

Summary of Product Characteristics

1. Name of the Medicinal Product

1.1 Product Name

MUTAFLOR Suspension

1.2 Strength

10^8 CFU/ml

1.3 Pharmaceutical Dosage Form

Suspension for oral use.

2. Qualitative and Quantitative Composition

2.1 Qualitative Declaration

2.2 Quantitative Declaration

1 ml contains as active substance:

Bacterial culture of *Escherichia coli* strain Nissle 1917 corresponding to 10^8 viable cells (CFU)

For a full list of excipients, see section 6.1.

3. Pharmaceutical Form

Suspension for oral use.

4. Clinical Particulars

4.1 Therapeutic Indications

- Diarrhoea in infants, toddlers, and children who considered by doctor to use.

4.2 Posology and Method of Administration

Posology:

Diarrhoea:

Infants, toddlers, and children: 1–3 x 1 ml daily.

Method of administration:

The suspension can directly be administered from the container into the mouth, with infants before nursing, with toddlers and children after a meal.

Furthermore, the suspension can be applied via a gastric-/ intestinal -tube as well.

Duration of administration:

Diarrhoea, acute: At least 5 days

Diarrhoea, prolonged: At least 15 days

4.3 Contraindications

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

4.4 Special Warnings and Precautions for Use

- With diarrhoea, the risk of dehydration exists. Therefore, even under treatment with MUTAFLOR Suspension, sufficient intake of liquid and electrolytes shall be ensured.

- In incomplete digestive tract tissue case, there is a chance to be sepsis.

4.5 Interactions With Other Medicinal Products and Other Forms of Interactions

Antibiotics against Gram-negative bacteria and sulphonamides may reduce the efficacy of MUTAFLOR Suspension.

4.6 Pregnancy and Lactation

E. coli strain Nissle 1917 is a commensal gut inhabitant of human beings and is not absorbed. With intended use effects on pregnancy and lactation are not to be expected. However, MUTAFLOR Suspension is only intended for the treatment of infants, toddlers and children.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable Effects

The assessment of undesirable effects was based on the following frequencies:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $1/1,000$)

Very rare ($< 1/10,000$)

Not known (cannot be estimated from the available data)

Undesirable effects of the gastrointestinal tract

Flatulence, diarrhoea, vomiting or abdominal pain were observed very rarely.

Undesirable effects of the skin

Urticaria or allergic reactions were observed very rarely.

Infections and infestations

In extremely premature infants (birth weight < 1000 g), the occurrence of a sepsis has been observed in isolated cases. Its frequency cannot be estimated from the available data.

4.9 Overdose

No case of overdose has been reported.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antidiarrheal microorganisms

ATC-Code: not yet assigned

Modes of action:

MUTAFLOR Suspension contains a defined non-pathogenic strain of the species *Escherichia coli* (*E. coli* strain Nissle 1917) in a viable form. The effects of *E. coli* strain Nissle 1917 were proven by *in-vitro* and *in-vivo* experiments as well as by clinical studies. The following properties and modes of action were observed:

Antagonism against pathogenic and potentially pathogenic micro-organisms and strengthening of the intestinal barrier:

- *E. coli* strain Nissle 1917 produces antimicrobial substances, which are responsible for the antagonistic activity against pathogens.
- By means of special adhesive organells (fimbriae) the strain is able to attach to the mucine layer, which covers the colon wall. The strain is well mobile due to its flagellae, which is an advantage for the colonization of the colon.
- *E. coli* strain Nissle 1917 stimulates in gut cells the synthesis of inducible antimicrobial acting defensines (HBD-2, HBD-3)
- In animal experiments *E. coli* strain Nissle 1917 increases the concentration of calprotectin on the gut wall and thus prevents bacteria from direct adhesion to epithelial cells of the gut mucosa.
- *E. coli* strain Nissle 1917 prevents enteroinvasive pathogens from invading into gut epithelial cells.
- In gnotobiotic mice *E. coli* strain Nissle 1917 increases the expression of the zonula-occludens protein ZO-1 in the tight junctions of the intestinal epithelium. This leads to a strengthening of the intestinal barrier function.

MUTAFLOR Suspension possesses immuno-modulatory properties:

In-vitro- and *in-vivo* experiments demonstrated, that the immuno-modulatory properties of *E. coli* strain Nissle 1917 act on the humoral as well as on the cellular immune system of newborns.

1. Effects on the specific immune system:

- Pre- and full-term infants show after colonisation with *E. coli* strain Nissle 1917 an early increase of immune competence, which is reflected by the increase of the IgA- and IgM-levels in stool filtrates and serum. In contrast, an increase of the IgG-level in serum is not observed. Furthermore, case reports indicate an increase of IgA in saliva. Additionally, in preterm infants an increase of cell mediated immune responses can be observed after the oral administration of *E. coli* strain Nissle 1917.

2. Effects on the non-specific immune system:

- In preterm infants a stimulation of the unspecific natural immunity after the oral administration of *E. coli* strain Nissle 1917 was observed.

- *In-vitro*- and *ex-vivo*-experiments showed a significant increase of secretory and cytotoxic properties in mice macrophages. Furthermore, an increase of the cytotoxic capabilities of mouse macrophages directed against intracellular parasites could be demonstrated *ex vivo*, thus indicating a strengthening of the defense against intracellular germs. In mice an infection prophylactic effect acting against systemic infections could be demonstrated *in vivo*.

Further properties:

- The strain metabolizes different carbohydrates, sugar alcohols and other substances in an aerobic pathway. Thereby, an anaerobic milieu is developed in the colon.

- The strain produces short-chain fatty acids, which are very important for the energy supply of the colonic mucosa. The short-chain fatty acids stimulate colonic motility and blood flow in the colonic mucosa as well as sodium and chloride absorption.

5.2 Pharmacokinetic Properties

As shown in clinical studies with newborns, the active substance *E. coli* strain Nissle 1917 colonizes the gut as a naturally occurring bacterium. It is not absorbed and no subject to metabolization. *E. coli* strain Nissle 1917 is secreted via the feces.

5.3 Preclinical Safety Data

E. coli strain Nissle 1917 has neither toxic nor pathogenic properties. The strain does not produce enterotoxins and hemolysin, it is not enteroinvasive, it has no pathogenic adhesion factors, it is not serum-resistant, it has no uropathogenic properties, it is sensitive to frequently used antibiotics against Gram-negative bacteria and shows no signs of immuno-toxic properties.

6. Pharmaceutical Particulars

6.1 List of Excipients

Purified water, sodium chloride, potassium chloride, magnesium sulphate heptahydrate, calcium chloride dihydrate, magnesium chloride hexahydrate, sodium hydroxide solution 32 %.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

- Sealed container: 12 months
- After opening the sachet, use content within three months.

6.4 Special Precautions for Storage

Store in a refrigerator (2°C – 8°C). Do not freeze.

After their opening 5 ml containers must be stored between 2 – 8°C in their carton.

6.5 Nature and Contents of Container

Nature of container:

Polyethylene ampoules.

Package sizes:

Pack with 5 x 1 ml

Pack with 10 x 1 ml

Pack with 25 x 1 ml

6.6 Special Precautions for Disposal and Handling

Disposal:

No special requirements.

Handling:

Tear off a single dose container from the block. Shake well and twist off cap before use.

The packs with 5 ml ampoules contain additionally a dosing spoon. Filling up to its indication mark results in 1 ml. Clean the dosing spoon with warm water and dry it with a clean cloth after use.

7. Marketing Authorisation Holder

MEGA LIFESCIENCES Public Company Limited

Samutprakarn, Thailand

8. Marketing Authorisation Number

1C 21/63 (NBC)

9. Date of Authorisation

31 July 2020

10. Date of Revision of the Text

May 2021