Taiwan Food and Drug Administration

Assessment Report

Trade Name：億活散 250 毫克 / Bioflor 250mg powder for oral suspension

Active Ingredient：*Saccharomyces boulardii* (CNCM I-745)

License Number：MOHW-PI 028525

Applicant：微功商行有限公司

Approval Date： 112.08.28

Indication：
緩解輕度急性腹瀉。
Relief of acute mild diarrhea。

Background Information

Trade Name	億活散 250 毫克 / Bioflor 250mg powder for oral suspension
Active Ingredient(s)	*Saccharomyces boulardii* (CNCM I-745)
Applicant	微功商行有限公司
Dosage Form & Strengths	散劑 *Saccharomyces boulardii* 250 mg
Indication	緩解輕度急性腹瀉。
Posology	成人：每次 1-2 小包；1 天 2 次 兒童(3 歲以上)：每次 1 小包；1 天 2 次 使用天數：小於 1 週
Pharmacological Category **ATC Code**	A07FA02

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance is *Saccharomyces boulardii* CNCM I-745, a yeast probiotic strain. *Saccharomyces boulardii* CNCM I-745 is manufactured under current good manufacturing practice. Manufacturing process is sufficiently described including the material inputs, critical process parameters, microbial controls, in-process controls, as demonstrated during process validation. The biological characterization of *Saccharomyces boulardii* CNCM I-745 are considered enough. Controls of raw materials are considered adequate to ensure the safety of *Saccharomyces boulardii* CNCM I-745.

The specification of *Saccharomyces boulardi*i CNCM I-745 is provided and the acceptance criteria is well-justified. All batch results are within acceptable criteria to demonstrate DS quality consistency. In addition, CoAs show that analytical results meet specification requirements. The stability data provided are enough to support storage conditions for *Saccharomyces boulardii* CNCM I-745.

2.1.2 Drug product

Saccharomyces boulardii CNCM I-745 is the active ingredient in Bioflor®. Bioflor®, is provided as powder for oral suspension. The drug product is formulated as 250 mg *Saccharomyces boulardii CNCM I-745* which is supplied in paper / aluminum foil / polyethylene sachet.

Details of formulation development are provided. The drug product manufacturing process is sufficiently described and in-process controls are considered adequate. The compatibility and

safety of the container closure system are demonstrated by stability study. The release and stability specifications for *Saccharomyces boulardii CNCM I-745* drug product are acceptable. The results of long-term stability data are provided and supported DP stored below 30 °C.

In summary, the information on the drug substance and drug product is sufficiently provided and the quality of Bioflor® is considered acceptable.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

The main component of this product, *Saccharomyces boulardii*, has been extensively studied in many literature references of pharmacology. Literature reported the action mechanism and efficacy of *Saccharomyces boulardii*, indicating that *Saccharomyces boulardii* can be used to treat diarrhea caused by infection and has the effect of improving intestinal inflammation.

2.2.2 Toxicological Studies

The toxicology studies of *Saccharomyces boulardii* were performed in the early years, which did not meet the GLP requirements. These data showed no adverse reactions in the six-month toxicology studies of rats and rabbits. Although the toxicology information of *Saccharomyces boulardii* does not fully meet the requirements of current regulations, the long-term clinical human use and experience of probiotics could support the safety of patients with the proposed indications.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Two randomized and controlled studies (Studies [SABINA] and [AAD2]) were selected and evaluated by CDE reviewers to examine the efficacy of Bioflor 250 mg powder for oral suspension for the claimed indication. The key efficacy findings for each study are summarized below.

- ***Study [SABINA]***

Study [SABINA] was a Phase IV, randomized, allocation-blinded (open-label), multi-center, parallel-group, active-controlled study to compare the efficacy of *S. boulardii* versus the Enterogermina® in the treatment of pediatric acute gastroenteritis (PAGE) in children aged from 6 months to 5 years. Eligible subjects were randomized in a 1:1 ratio to either *S. boulardii* sachet 250 mg bid or Enterogermina® 5 ml bid for 5 days. Most of the enrolled subjects had mild illness (i.e., modified Vesikari score ≤ 8).

The primary efficacy endpoint was the mean duration of acute diarrhea. The primary endpoint analysis showed that the adjusted mean duration of diarrhea was lower in the *S.*

boulardii group (64.61 hours) compared to the Enterogermina® group (77.98 hours), and the difference was statistically significant (p = 0.04). Similar trends were observed in mFAS, PPS, and mPPS.

- ***Study [AAD2]***

Study [AAD2] was a prospective, double-blind, multi-center, placebo-controlled study to evaluate the prevention of beta-lactam associated diarrhea by *S. boulardii* in hospitalized adult patients. Eligible subjects were randomized in a 1:1 ratio to *S. boulardii* 2 capsules (500mg) bid or placebo.

The primary efficacy endpoint was the incidence of antibiotic-associated diarrhea (AAD). The incidence of developing AAD was 7.2% in the *S. boulardii* group compared with 14.6% in the placebo group. The difference in proportion (*S. boulardii* – placebo) was -7.37% (95% CI: -16.55%, 1.61%) and the relative risk of *S. boulardii* versus placebo was 0.49 (95% CI: 0.21, 1.17). As there was no significant difference between the two groups, no definitive conclusions could be drawn from Study [AAD2].

2.4.2 Safety Results

Saccharomyces boulardii CNCM I-745 has been marketed for several decades. The estimated cumulative exposure for all formulations was over 300 million patients worldwide. The product is generally safe and well-tolerated. However, patients may develop fungemia for those with central venous catheters, and those who were critically ill or immunocompromised. The incidence was extremely low but some events had led to serious outcomes including death. The risk should be mitigated through adequate labeling.

According to the published literatures, the percent reduction in the incidence of antibiotic-associated diarrhea (AAD) by *S. boulardii* CNCM I-745 were generally similar in different countries worldwide. The safety profile of East Asian subjects was consistent with that of the overall population. The ethnic difference in treatment of acute diarrhea was scientifically justified. The ethnic difference of clinical efficacy and safety was minimal, thus the bridging study could be waived.

2.6 Conclusion

In conclusion, Bioflor powder for oral suspension for the treatment of acute mild diarrhea demonstrates a favorable risk-benefit profile to recommend regular approval. However, as a OTC drug, the usage should be restricted to patients older than 3 years old. The benefit of prevention of antibiotic-associated diarrhea was not established and approval for this indication was not recommended.

3. Post-Marketing Requirements

Post-marketing study was not required.