaire through its Distributors in order to collect data from consumers related to safety and efficacy (Annex 1).**
  The data collected from the questionnaires will be evaluated annualy by the Vigilance Manager and reporting the results to Clinical Evaluation Manager.

- **Based on the collected data, if significant new information affecting risks and benefits becomes available, the Manufacturer (Regulatory team and Risk Manager) will update the Risk Assessment in order to confirm the performance of MD in relation with the results reported in scientific literature, the continued acceptability of identified risks and to detect emerging risks on the basis of factual evidence.**

If the benefit/risk ratio is not positive, the Manufacturer shall undertake to take corrective actions such as modifying instruction leaflet or implementing clinical studies on the device.

9.1 Vigilance results

The Manufacturer, S.I.I.T. SRL, resume the history of the medical device object of this CER in terms of production and adverse events in order to collect post market safety and efficacy data related to the present medical device.

From **2015** to **2017** S.I.I.T. Srl produced and delivered:

- [redacted] boxes of **Femannose** (D - mannose + Cranberry extract)
  - [redacted] boxes of Femannose CH (14 sachets)
  - [redacted] boxes of Femannose CH (30 sachets)
  - [redacted] boxes of Femannose international (30 sachets)
  - [redacted] boxes of Femannose international (14 sachets)

From **2017** S.I.I.T. Srl has produced and delivered:

- [redacted] boxes of **Femannose N** (D-mannose)
  - [redacted] boxes of Femannose N international (14 sachets)
  - [redacted] boxes of Femannose N international (30 sachets)
  - [redacted] boxes of Femannose N Germany (14 sachets)
  - [redacted] boxes of Femannose N Germany (30 sachets)
  - [redacted] boxes of Femannose N CH (14 sachets)
  - [redacted] boxes of Femannose N CH (30 sachets)

From 2015, the date of first emission on the market of the formulation with Cranberry (Femannose), to date (2018) the Manufacturer experienced the following complaints from consumers claiming various categories of

2018

COMPLAINTS RELATED TO THE APPEREANCE OF SIDE EFFECTS			
BRAND NAME	**COMPLAINT N°**	***ADVERSE EVENT***	***EXPERT RESPONSE***
FEMANNOSE	[redacted]	*The patient experienced rash, pimples and intense itching after twice intake of product in association to antibiotics.*	*The symptoms reported are probably due to an allergic reaction considering that the patient claimed a lot of different allergies. All the ingredient are clearly indicated into the ingredient list. Anyway, it is not possible understand if the allergic reaction is to Femannose or to the antibiotic taken in association.*
FEMANNOSE N	[redacted]	*The patient experienced flatulence after taking the product.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE N	[redacted]	*The patient experienced diarrhea after taking the product.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE N	[redacted]	*The patient experienced diarrhea after taking the product.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*Female patients experienced frequent, soft, flaky stool under Femannose. One*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*

		of the patients experienced in addition nausea.	
FEMANNOSE N	[redacted]	*A female patient experienced an allergic reaction after one sachet Femannose N.*	*The product contains fructose as excipient that is clearly indicated into the ingredient list onto the leaflet, therefore people who are intolerant to fructose may experience allergic reactions that can be avoided by reading the product composition in the leaflet.*
FEMANNOSE N	[redacted]	*The patient experienced diarrhea after taking the product.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*The patient (ALLERGIC TO ASPIRIN) experienced diarrhea after taking the product.*	*The symptoms reported are expected side effect, but, if the patient is allergic, could be also due to allergy to acetylic acid contained in cranberry, in fact the product should not be used in people who are allergic to aspirin (as reported in the leaflet).*
FEMANNOSE N	[redacted]	*The patient experienced diarrhea after taking the product.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE N	[redacted]	*A female patient experienced intense burning in bladder, vagina till rectum under three different therapies with Femannose N.*	*The patient has complained burning in bladder till rectum and vagina about 6 hours after taking Femmanose. Burning was still present after 5 days of discontinuation and worsened after restart of the product. The symptoms are likely to be due to the presence of a pre-existing irritation of the perineal mucosa, worsened by the presence of the salicylic acid, which can be irritating, contained in the Cranberry extract.*
FEMANNOSE	[redacted]	*The client states that after taking 3 sachets area's with little pimples appeared on her cheeks while she didn't change anything in her daily care*	*The consultant declares that The sign reported (little pimples) are probably due to an allergic reaction.* *The product leaflet reports the possibility of allergic reactions to salicylic acid because it is the most allergenic component of the product.* *An individual hypersensitivity may always be present, which results in an unpredictable allergy to any of the components of a product.*
FEMANNOSE N	[redacted]	*The patient experienced diarrhea after taking the product.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE N	[redacted]	*The patient experienced diarrhea after taking the product.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE N	[redacted]	*The patient experienced gastric disturbs after taking the product.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE N	[redacted]	*The patient experienced diarrhea after taking the product.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE N	[redacted]	*The patient experienced diarrhea and nausea after taking the product.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE N	[redacted]	*A female experienced dizziness (nausea, vomiting and headache) after taking the product*	*It is unlikely that dizziness and headache are due to the product, as there are no scientific rationale for the product to cause these effects, while nausea and vomiting are expected events and reported in the package insert.*

			However, all the symptoms complained of by the patient are likely to be due overall to an individual hypersensitivity
FEMANNOSE N	[redacted]	*The patient experienced strong abdominal cramps and soft stool.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE N	[redacted]	*The patient experienced intense and nausea after taking the product.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
COMPLAINTS RELATED TO LACK OF EFFICACY			
BRAND NAME	**COMPLAINT N°**	***ADVERSE EVENT***	***EXPERT RESPONSE****
FEMANNOSE	[redacted]	*Lack of efficacy in case of intense cystitis*	*This event is not considerable as suspect adverse event. The product does not replace an antibiotic treatment for acute cystitis as clearly indicated onto the leaflet*
FEMANNOSE	[redacted]		
FEMANNOSE N	[redacted]		
FEMANNOSE N	[redacted]		
FEMANNOSE N	[redacted]		
FEMANNOSE N	[redacted]		
FEMANNOSE N	[redacted]		
FEMANNOSE N	[redacted]		
FEMANNOSE N	[redacted]		
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FEMANNOSE N	[redacted]		
FEMANNOSE N	[redacted]		
FEMANNOSE N	[redacted]		
FEMANNOSE N	[redacted]		
FEMANNOSE N	[redacted]		
FEMANNOSE N	[redacted]		
FEMANNOSE N	[redacted]		
COMPLAINTS RELATED TO PATIENTS PATHOLOGICAL CONDITIONS			
BRAND NAME	**COMPLAINT N°**	***ADVERSE EVENT***	***EXPERT RESPONSE****
FEMANNOSE N	[redacted]	*A female experienced sore and burning throat immediately after intake of Femannose N. The patient suffered from gastric reflux and was under treatment with antireflux drugs.*	*The consultant declares that the suspect adverse event could be due to the worsening of the pre-existent reflux linked to citric acid contained as excipient.*

COMPLAINTS RELATED TO ALTERATION OF URINE COLOR			
BRAND NAME	**COMPLAINT N°**	***ADVERSE EVENT***	***EXPERT RESPONSE****
FEMANNOSE N	[redacted]	*Patient experienced since some days discoloration of urine (orange but clear). the urine was tested with the result that there was no blood in urine*	*The consultant declares that the suspect agent event is very likely due to coloring agent present in the formulation, as indicated on the leaflet. The suspect effect events cannot be considered as incident according to the definition provided*
COMPLAINTS UNLIKELY LINKED TO THE INTAKE OF THE PRODUCT			
BRAND NAME	**COMPLAINT N°**	***ADVERSE EVENT***	***EXPERT RESPONSE****
FEMANNOSE N	[redacted]	*Increased liver values*	*The consultant declares that it is highly unlikely that the product can cause the symptoms/physiological alteration described in these complaints. These suspect effect event cannot be considered as incident according to the definition provided by MedDev Guideline 2.12_01.*
FEMANNOSE N	[redacted]	*Increased nocturnal urinary frequency (ca. 5 * per night, normally ca.3* per night).*	
UNKNOWN IF FEMANNOSE OR FEMANNOSE N	[redacted]	*Female consumer experienced sweating after the intake of the product*	
FEMANNOSE N	[redacted]	*The patient experienced nocturnal sensation of heat after the intake of the product*	
FEMANNOSE N	[redacted]	*The patient experienced that her legs and hands swelled with edema after 3 sachets of the product*	
FEMANNOSE N	[redacted]	*The patient experienced intense headache one-sided eye and around.*	
FEMANNOSE	[redacted]	*Femannose was administered in the evening concomitantly with different psychotropic drugs and neuroleptics. The consumer reported that she was massive mentally impaired after one week.*	
UNKNOWN IF FEMANNOSE OR FEMANNOSE N	[redacted]	*A consumer contacted Melisana stating that she has been taking Femannose for 4 days and she experienced that her menstruation didn't come through.*	
COMPLAINTS CLOSED AS UNFOUNDED			
BRAND NAME	**COMPLAINT N°**	***ADVERSE EVENT***	***EXPERT RESPONSE****
FEMANNOSE N	[redacted]	*The patient took daily Femannose N. No pathological reaction reported. With recommended interruption she took Femannose N since 18 months and she tolerated it very well.*	***COMPLAINTS UNFOUNDED***
FEMANNOSE N	[redacted]	*The patient has taken Femannose N since months twice daily. No adverse event reported.*	

FEMANNOSE N	[redacted]	*The patient has taken Femannose N for 3 months with good tolerance despite of her fructose intolerance. No adverse event reported*	

**Detailed Expert responses are saved into Quality Assurance archives.*

2017

COMPLAINTS RELATED TO THE APPEREANCE OF SIDE EFFECTS			
BRAND NAME	**COMPLAINT N°**	***ADVERSE EVENT***	***EXPERT RESPONSE***
FEMANNOSE	[redacted]	*A consumer experienced flatulence and gastric spasms after*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*A consumer stated stomach ache and flatulence after intake of Femannose. Patient had a fructose-intolerance*	*the product labelling contains all the information necessary to avoid the use for intolerance subjects, also the presence of fructose*
FEMANNOSE	[redacted]	*A consumer stated stomach cramps and diarrhea after intake of Femannose.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*A pharmacist reported about a consumer who does not tolerate Femannose, because she is allergic to aspirin.*	*The leaflet clearly indicates that the product should not be taken by subjects allergic to aspirin.*
FEMANNOSE	[redacted]	*A consumer stated diarrhea after intake of Femannose.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*A female patient experienced an allergic reaction with swollen tongue.*	*The product labelling contains all the information necessary to avoid the use for intolerance subjects.*
FEMANNOSE	[redacted]	*A female patient administered 7 sachets (from [redacted] 2017 until [redacted].2017). She rated this as overdose, but experienced no adverse reactions.*	*The labelling contains all the information necessary to avoid a misuse of the product*
FEMANNOSE	[redacted]	*Female patient experienced pain and pressure on stomach since the administration of Femannose.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*Intake of Femannose in 9th week of pregnancy without consultation with her physician. Twice intake of product without further dosage details. No adverse event reported. Consumer asked whether the intake could be a problem.*	*The labelling contains all the information necessary to avoid a misuse of the product even in case of pregnancy and lactation.*
FEMANNOSE	[redacted]	*After first sachet of Femannose the patient experienced stomach ache, after the second sachet again stomach ache with flatulence and after the third sachet diarrhea (no soft stool).*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*Soreness of mouth, rough spots and burning on the oral mucosa.*	*Patient reaction is due to individual hypersensitivity and not to defectiveness of the product. The suspect effect*

			event is an expected side effect as reported in the leaflet of the product.
FEMANNOSE	[redacted]	*Flatulence after administration of Femannose*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*Patient took 2 sachets Femannose despite of fructose intolerance.*	*The suspect adverse event is not attributable to the product FEMANNOSE because the product labelling contains all the information necessary to avoid the use for intolerance subjects (also the presence of fructose).*
FEMANNOSE	[redacted]	*Patient allergic to aspirin: skin reaction, urticarial*	*The suspect adverse event is not attributable to the product FEMANNOSE because the product labelling contains all the information necessary to avoid the use for intolerance subjects (also the warning not to take in case of aspirin allergy as cranberry contains traces of acetylsalicylic acid)*
FEMANNOSE	[redacted]	*Patient experienced diarrhea after intake of Femannose.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*Patient allergic to aspirin: allergic reaction*	*The suspect adverse event is not attributable to the product FEMANNOSE because the product labelling contains all the information necessary to avoid the use for intolerance subjects (also the warning not to take in case of aspirin allergy as cranberry contains traces of acetylsalicylic acid)*
FEMANNOSE	[redacted]	*Consumer experienced after first sachet of Femannose severe stomach pain and bloating*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*Patient experienced diarrhea after intake of Femannose*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*Patient with tannins intolerance elt bad after taking Femannose: vomit and colic.*	*The side effects are related to an individual hypersensitivity of the subject to tannins, which are consituents of one of the ingredients of Femannose that is cranberry. As the product leaflet refers that Femmannose must not be used in case of hypersitivity to components, we can exclude inadequacy of product labelling.*
FEMANNOSE	[redacted]	*Patient experienced belly ache and diarrhea.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*Patient with existing fructose-intolerance administered Femannose.*	*The suspect adverse event is not attributable to the product FEMANNOSE because the product labelling contains all the information necessary to avoid the use for intolerance subjects (also the presence of fructose).*
FEMANNOSE	[redacted]	*The patient experienced diarrhea (for 3 days) after one sachet Femannose.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*The patient experienced stomachache*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*The patient experienced flatulance*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*

FEMANNOSE	[redacted]	*The consumer reported malaise and bloating.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*A female consumer suffered after intake of Femannose from circulatory disorder with shortness of breath*	*The suspect adverse event is classified as allergic reaction. No more info about the clinical case was given to the Manufacturer to investigate (anamnesis for example)*
FEMANNOSE	[redacted]	*Consumer experienced vomiting after intake of Femmanose.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*A female consumer suffered after intake of Femannose from circulatory disorder with shortness of breath*	*The suspect adverse event is classified as allergic reaction. No more info about the clinical case was given to the Manufacturer to investigate (anamnesis for example)*
FEMANNOSE	[redacted]	*A female patient experienced after the administration of Femannose nausea and stomach upset.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*Headache due to acidity of oxalic acid in Femannose is mentioned, several hours after the intake of Femannose.*	*Patient reaction is due to individual hypersitivity or non-casual concomitance and not to defectiveness of the product.*
FEMANNOSE	[redacted]	*A patient had diarrhoea after use of Femannose.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*High levels of blood glucose in elderly patient.*	*The suspect adverse event can be due to fructose cointened as excipient, as given in the leaflet (composition). However, after suspension of the product levels of blood glucose are still high, so it is likely that the increase is attributable to an underlying hyperglycemia due to age of the patient and not at Femannose itself*
FEMANNOSE	[redacted]	*gastrointestinal problems*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*Patient got nausea and circulatory problems after the intake of Femannose*	*The nausea is an expected side effect as reported in the leaflet of the product. The suspect adverse effect "circulatory problems" are not attributable to the product with the information currently available*
FEMANNOSE N	[redacted]	*rash, burning and itching in patient under psychotropic dugs*	*The allergic reaction to some components of the product is probably due to individual allergic diathesis, therefore it cannot be considered as attributable to the product.*
FEMANNOSE	[redacted]	*the consumer suffered from irritation of skin, mucous membranes (mouth, stomach, esophagus)*	*This event are probably due to an allergic reaction to some components of the product caused by individual allergic diathesis. Therefore the reaction cannot be considered as attributable to the product.*
FEMANNOSE	[redacted]	*A consumer who experienced severe diarrhea for some days after Femannose.*	*The suspect effect event is an expected side effect as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*A patient complaint about flatulence and gastric spasms*	*These event is classified as gastrointestinal symptoms and are expected side effects, as reported in the leaflet of the product.*

FEMANNOSE	[redacted]	*A female patient experienced vomiting and massive bloating*	*These event is classified as gastrointestinal symptoms and are expected side effects, as reported in the leaflet of the product.*
FEMANNOSE N	[redacted]	*After first intake of Femannose N the patient experienced constipation.*	*The consultant declares that obstipation is probably due to individual reaction to some of product components, as the product may cause diarrhea as side effect, as reported in the Leaflet.*
FEMANNOSE	[redacted]	*A consumer experienced vomiting approximately one hour after administration of Femmanose.*	*These event is classified as gastrointestinal symptoms and are expected side effects, as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*A consumer experienced diarrhea approximately one hour after administration of Femmanose.*	*These event is classified as gastrointestinal symptoms and are expected side effects, as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*Intolerance: massive heartburn*	*The suspect adverse event is probably due to individual gastro-sensitivity to some of product component.*
FEMANNOSE	[redacted]	*Intolerance: Allergy salicylic acid*	*Taking the product may cause side effects in people affected by allergy to aspirin. The product should not be used in people who are allergic to aspirin, as reported in the leaflet (Warnings and precautions for use)*
FEMANNOSE	[redacted]	*Intolerance without medical effect*	*It is not possible for the consultant to give a proper answer without knowing the symptoms of intolerance. It is important to know what is the effective adverse reaction to manage the reporting. It would be useful also to know diseases and concomitant therapies.*
FEMANNOSE	[redacted]	*Intolerance: diarrhea*	*These event is classified as gastrointestinal symptoms and are expected side effects, as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*Client vomited 1 hour after the intake*	*These event is classified as gastrointestinal symptoms and are expected side effects, as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*A patient experienced extreme slime formation on his neo bladder (made from bowel issue). Urination was not possible.*	*The formation of slime urine is unlikely to directly depend on the product, but on the personal history of the patient who has suffered from urination disorder after stroke and neobladder. One possible explanation is that a) the sugars present in the product may have increased the specific weight of the urine and b) this may have contributed to increase the density of the urine with difficulty of emission, considering the patient's medical history.*
FEMANNOSE	[redacted]	[redacted] *year old woman experienced heavy abdominal cramps which lasted an entire night. She took too much sachets in few hours.*	*The consultant declares that it is very likely that the symptoms are the consequence of concentrating in a few hours the maximum quantity or even higher of product that is suggested to be taken during 24 hours, as reported in the product leaflet (paragraph 4. Posology and administration)*
FEMANNOSE N	[redacted]	*Patient with fructose and sorbitol intolerance experienced stomach ache, like a rumbling. After the second sachet she experienced high blood pressure and 3 hours heart racing.*	*The patient has a known intolerance to a component of product. As reported in the leaflet the product it must not be taken by people with known intolerance to components of the same.*

FEMANNOSE N	[redacted]	*A consumer experienced stomach ache and rumbling after the use of Femannose N. It was like a stomach mucosa inflammation.*	*These event is classified as gastrointestinal symptoms and are expected side effects, as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*A patient allergic to citric acid experienced itching all over the body*	*The suspect adverse event is not attributable to the product FEMANNOSE because the product labelling contains all the information necessary to avoid the use for intolerance subjects (also the presence of fructose).*
FEMANNOSE	[redacted]	*A patient experienced restlessness, malaise and mild nausea*	*These event is classified as gastrointestinal symptoms and are expected side effects, as reported in the leaflet of the product.*
FEMANNOSE	[redacted]	*A patient experienced incremented heart pulse after in taking the product.*	*Information to find a correlation between the product and the tachycardia is insufficient. In any case, there is no scientific reason to find a correlation between the product and the appearance of tachycardia.*

COMPLAINTS RELATED TO LACK OF EFFICACY

BRAND NAME	**COMPLAINT N°**	***ADVERSE EVENT***	***EXPERT RESPONSE****
FEMANNOSE	[redacted]	*Lack of efficacy in case of intense cystitis*	*This event is not considerable as suspect adverse event. The product does not replace an antibiotic treatment for acute cystitis as clearly indicated onto the leaflet*
FEMANNOSE	[redacted]		
FEMANNOSE	[redacted]		
FEMANNOSE	[redacted]		
FEMANNOSE	[redacted]		
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FEMANNOSE	[redacted]		
FEMANNOSE	[redacted]		
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COMPLAINTS CLOSED AS UNFOUNDED			
BRAND NAME	**COMPLAINT N°**	***ADVERSE EVENT***	***EXPERT RESPONSE****
FEMANNOSE	[redacted]	*Intake of Femannose followed by severe diarrhea (4-5 times). First use of Femannose. The consumer affirms that possibly the reason for diarrhea was a salad with yoghurt dressing. After some foods (e.g. ice with cream) she suffers from belly ache. Negative lactose intolerance test. If she takes Femannose again with experience of diarrhea she will contact company.*	***COMPLAINTS UNFOUNDED***
FEMANNOSE	[redacted]	*The consumer received Femannose after an antibiotic treatment: he stated that Femannsoe was overdosed in the last days. Femannose was tolerated well, she did not experience any ADR. She just wanted to know whether Femannose can impact her bowel inflammation.*	
FEMANNOSE	[redacted]	*After the second day of Femannose administration she experienced 'vaginal yeast'. She had suffered from a grippal infection (without antibiotic treatment) – thus the patient was not sure whether 'vaginal yeast' was caused by her bad immune system and not by Femannose.* *Afterwards she had an appointment with her gynaecologist who assessed the causality between the event and Femannose as 'unlikely' related and suspected a relationship with the weak immune system. Femannose helped against the bladder infection and the patient is very content with Femannose and continues with it.*	
FEMANNOSE	[redacted]	*A female consumer who suffered from a salicylic acid allergy, purchased Femannose. Afterwards she read in the package information that Femannose should not be taken in case of this allergy. Thus, she had not administered Femannose.*	
FEMANNOSE	[redacted]	*Femannose was taken without ADR and helped initially.*	
FEMANNOSE	[redacted]	*Femannose was taken without ADR and helped initially.*	
FEMANNOSE	[redacted]	*A pregnant female (14th week took Femannose. She did not experience an adverse event.* *The pharmacist did not receive information from the patient regarding the outcome of pregnancy. No patient's contact available.*	

FEMANNOSE	[redacted]	*A female consumer reported that her son ([redacted] years old) has taken Femannose for at least 3 months (without interruption). She asked whether Femannose could also be taken with juice or tea because he does not like the taste of Femannose solved in water anymore.*	
FEMANNOSE	[redacted]	*Recurrence of an E. coli urinary tract infection and application of 3x 1 Sachet of Femannose daily two weeks long. Following this the urine was sterile and the patient was symptom-free.*	
FEMANNOSE/FEMANNOSE N	[redacted]	*The patient started in 02/2017 with Femannose and switched later to Femannose N. No ADR reported*	
COMPLAINTS RELATED TO ALTERATION OF URINE COLOR			
BRAND NAME	**COMPLAINT N°**	***ADVERSE EVENT***	***EXPERT RESPONSE****
FEMANNOSE	[redacted]	*A pharmacist reported about a consumer who experienced blue/purple urine.*	*The consultant declares that the suspect agent event is very likely due to coloring agent present in the formulation, as indicated on the leaflet. The suspect effect events cannot be considered as incident according to the definition provided.*
FEMANNOSE	[redacted]	*The consumer (boss of the pharmacy) experienced light red urine after Femannose.*	
FEMANNOSE	[redacted]	*A pharmacist called: a customer has a coloration of urines (pinky) after taking Femannose*	
FEMANNOSE	[redacted]	*the consumer experienced discoloured urine (same colour like product) after intake of Femannose*	
FEMANNOSE	[redacted]	*A pharmacist called: a customer has a coloration of urines (pinky) after taking Femannose*	
FEMANNOSE	[redacted]	*The consumer (female) experienced red urine after intake of Femannose.*	
FEMANNOSE N	[redacted]	*A female patient experienced massive dark yellow urine after intake of Femannose N. Blood in urine was excluded by physical examination, no symptoms of bladder inflammation.*	

COMPLAINTS UNLIKELY LINKED TO THE INTAKE OF THE PRODUCT			
BRAND NAME	**COMPLAINT N°**	***ADVERSE EVENT***	***EXPERT RESPONSE****
FEMANNOSE	[redacted]	*A consumer (female) experienced blood sugars levels increasing to 200 mg/dl.*	*The consultant declares that it is highly unlikely that the product can cause the symptoms/physiological alteration described in these complaints. These suspect effect event cannot be considered as incident according to the definition provided by MedDev Guideline 2.12_01.*
FEMANNOSE	[redacted]	*A Patient experienced itching at her back and her buttocks and burning of her mucous membranes.*	
FEMANNOSE	[redacted]	*About 8 hours after intake of Femannose patient experienced dry eyes and dry skin. According to the patient the reactions might also have been caused by antibiotics taken. No treatment of reactions. No experience of such reactions in the past. Patient assessed the causality with Femannose as possible related. Patient had an appointment with her gynecologist. She stated that her hormones are not okay and that she needs to take estrogens.*	
FEMANNOSE	[redacted]	*After administration of Femannose (no information on dosage) the consumer experienced vaginal itching and swelling which abated after discontinuation of the product.*	
FEMANNOSE	[redacted]	*Urine test stripes showed moderate glucosuria.* *Patient ate normal food, no extra sweets. First-time use of Femannose. No glucosuria in the past. Consumer assessed causality as 'possibly' related.*	
FEMANNOSE	[redacted]	*Before intake of Femannose the consumer suffered from diarrhea (resolved before start of Femannose) and was afraid that this could lead to bladder infection. Her physician gave her Femannose. She had enterococci and other not further specified germs in her urine. After taking Femannose she suffered from urinary urgency (possibly also caused by coming bladder infection) and soft stool.*	
FEMANNOSE	[redacted]	*Employee of pharmacy experienced always heartburn after administration of the product.*	
FEMANNOSE	[redacted]	*With the start of Femannose he experienced obstipation.*	
FEMANNOSE	[redacted]	*Femannose (with cranberry) was taken 30 days for cystitis prophylaxis. After 14 days the urine started to smell strange and the frequency of urinating increased. After day 30 of intake the patient made a break of 5 days. Since day 2 of this break, the smell was normal again and the frequency of urinating*	

		decreased. In the meantime she started with a new package of Femannose (without cranberry, without worsening of the urine frequency.	
FEMANNOSE	[redacted]	*A consumer experienced intolerance after Femannose. No more details were reported.*	
FEMANNOSE N	[redacted]	*Patient took one sachet of Femannose N and experienced enuresis. In the night she had to go to the toilet six times with micturition urgency.*	
FEMANNOSE	[redacted]	*A female consumer experienced heart pain (could not be further specified) after intake of Femannose. Consumer has the impression that one sachet of Femannose was too much, less than one sachet made no problem.*	
FEMANNOSE N	[redacted]	*A female patient has taken Femannose N for some time. The dose is unregular. Sometimes she has taken 2 sachets daily, then for some days 1 sachet daily and then for 5 days 3 sachets. Now increased protein levels in urine were found.*	

**Detailed Expert responses are saved into Quality Assurance archives.*

2016

COMPLAINTS RELATED TO SIDE EFFECTS			
BRAND NAME	**COMPLAINT N°**	***ADVERSE EVENT***	***EXPERT RESPONSE****
FEMANNOSE	[redacted]	*The patient stated, that she took one dose in the evening and found that she had developed a red rash in the abdominal region the next morning. She further stated that she is allergic to cranberry extract.*	*Side effect indicated into the leaflet: the warning for hypersensitive patients is reported. The ingredient list indicates that the product contains cranberry*

**Detailed Expert responses are saved into Quality Assurance archives.*

1) The detailed analysis of clinical complaints received by the consumers from 2016, date of first emission on the market, shows that no relevant clinical event linked to the direct intake of the product took place; indeed, the majority of complaints collected by the Vigilance office concerned the appearance of common side effects that:
- are clearly described in scientific literature and, as a consequence, reported onto the leaflet
- are very often not directly linked to the intake of the product itself but to pre-existing consumers pathological disturbs

Having analyzed the side effects claimed by the consumers, to date, the Manufacturer thinks that no further side effects should be added to the leaflet into the warning section as the current master texts perfectly cover and consider the current post market scenario.

2) A few complaints claimed the absence of efficacy of the product: anyway, the received alert came from patient who were experiencing intense episode of cystitis (often hemorrhagic) for which the use of antibiotics is inevitable. This is why, the Manufacturer clearly indicate onto the leaflet that "The medical device does not replace the need for antibiotic therapy treatment of urinary tract infections."

3) A few complaints were classified as isolated cases whom impact were not significant compared to the number of marketed boxes (n°8 pinky/orange urine probably due to the presence of beet red into formulation, n° 1 increase of gastric reflux due to the presence of citric acid as excipient).
For this reason, the Manufacturer did consider necessary to insert the warnings on the alteration of urine color and on the worsening of gastric reflux because they occurred only in patients who already had strong predisposing factors (hemorrhagic cystitis and pre-existent GERD).

Nevertheless, the post marketing data will be carefully monitored with regard to this or similar events.

4) The manufacturer also received a few complaints that were not linked to the intake of the product itself as it was scientifically impossible to attribute the cause of the claimed adverse event to the intake of the products (absence of menstruations, eye pain, hands oedema, sweating, nocturnal heat, mental confusion, dry eyes and dry skin etc).
5) Finally, a little number of complaints, were not considered as "incidents" or "adverse events" as the consumers claimed a positive outcome after taking the product. This is why they were closed as "unfounded".

To date, these vigilance data show that the formulation based on D-mannose manufactured by SIIT can be considered as safe from a clinical point of view.

The lack of misuse accidents, the lack of appearance of not listed side effects and the absence of complaints related to posology prove that the current instructions of use satisfies the usability requirements applicable to substance-based medical devices.

The Manufacturer can conclude that, to date, the leaflet provided by the Manufacturer is suitable and sufficiently explicative to be used by a "lay person", otherwise an individual who does not have formal education in a relevant field of healthcare or medical discipline.

The only suspect event that the Manufacturer will carefully monitor through the post market surveillance system, is the appearance of pinky colored urine that are probably due to the presence of beet red as color agent into formulation; to date, the Manufacturer doesn't consider necessary to insert the warnings on the alteration of urine color and on the worsening of gastric reflux because they occurred only in a patient who already had strong predisposing factors (hemorrhagic cystitis and pre-existent GERD).

Additionally, our distributor Klosterfrau, has finalized a detailed post market clinical follow-up analysis to evaluate the safety and performance as well as the usability of the medical devices Femannose N. Indeed, in 2017 and 2018, with the help of YouGov Germany, Klosterfrau carried out a user survey for the products Femannose and Femannose N, both manufactured by S.I.I.T. srl and distributed by the Klosterfrau Healthcare group. The results of this post market analysis are added as addendum in this Annex ("Addendum 2018-10-15_PMCF-Report-Femannose-FemannoseN_signed").

10. General conclusions and no need of clinical trials

The safety and the performances of device have been evaluated with respect of the intended use and evidenced conformity with Essential Requirements. The performance of MD is consistent with the updated scientific literature.
The side effects highlighted within the literature analysis are acceptable when weighed against the performance related to the MD usage. The risks associated to the usage of the MD and described in the above reported risk analysis have been managed in order to obtain acceptable residual risks which are compatible with the safety of the users.
In light of what has been shown, the MD developed by the manufacturer reflects the security requirements applicable in relation to the function and performance highlighted by the clinical data considered. **With the exception of individual cases of intolerance, there are no scientific publications that point out harmful side effects of the components of the Medical Device at the designed doses. The side effects were always negligible and transient, also in children, and are nowadays well described. However, for people under 14 years, or if taking drugs concomitantly to the medical device, it is advisable to consult a physician before beginning to use the product.**

To date, the manufacturer believes that the he literature analysis about the components leads to the conclusions that there is sufficient demonstration of the clinical activity and the safety of the functional component included in the medical device.
Having said that, evidences reported in the evaluated scientific literature, the positive results derived from the QA vigilance system on equivalent and analogue devices are exhaustive in demonstrating the efficacy and the safety of the functional component present in the Medical Device.
Taking together these data, the manufacturer deems that no additional clinical trials are necessary to confirm the efficacy of the Medical Device.
Anyway, in order to keep trace of the safety and efficacy results during the marketing timeline, the Manufacturer will implement a Questionnaire through its Distributors in order to collect data from consumers' experiences. The data collected from the questionnaires will be evaluated annualy by the Vigilance Manager and reporting the results to Clinical Evaluation Manager:

ANNEX 1

Surveillance Questionnaire for Medical Device

- ***Age****: ___*
- ***Sex:***

  ☐ *M*

  ☐ *F*
- ***How long are you using the Product? ___***
- ***Do you think that Product was useful to solve your problem?***

  ☐ *Yes*

  ☐ *Enough*

  ☐ *Not so much*

  ☐ *No*
- ***If so, which kind of improvement did you experience since the beginning of the treatment, and how soon?***

  _____

  _____
- ***Did you observe side effects listed in the leaflet ?***

  ☐ *Yes (please specify): _____*

  ☐ *No*
- ***Did you observe side effects not listed in the leaflet?***

  ☐ *Yes (please specify): _____*

  ☐ *No*
- ***Did you follow particular therapies during the assumption of the Product?***

  ☐ *Yes (please specify): _____*

  ☐ *No*
- ***Do you suffer of some kind of allergy?***

  ☐ *Yes (please specify): _____*

  ☐ *No*
- ***Did you find the instruction for use clear enough?***

  ☐ *Yes*

  ☐ *No (please specify): _____*
- ***Additional comments:***

  _____

  _____

11. Declaration of interest and Curriculum Vitae (Appendix 11)

Declarations of interests of the evaluators should be held by the manufacturer and cover relevant financial interests outside the current work as an evaluator.
In the attached file, we show the declaration of interests and the CV provided by the company figures that have participated to the the CER writing.