Annex II

Scientific conclusions

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Symbioflor 2 (*Escherichia coli* bacteria (cells and autolysate)) and associated names (Symbioflor 2) is a probiotic containing living *Escherichia coli* bacteria, which exist in normal gut flora in humans. Symbioflor 2 is composed of 10 different isolates of *Escherichia coli* which are partly autolysed and partly presented as living bacteria. Symbioflor 2 is available in the European Union (EU) in Austria (AT), Germany (DE) and Hungary (HU) as a medicine not subject to prescription or over-the-counter (OTC). Symbioflor 2 has been marketed in Germany since 1954 and in Austria since 1975.

Symbioflor 2 is currently used for the indications:

- Regulation of the immune system, gastrointestinal disorders, irritable bowel syndrome (DE).
- Functional disturbances of the gastrointestinal tract and irritable bowel syndrome (Colon irritable) (AT).
- To regulate the immune system (immune-regulation): functional disturbances of the gastrointestinal system (HU).

The marketing authorisations were granted in Austria in 2000 (renewed on 12 February 2014) and in 2003 in Hungary (HU) respectively. In Germany, since Symbioflor 2 was placed on the market before the entry into force of the German Drug Law in 1978, Symbioflor 2 had to undergo the renewal procedure according to § 105 German Drug Law in order to achieve the conformity of the authorisation in Germany with the Union legislation.

In 2005, based on the evaluation of the available evidence at that time in the claimed indications ("functional gastrointestinal disorders'', "irritable bowel syndrome"), the application was refused by the German National Competent Authority on the ground that a positive benefit-risk had not been adequately established. Following the rejection of the application, the Marketing Authorisation Holder (MAH) requested to be granted a German National Marketing Authorisation on the basis that an authorisation had already been granted in another country of the European Union (Austria).

On 30 March 2016 Germany triggered a referral under Article 31 of Directive 2001/83/EC, and requested the CHMP to assess the benefit-risk balance of Symbioflor 2 in the claimed indications ("functional gastrointestinal disorders'', "irritable bowel syndrome") and to issue an opinion on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation by the CHMP

Two reports in support of the claimed indication in the treatment of irritable bowel syndrome (IBS) were submitted in the context of this referral procedure:

- A 2005 re-analysis of a 1988 study “Efficacy and tolerability of Symbioflor2: A randomised, multicentre, double-blind, placebo-controlled trial in 298 patients with irritable bowel syndrome treated continuously for 8 weeks with Symbioflor 2 (clinical phase IV). Supplementary Integrated Clinical Study Report Final PAZ 9527-5-S2”, of the study conducted in 1988 in Germany entitled “Schaffstein, W. and Burkard, I.: Symbioflor 2 - Eine therapeutische Alternative zur Behandlung des irritablen Kolons. Jatros Gastroenterol, 1993” (Study S2)”, and
- An observational non-interventional study in 203 children and adolescents conducted between 2007 and 2008 in Germany “Efficacy and tolerability of Symbioflor 2 in children with Irritable Bowel Syndrome”.

No study was submitted to support the indication in the treatment of functional gastrointestinal disorders.

In addition, an ad-hoc expert group was convened on 13 January 2017, where the CHMP requested feedback from experts in the treatment of IBS on specific questions regarding the therapeutic role of Symbioflor 2.

Indication in the treatment of functional gastrointestinal disorders

"Functional gastrointestinal disorders" defines a heterogeneous group of individual diseases, ranging from functional oesophageal, gastric, intestinal, biliary, pancreatic to functional anorectal disorders, with a wide range of different underlying pathophysiologies and symptomatic entities that require different treatment modalities. Apart from data on IBS, no controlled or uncontrolled clinical study or literature data are available to assess the efficacy and safety of Symbioflor 2 in the treatment of these diseases. Given the heterogeneity of the disease and the absence of data, the CHMP asked the MAH to submit evidence to support this indication. The MAH did not provide such data and decided to withdraw this indication. The CHMP acknowledged the deletion of the indication "functional gastrointestinal disorders" during this procedure.

Indication in the treatment of irritable bowel syndrome

IBS is a highly prevalent disease and a chronic condition that needs to be managed on a long term basis. It is not life threatening but can significantly impact the quality of life of patients. Whereas it cannot generally be stated that probiotics are efficacious or not efficacious in the treatment of IBS, it appears that specific probiotic species or strains could potentially be efficacious for specific symptoms of the disease. Which species and strains are most beneficial has to be determined individually case by case, and the mechanism of action of probiotics remains speculative.

The evaluations presented in the Study Report of Study S2 (1989), based on a primary endpoint of "global evaluation" of efficacy by the investigator at the end of the trial, showed that Symbioflor 2 administered over an 8-week period had better outcomes than placebo on most of the evaluated endpoints. Overall, the evaluations presented by the MAH indicated that the decrease in symptom score was more important in the Symbioflor 2 than in the placebo arm.

In the re-evaluation report of Study S2 (2005), the endpoints were redefined, combining parameters of a patient-centred assessment of spontaneous symptoms with endpoints based on physical examination by the physician. The newly defined primary endpoints in this re-evaluation were evaluated with adequate statistical methodology and were strict with regards to treatment success, because only patients completely free of symptoms were counted as "responders". The analyses showed statistical significant superiority of the active treatment over placebo in almost all endpoints evaluated. The findings were consistent across age and gender subgroups.

The CHMP also noted that results of the observational study in children older than 4 years with IBS suggested a possible efficacy of Symbioflor 2.

Although Study S2 was conducted before requirements of the current IBS guideline "Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome" (CPMP/EWP/785/97) or the previous CHMP point to consider on IBS came into force, the original protocol of Study S2 neither defined a primary endpoint nor planned for a statistical analysis. The evaluation of the results was descriptive and thus did not allow establishing whether the differences in efficacy between Symbioflor 2 and placebo were statistically different and clinically meaningful. Additional bias might have been introduced by various other deficiencies encountered in the conduct of Study S2, including the fact that the endpoint was solely based on the rating by the investigator on a weekly basis rather than self-assessed by the patient closer to the administration of Symbioflor 2. In the absence of a run-in phase and specific inclusion criteria, there was also insufficient assurance that the patient population suffered from IBS. In addition, the CHMP was of the opinion that the adequacy of a global evaluation criterion defined by the MAH for the assessment of the efficacy of Symbioflor 2 in the treatment of IBS was

questionable in comparison to the specific, better measurable and less subjective evaluation of changes in stool related abnormalities and pain.

Although the results of Study S2 point at a possible efficacy of Symbioflor 2 in the treatment of IBS, a large unexplained heterogeneity was observed among centres in terms of treatment effect and response rate. While several centres did not report any responder, the overall results were driven by one centre. When excluding this centre, a statistically significant centre effect was seen and the statistical significance was lost for both co-primary variables, as well as for the physician's global assessment endpoint. In addition, possible irregularities in the conduct of the study cast doubt over the integrity of the data: for instance, for two centres, the visits for all but one patient occurred in accordance with the study protocol at the exact interval for the whole duration of the study, one of the dates being a public holiday. Source data are, however, no longer available.

In 2005, rather than conducting a new study in line with the "Note for guidance on statistical principles for clinical trials" (CPMP/ICH/363/96) then in force, the MAH decided to perform a post-hoc re-evaluation of Study S2, i.e. establishing the definition of the primary hypothesis, the corresponding evaluation plan and the statistical analysis methods in full knowledge of the results. Such a re-analysis in full knowledge of the results carries the risk of introducing bias that can compromise the integrity of a study.

The CHMP therefore concluded that the possibility that significant bias had compromised the validity of the results of this study could not be ruled out. In addition, the CHMP noted that data generated in study S2 have not established the long term efficacy of Symbioflor 2 beyond 8 weeks of treatment.

Finally, the value of an observational study in children and adolescents for substantiating the efficacy of the product in this patient population is limited. Data were not controlled and did thus not account for the contribution of spontaneous fluctuations of IBS symptoms or for a placebo response in the assessment of the benefit-risk of Symbioflor 2. Proof of the efficacy of Symbioflor 2 in this patient population would have required a prospective, double-blinded, randomized and placebo-controlled trial as per the guideline CPMP/EWP/785/97 in force at the time of the conduct of the study. The CHMP concluded that this study cannot be regarded as adequately supporting an indication for Symbioflor 2 in this age group. In the absence of relevant data submitted by the MAH and in view of the uncertainties about proof of efficacy in Study S2, the CHMP concluded that these results cannot be extrapolated from adults to children or to adolescents. The SmPC was amended to reflect that efficacy in children has not been established.

In summary, in the absence of valid statistical evaluation and given the risk of bias and the paucity of elements contributing to support the robustness and the strength of the results (the evidence being based on a single pivotal trial), the CHMP was not able to confidently draw a conclusion with regards to the efficacy of Symbioflor 2 in IBS or a sub-type of IBS. On this basis and considering the absence of new data since the initial marketing authorisation, the CHMP considered changes to the product information to include the information of this review necessary. Furthermore, the CHMP requested that the MAH conduct a well-designed and adequately powered multi-centre, double blind, randomised, placebo controlled post approval efficacy study allowing for relevant subpopulation analyses to assess the efficacy of Symbioflor 2 in the treatment of IBS in general versus subtypes of the disease such as IBS C and IBS D, gender, disease severity and address the sustainability of efficacy to confirm the efficacy of Symbioflor 2 in IBS.

In the clinical development program, there were respectively 50 adverse drug reactions reported in the Symbioflor 2 group, and 44 in the placebo group for Study S2 in 79 patients. The adverse events were generally benign in nature, and mostly restricted to the gastrointestinal tract (such as abdominal pain and nausea) or related to the occurrence of skin efflorescences. This relatively benign safety profile was confirmed by post-marketing data.

No adverse events were reported in the observational study conducted in children and adolescents. The CHMP was of the opinion that a significant number of adverse events would have been expected to be reported in this study due to the underlying disease regardless of the safety profile of Symbioflor 2. This study therefore cannot be considered to contribute to further establishing the safety profile of Symbioflor 2.

The CHMP noted that in the clinical development program no data were available for treatment beyond 8 weeks. From post-marketing experience, only 18 adverse reactions have been reported to Eudravigilance for Symbioflor 2, covering both the treatment of IBS and other functional gastrointestinal disorders despite significant exposure over several decades of marketing and the pharmacovigilance system put in place by the MAH since the early 2000. Finally, the CHMP noted that the total number of reports was low, and as per the Weber effect, a decline in reporting of adverse events is likely over time. It is therefore unlikely that post-marketing data will provide significant further information on the safety profile of Symbioflor 2 in the treatment of IBS. In general, the CHMP was of the opinion that, although the reporting might have been suboptimal and uncertainties remain with regards to the nature and frequency of the adverse events occurring with Symbioflor 2 in order to fully characterize its safety profile and notably its long term safety profile, the analysis of the safety data did not raise particular concerns. However, indirect risks associated with the intake of a potentially inefficacious medication for IBS with regards to continued impairment of quality of life and potential consequences regarding work- and health-care-seeking -related behaviour need to be considered.

The CHMP agreed with the MAH's proposal to amend the product information to include the information of this review and concluded that, considering its long presence on the market with limited adverse drug reactions reporting, the safety profile of Symbioflor 2 is generally expected to be benign.

Grounds for CHMP opinion

Whereas,

- The CHMP considered the procedure under Article 31 of Directive 2001/83/EC for Symbioflor 2 (*Escherichia coli* bacteria (cells and autolysate)) and associated names (Symbioflor 2);
- The CHMP reviewed all available data from clinical studies, published literature, post-marketing experience, including responses and communications submitted by the MAH in writing, on the efficacy and safety of Symbioflor 2 in their proposed indications and sought as well views of the ad hoc expert group on Symbioflor 2;
- The CHMP considered that "functional gastrointestinal disorders" is a heterogeneous group of individual diseases with a wide range of different underlying pathophysiologies and symptoms that require different treatment modalities. The CHMP acknowledged the MAH's proposal to delete this indication as, in the absence of any data to support the treatment of functional gastrointestinal disorders, a positive benefit-risk balance of Symbioflor 2 could not be established;
- The CHMP was of the opinion that, although the results of Study S2 seemed to suggest possible efficacy of Symbioflor 2 in IBS in adult patients, the possibility that significant bias had been introduced compromising the validity of the results could not be ruled out. In addition, in the absence of valid statistical evaluations and given the paucity of elements contributing to support the robustness and the strength of the results, the CHMP was, neither able to draw reliable conclusions with regards to the efficacy of Symbioflor 2, nor to establish whether Symbioflor 2 is efficacious in IBS in general or any sub-type of IBS. However, the CHMP concluded that there were

no new elements to motivate a change in the established benefit risk balance since the initial marketing authorisation for Symbioflor 2 in adult patients for the treatment of IBS;

- The CHMP also noted that results of the observational study in children older than 4 years with IBS suggested a possible efficacy of Symbioflor 2. Data, however, were not controlled. The value of an observational study for substantiating the efficacy of the product in this patient population is limited and therefore the CHMP concluded that this study could not be regarded as adequately supporting the efficacy of Symbioflor 2 in this age group. In the absence of relevant data submitted by the MAH to support the paediatric use and in view of the uncertainties about the benefit-risk in Study S2 conducted in adult patients only, the CHMP concluded that extrapolation of the results from adults to children or adolescents was not justified. In this regards, the SmPC is amended to reflect that efficacy in children has not been established;
- Acknowledging the limitations of the established efficacy profile of Symbioflor 2, the CHMP requested the MAH to conduct a well-designed and adequately powered multi-centre, double blind, randomised, placebo controlled post approval efficacy study allowing for relevant subpopulation analyses to confirm the efficacy of Symbioflor 2 in the treatment of IBS in general versus subtypes of the disease such as IBS C and IBS D, gender, disease severity and address the sustainability of efficacy to confirm the efficacy of Symbioflor 2 in IBS;
- Considering available safety data from the clinical trial and post-marketing experience with Symbioflor 2, the CHMP came to the conclusion that the demonstrated risks were overall low.

CHMP opinion

Based on the review of all available data in the framework of this Article 31 procedure, the CHMP concludes that there are no new elements since the granting of the marketing authorisation for Symbioflor 2 (*Escherichia coli* bacteria (cells and autolysate)) and associated names, and therefore the previous conclusion of the national competent authorities on a positive benefit-risk balance remains unchanged. The CHMP recommends amendments to the product information and in view of the limitations of the currently available efficacy data for Symbioflor2 in the treatment of irritable bowel syndrome (IBS), the CHMP is of the view that a post-authorisation efficacy study should be conducted. Therefore, the CHMP recommends a variation to the terms of the marketing authorisation.