SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ENTEROGERMINA 2 billion / 5 ml oral suspension
ENTEROGERMINA 2 billion hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains:

Active ingredient:
2 billion polyantibiotic-resistant *Bacillus clausii* spores (strains SIN, O/C, T, N/R).

One hard capsule contains:

Active ingredient:
2 billion polyantibiotic-resistant *Bacillus clausii* spores (strains SIN, O/C, T, N/R).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension.
Hard capsules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prevention of intestinal dysmicrobism and subsequent endogenous avitaminosis.
Coadjuvant treatment to restore the intestinal microbial flora, altered during treatment with antibiotics or chemotherapy.
Acute and chronic gastrointestinal disorders in infants, attributable to poisoning or intestinal dysmicrobism and avitaminosis.

4.2 Posology and method of administration

Adults: 2-3 vials per day or 2-3 capsules per day.
Children: 1-2 vials per day or 1-2 capsules per day.
Infants: 1-2 vials per day.
Vials: administration at regular intervals. Take the vial content as it is or dilute it in water or other beverages (e.g., milk, tea, orange juice).
Capsules: swallow accompanied by a sip of water or other drinks.

Particularly in younger children, if they have difficulty swallowing hard capsules, use oral suspension instead.
This medication is for oral use only. Do not inject or administer in any other way (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Special warnings

Bacteraemia/sepsis
Post-marketing cases of bacteraemia, septicaemia and sepsis have been reported in patients being immunocompromised or severely ill, and in preterm infants. In some critically ill patients, the outcome was fatal. ENTEROGERMINA should be avoided in these patient groups (see section 4.8).

This medicinal product is for oral use only. Do not inject or administer in any other way. Incorrect use of the medicinal product has caused severe anaphylactic reactions such as anaphylactic shock.

Precautions for use

During treatment with antibiotics, it is recommended that the preparation be administered between antibiotic administrations.
Any presence of visible corpuscles in the vials of ENTEROGERMINA is due to aggregates of *Bacillus clausii* spores; it does not therefore suggest that the product has been altered.
Shake the vial before use.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
No data are available on the use of Enterogermina in pregnant women; therefore no conclusions can be drawn regarding the safety of the use of Enterogermina during pregnancy.
Enterogermina should be used during pregnancy alone if the benefits for the mother outweigh the risks, including those for the foetus.

Breast-feeding

No data are available on the use of Enterogermina during breastfeeding with regard to the composition of breast milk and the effects on the baby. It is not possible to draw conclusions on the safety of the use of Enterogermina during breastfeeding.
Enterogermina should be used during breastfeeding only if the potential benefits for the mother outweigh the potential risks, including those for the breastfed baby.

Fertility
No data are available on the effect of Enterogermina on human fertility.

4.7 Effects on ability to drive and use machines

Enterogermina has no influence on the ability to drive and use machines.

4.8 Undesirable effects

During the treatment with this medicinal product the following undesirable effects were observed and classified according to MedDRA classification in organ classes and according to the following frequency classes:
Very common (≥1/10); Common (≥1/100,<1/10); Uncommon (≥1/1.000,<1/100); Rare (≥1/10.000,<1/1.000); Very rare <1/10.000); Unknown (the frequency cannot be defined based on available data).

Classification based on systems and organs	**Common**	**Uncommon**	**Rare**	**Very rare**	**Unknown**
Infections and infestations					Bacteraemia, septicaemia and sepsis (in immunocompromised or severely ill patients) (see section 4.4)
Skin and subcutaneous tissue disorders					hypersensitive reactions, including rash, hives and angioedema

Reporting of suspected adverse reactions.
Reporting suspected adverse reactions after authorisation of the medicinal product is

important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system at https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse.

4.9 Overdose

No cases of overdose have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antidiarrhoeal microorganisms

ATC Code: A07FA

ENTEROGERMINA is a preparation consisting of a suspension of 4 strain (SIN, O/C, T, N/R) spores of *Bacillus clausii* , which occurs naturally in the intestine and is non-pathogenic.

When administered orally, *Bacillus clausii* spores, thanks to their high resistance to both chemical and physical agents, cross the barrier of the acidic gastric juice, reaching the intestinal tract unharmed and there they are transformed into metabolically active vegetative cells.

Spores can survive heat and gastric acidity, by nature. In a validated *in vitro* model *Bacillus clausii* spores demonstrated to survive in a simulated gastric environment (pH 1.4-1.5) until 120 minutes (survival rate of 96%). In a model that simulates the intestinal environment (saline solution of bile and pancreatin - pH 8), *Bacillus clausii* spores demonstrated their capability to multiply compared to the initial amount, in a statistically significant way (from 10^9 to 10^{12} CFU – Colony-Forming Units), starting from 240 minutes after the incubation.

In a study that was conducted on 20 individuals, it was noticed that, in humans, *Bacillus Clausii* spores persist in the intestine and can be found in faeces until 12 days after a single oral administration.

The administration of ENTEROGERMINA contributes to the restoration of intestinal microbial flora that is altered by dysmicrobism, also known as dysbiosis, that results from the antibiotic therapy and that can be associated with gastrointestinal symptoms, e.g. diarrhoea, abdominal pain and increase of air in the intestine.

In two open randomized controlled clinical trials, ENTEROGERMINA demonstrated to reduce the duration of acute diarrhoea in children older than 6 months.

When taken during the antibiotic treatment and the next 7-10 days, ENTEROGERMINA demonstrated to reduce the incidence of abdominal pain and diarrhoea that are associated with the antibiotic treatment.

A prospective, observational, multicentre study conducted on 261 patients evaluated the 'real-world' use of the probiotic *Bacillus clausii* for symptoms such as diarrhoea, pain, bloating, meteorism, constipation and abdominal tension through the administration of a questionnaire by the pharmacist before starting to take it and after 30 days.
Patients reported taking the medicinal product mainly for diarrhoea (56.7%), abdominal pain (13.41%) and bloating (12.64%). The mean duration of treatment was 7.1 days. On average, the improvement in symptoms was perceived after it had been taken for 3 days. After treatment, 95% of patients reported an improvement in diarrhoea and 97% an improvement in abdominal pain.

The 2 main mechanisms, reported below, contribute to *Bacillus clausii* effect of restoring the intestinal bacterial flora.

Growth Inhibition of Pathogenic Bacteria

The three *B. clausii* supposed mechanisms of action are: colonization of free ecological niches, that are made unavailable by the growth of other microorganisms; competition for the bond with epithelial cells, that is particularly relevant for the spores in the germination initial and intermediate phases; production of antibiotics and/or enzymes that are secreted in the intestinal environment. In an in vitro study *Bacillus clausii* spores demonstrated to produce bacteriocins and antibiotics such as clausin, with antagonist activity against Gram-positive bacteria *Staphylococcus aureus*, *Clostridium difficile*, *Enterococcus faecium.*

Immunomodulatory activity

Bacillus clausii spores, administered through the oral route, in in vitro and in vivo murine models demonstrated to stimulate the production of Interferon-gamma and to increase the CD4+ T Lymphocyte proliferation.

Furthermore, *Bacillus clausii* demonstrated its capability of producing various B vitamins, aiding in correcting avitaminosis due to intestinal bacterial flora imbalance.

Furthermore, the high level of artificially induced heterologous resistance to antibiotics creates the therapeutic conditions for preventing the alteration of intestinal microbial flora, by the selective action of antibiotics, particularly broad-spectrum antibiotics, or for restoring the intestinal microbial flora.
Due to its antibiotic resistance, ENTEROGERMINA may be administered between two subsequent administrations of antibiotics.
Antibiotic resistance refers to: penicillins, if not in combination with beta-lactamase

inhibitors, cephalosporins (partial resistance in most cases), tetracyclines, macrolides, aminoglycosides (except for gentamicin and amikacin), chloramphenicol, thiamphenicol, lincomycin, clindamycin, isoniazid, cycloserine, novobiocin, rifampicin, nalidixic acid and pipemidic acid (intermediate resistance), metronidazole.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Vials: Purified water.

Capsules: Microcrystalline cellulose, Magnesium stearate, Gelatine, Titanium dioxide (E171), Purified water.

6.2 Incompatibilities

None.

6.3 Shelf life

Vials

2 years.

After opening the vial, consume the preparation within a short time to avoid any pollution of the suspension.

Capsules

3 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Vials: lithographed cardboard box containing 10 or 20 vials.

Capsules: lithographed cardboard box containing 1 or 2 blister packs, each with 12 capsules.

6.6 Special precautions for disposal and other handling

Vials: shake the vial before use.

7. MARKETING AUTHORISATION HOLDER

Opella Healthcare Italy S.r.l. – Viale L. Bodio, 37/b – IT-20158 Milan (Italy)

8. MARKETING AUTHORISATION NUMBERS

AIC 013046038 2 billion Pack of 10 vials

AIC 013046040 2 billion Pack of 20 vials

AIC 013046053 2 billion Pack of 12 capsules
AIC 013046065 2 billion Pack of 24 capsules

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 November 2001
Date of latest renewal: 30 July 2008

10. DATE OF REVISION OF THE TEXT

August 2024