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PRODUCT DATA SHEET

FOR DIFFBIOME MTT CAPSULES

1. Name of Product, General Information

1.1 Name of Product

DiffBiome

1.2 Full Name of Product

DiffBiome standardized intestinal microbiota graft for MTT

1.3 Product variations

DiffBiome 30(V), DiffBiome30+, where the Arabic number (30) stands for the number of capsules within the container, while the Roman number (V) indicates the dosage level, derived from the dry matter content of the lyophilized product. The "+" sign indicates that the preparation contains a homogenized mixture of raw materials collected over several days from the same donor.

1.4 Description

DiffBiome is an orally administered human microbiota transplantation (MT) capsule developed to restore healthy gut microbiota in patients experiencing recurrent *Clostridioides difficile* (*C. difficile*) infections (rCDI). Each capsule contains a standardized intestinal microbiota graft, optimized for scalable treatment protocols to ensure consistent therapeutic outcomes. Initially designed as part of the TransferBiome protocol, DiffBiome is specifically formulated to enhance microbiota diversity and functionality. Manufactured under stringent safety and efficacy standards, it provides a dependable and effective solution for microbiota transfer therapy (MTT).

2. Scope of Use, Active Ingredients, Mechanism of Action

2.1 Indications

DiffBiome is specifically designed for the treatment of patients with *Clostridioides difficile* infections (CDI) at home. It is particularly recommended for individuals who have not responded adequately to antibiotic therapy or have experienced multiple recurrences of CDI. The product aids in restoring gut health by introducing a highly diverse and well-balanced microbiota concentrate that helps suppress the overgrowth of pathogenic organisms.

2.2 Active Substance

DiffBiome contains a biologically active substance obtained from carefully screened human donors, specifically designed for use in microbiome transfer therapy. Its main component is a standardized suspension of human colon-derived microbiota in a lyophilized form, prepared in accordance with strict quality and safety guidelines.

2.3 Mechanism of action

The active component in DiffBiome is a diverse community of live gut microorganisms derived from healthy, screened donor stool. When ingested, these microorganisms colonize the patient's gastrointestinal tract, restoring microbial diversity and balance, which helps suppress the overgrowth of pathogenic bacteria like *C. difficile*.

3. Method of Use, Packaging, Storage, Dosage and Tapering

3.1 Method of use

- **Oral Administration**: DiffBiome capsules should primarily be taken orally without chewing or opening them, on an empty stomach, accompanied by plenty of fluids. Thirty minutes after taking the capsules, additional fluids should be

consumed to ensure proper hydration and optimal absorption. Following this, other medications can be taken, and the regular daily routine may resume.

- **Timing:** capsules should be taken first thing in the morning. Avoid simultaneous consumption with alcoholic beverages or hot liquids.

3.2 Packaging

- Dark Glass Containers: DiffBiome capsules are packaged in dark glass bottles to ensure effective protection from light and maintain product quality. This packaging is designed to preserve the viability of the microorganisms and ensure consistent therapeutic efficacy throughout the treatment period.
- **Each bottle contains 30 capsules, representing the 10 day dose referred to as the packaging unit. To support typical treatment protocols, a single glass container is adequate to cover the entire treatment period for one patient.**
- Moisture and Contaminant Control
    - Tamper-Evident Seal: Each container is equipped with a tamper-evident closure to safeguard product integrity and ensure it remains uncompromised.
    - Child-Resistant Closure: In compliance with local regulations, a child-resistant cap may be included to enhance safety and prevent unauthorized access. The product you ordered is equipped with a child-resistant closure if it is required by the regulations in your country.
- Labeling
    - The label clearly displays the product name, the number of capsules, the batch number, the expiration date and storage instructions for easy reference.
    - It includes a designated area for healthcare providers or pharmacists to record the dispensing date if required.

3.3 Storage

- **Room Temperature (up to 25°C / 77°F):** Store in the unopened, original packaging. The product remains stable for up to 3 months (90 days) when kept away from excessive heat and direct sunlight.
- **Refrigerated (+4°C to +8°C / 39–46°F):** When stored in a sealed, dark glass container, the product is stable for up to 12 months.
- **Deep Freeze (below –20°C / –4°F):** Properly sealed and protected from light, the product can be stored for up to 5 years.
- Handling Recommendations:
    - Ensure the container is tightly closed when not in use.
    - Store in an upright position to reduce the risk of capsule damage.
    - Minimize frequent opening and closing, as this may alter humidity levels inside the container.

3.4 Dosage

- **Standard Treatment Course:** The recommended regimen involves taking 3 capsules daily for a specified duration, typically around 10 days, depending on the treatment protocol.
- **Physician's Discretion:** The exact dosage and duration should be determined by the treating physician, customized to the patient's clinical status, medical history, and tolerance. Treatment usually starts with DiffBiome 30(V), administered for at least 10 consecutive days. If the frequency of bowel movements does not decrease, treatment should be attempted with DiffBiome+ capsules, which should be continued until all symptoms and clinically significant complaints have fully resolved.

3.5 Tapering

1. **Sequential Reduction:** In specific cases, such as frequent recurrences, a step-down protocol may be employed, where the initial daily dose is gradually decreased over time.
2. **Clinical Monitoring:** Patients should be closely observed during the tapering process for any signs of symptom recurrence or adverse reactions. If a relapse occurs, the maximum dosage can be reintroduced, and the treatment protocol may be repeated. After completing the repeat treatment, it is strongly recommended to switch to a different LOT.
3. **Follow-Up:** A post-treatment follow-up, typically conducted within 1–2 weeks after the final dose, is recommended to evaluate therapeutic outcomes and ensure patient recovery.

4. Advantages

4.1 Non-Invasive Delivery

Oral capsule administration provides a minimally invasive alternative to traditional MTT methods, such as colonoscopy or enema, reducing both patient discomfort and procedural risks.

4.2 High Efficacy

Clinical evidence demonstrates that MTT capsules can significantly lower recurrence rates of *C. difficile* infections by effectively restoring microbial diversity and inhibiting the overgrowth of harmful pathogens.

4.3 Ready-to-Use Therapy

DiffBiome is delivered as a fully prepared, rigorously tested product that can be directly administered by healthcare providers. It eliminates the need for in-house stool processing, donor screening, or complex MTT preparation steps, ensuring standardized, high-quality therapy while saving time and resources.

4.4 Convenience

Oral capsules are easy to store and administer, making them suitable for outpatient settings. This reduces logistical challenges for healthcare facilities and decreases dependence on specialized procedures. The capsule form significantly enhances patient adherence to therapy.

5. Pricing, Quantity Discounts, and Packaging Options

5.1 Pricing

The final cost of DiffBiome may vary depending on distributor agreements and local regulations. For moderate illnesses, the average treatment volume falls between 30 and 60 capsules, while in cases of severe infections resistant to antibiotic therapy, treatment may require the use of longer treatment. Pricing is structured per one-day treatment unit, providing flexibility for healthcare providers to customize treatment plans.

5.2 Quantity Discounts

Discounted rates may be available for bulk purchases, offering cost savings for larger orders.

5.3 Product Bundles

DiffBiome can be ordered in bundles containing a minimum of 30 capsules, sufficient for a complete treatment regime for one patient. Additional discounts based on

packaging or volume may also be available, depending on the order size and distributor terms.

6. Additional Information

6.1 Donor Screening and Safety

- **Rigorous Screening:** Human microbiota of donors stool is meticulously screened according to applicable guidelines (e.g., EMA, WGO, EAGEN, or local health authority standards).
- **Comprehensive Testing:** Stringent microbiological, serological, and parasitological tests are performed to ensure the absence of infectious pathogens.
- **Quality Assurance:** The GMP-compliant manufacturing process includes multiple quality control checkpoints to ensure consistency and safety of the product.

6.2 Drug Interactions

- **Antibiotics:** Concurrent antibiotic use may diminish the efficacy of DiffBiome. It is recommended to complete antibiotic treatment at least 48 hours before starting DiffBiome therapy.
- **Probiotics:** Data on interactions between DiffBiome and probiotic supplements is limited. Avoid concurrent probiotic use during DiffBiome treatment unless advised by a healthcare provider.

6.3 Known Side Effects

- **Common and Mild:** Gastrointestinal discomfort, bloating, flatulence, diarrhea, or constipation. These effects are usually temporary and resolve without medical intervention.
- **Rare but Serious:** Infections or allergic reactions may occur and require close monitoring. Any significant or unusual symptoms should prompt immediate medical evaluation and reporting.

6.4 Warnings and Precautions

- **Immunocompromised Patients:** Patients with severe immunodeficiency or those on immunosuppressive therapy require close monitoring due to a higher risk of infection.
- **Pregnancy and Lactation:** Limited data is available; treatment should only be initiated after careful assessment by a healthcare provider.
- **Other Contraindications:** Patients with severe active gastrointestinal conditions (e.g., toxic megacolon, fulminant colitis) or suspected bloodstream infections should undergo thorough evaluation before initiating DiffBiome therapy.

7. Manufacturing Process and Quality Control

7.1 Donor Eligibility and Comprehensive Medical Evaluation

- **Thorough Pre-Donation Assessment:** All potential donors undergo a comprehensive medical evaluation before donation, including a detailed medical history, physical examination, and standard diagnostic tests. These ensure that any diseases or conditions transmissible via microbiota transfer are excluded to the best of current medical knowledge.
- **Dietary and Nutritional Requirements:** Donors adhere to a prescribed diet recommended by medical experts, including antibiotic-free animal proteins to

support a stable, healthy microbiota. Regular medical evaluations are conducted to maintain the highest quality of donated material.

7.2 Serological Testing

- **Routine Screening:** Donors undergo at least two separate serological testing sessions 8 weeks apart to detect blood- and body-fluid-transmissible infections.
- **Tests Include:**
  - HIV 1–2 (Human Immunodeficiency Virus)
  - Hepatitis A, B, C, E
  - *Treponema pallidum* (syphilis)
  - Inflammatory markers in blood serum and stool
- **Eligibility:** Only donors with negative results across all repeated tests qualify for donation.

7.3 Microbiological Testing of the Donated Stool (Donatum)

- **Pathogen Screening:** Donated stool ("donatum") is analyzed using multiplex PCR or conventional microbiological methods to detect enteric pathogens, including:
  - *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*
  - Enteropathogenic *E. coli* (EAEC, EPEC, ETEC, STEC, EIEC)
  - *Clostridioides* species
  - *Plesiomonas*, *Vibrio*
  - *Cryptosporidium*, *Cyclospora*, *Entamoeba histolytica*, *Giardia lamblia*
  - Adenovirus, Astrovirus, Norovirus, Rotavirus, Sapovirus, SARS-CoV-2
  - *Helicobacter pylori*
  - Multidrug-resistant organisms (MRSA, MRSE, VRE, ESBL, CRE)
- **Results:** Only donor samples confirmed to be free of the specified pathogens will be utilized in the final formulation of DiffBiome capsules.

7.4 Processing and Formulation

- After pathogen clearance, donor stool is processed into a bacterial suspension, lyophilized, and encapsulated using specialized pharmaceutical techniques to ensure microorganism viability and stability.

7.5 Excipients and Vitalization Additives

- To ensure optimal bacterial viability and support manufacturing integrity, each capsule contains:
  - Amylum solani (potato starch)
  - Inulin (chicory-derived)
  - Pyridoxal 5'-phosphate (vitamin B6)
  - Cyanocobalamin (vitamin B12)
  - Pteroil-monoglutamic acid (folic acid, vitamin B9)

These components have been selected to promote microbial stability, bacterial viability during storage, and ensure patient safety.

7.6 Batch (LOT) Identification and Documentation

- Each production batch is assigned a unique identifier tracking all related manufacturing data, including donor information, date of production, and raw material usage.
- Mandatory tests (e.g., microbiological purity checks, viable bacterial counts and active substance content) are performed according to predefined specifications prior to release.

7.7 Microbiological Testing and Contaminant Exclusion

- Regular microbiological screening (e.g., conventional culture methods, multiplex PCR) ensures the absence of contaminants or unintended pathogens.
- While the product is not manufactured under sterile conditions—given it contains live bacteria—a strict exclusion protocol is in place to rule out critical pathogens.
- Testing protocols follow strict local and international guidelines (e.g., EMA, WGO, EAGEN) for microbiological quality in biological products.

7.8 Excipients and Additional Components

- All excipients (e.g., *Amylum solani* [potato starch], inulin) and vitamin additives (B6, B12, folic acid) undergo rigorous quality checks to confirm purity, identity, and the absence of undesirable contaminants (e.g., heavy metals, residual solvents).
- Certificates of Analysis (CoA) from suppliers may be required, and spot checks or additional in-house testing can be performed to verify compliance with the relevant pharmacopeial or internal specifications.

7.9 Ongoing Quality Oversight

- Quality Assurance (QA) teams routinely audit production processes, documentation, and QC test results to ensure compliance with GMP standards.
- Any deviations or out-of-specification (OOS) results are thoroughly investigated, and corrective actions are implemented to maintain product integrity and regulatory compliance.

8. Special Populations

8.1 Elderly Patients

- Due to the potential for multiple comorbidities and concurrent medication use, DiffBiome should be used with caution in elderly patients, accompanied by closer monitoring for any adverse effects or interactions.

8.2 Pediatric Use

- Currently, DiffBiome is not indicated for patients under 18 years of age. Research is ongoing regarding MTT safety and efficacy in pediatric populations.

9. Additional Considerations and Regulatory Status

9.1 Regulatory Classification

DiffBiome is classified as a medical therapy (MTT) derived from substances of human origin. Classification by EU regulatory authorities is anticipated by the end of 2026.

9.2 Prescribing and Dispensing

DiffBiome should only be used under the supervision of a qualified healthcare professional. Its use may require compliance with specific protocols or special authorization, depending on regional and national regulations.

9.3 Pharmacovigilance and Reporting

Any suspected adverse reactions must be reported to the relevant health authority (e.g., FDA, EMA, or local regulatory agencies) in line with applicable national regulations.

Note: This datasheet is provided for informational purposes and is intended for healthcare professionals and patients. Always seek advice from a healthcare professional before starting any new treatment.

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