NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC

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This notification is a referral under Article 31 of Directive 2001/83/EC to the CHMP made by the Member State DE:

Product Name (s) in the referring Member State if applicable	Symbioflor 2
Active substance(s)	Escherichia Coli bacteria (cells and autolysate)
Pharmaceutical form(s)	Suspension for oral administration
Strength(s)	All
Route of administration(s)	All
Marketing Authorisation Holder(s) in the referring Member State	Symbiopharm GmbH, Herborn, Germany

Background

The medicinal product under consideration, Symbioflor 2, is a suspension containing 1.5-4.5 x 10^7 Escherichia coli which are partly autolysed and partly presented as living bacteria and composed of 10 different strains. It has been on the market in Germany since 1954. In 1975 the medicinal product was placed on the market in Austria.
In addition to the marketing in Germany and the marketing authorisation in Austria, the medicinal product is also authorised in Hungary and available in some other Member States.

Since the medicinal product was placed on the market before the entry into force of the German Drug Law in 1978 (AMG), the medicinal product had to undergo the renewal procedure according to § 105 German Drug Law in order to achieve the conformity of the (provisional) authorisation in Germany with the Union legislation. According to the provisions of the cited paragraph of the Germany Drug Law (subparagraph 4c), the applicant was referring to an existing authorisation in another country of the EU (Austria). According to this subparagraph, the German National Authority had to mutually recognise the existing EU authorisation(s) - without the obligation of the Reference Member State to provide an assessment - unless there is a "risk to public health". Therefore an independent assessment of the dossier was undertaken by the German NCA in order to conclude whether a "risk to public health" could be associated with the use of the product.

Issues to be considered

Based on the evaluation of the available evidence at that time in the claimed indications ("functional gastrointestinal diseases", "irritable bowel syndrome"), the application was refused by the BfArM in 2005 due to the lack of sufficient evidence to establish a positive benefit risk balance in the claimed indications which led to the conclusion of a potential clinically relevant risk associated with the use of the product. The applicant has made a renewed attempt to claim the recognition of the Austrian authorization which was filed to the BfArM on 26th August 2014 according to the above cited § 105 (4c) German Drug Law.

The concerns with regard to the lack of sufficient evidence to establish a positive benefit risk balance are detailed as follows:

1. Therapeutic efficacy of the compound has not been adequately demonstrated:

For the claimed indication "functional gastrointestinal diseases", the indication term as such is not regarded to re-present an acceptable indication claim due to the heterogeneity of the total of all functional gastrointestinal diseases, ranging from functional oesophageal, gastric, intestinal, biliary, pancreatic to functional anorectal disorders, with a wide range of different underlying pathophysiologies and symptomatic entities. In addition, no adequate scientific evidence in support of this claim has been presented by the applicant who therefore has not established a positive benefit /balance for the claimed indication.

For the claimed indication "irritable bowel syndrome" (IBS), the applicant has presented as evidence for efficacy one clinical phase 3 study. This was a randomised, multi-centre, placebo-controlled study with a duration of 8 weeks conducted in the year 1988 in Germany (published in Germany language as: Schaffstein, W. and Burkard, I.: Symbioflor 2 – Eine therapeutische Alternative zur Behandlung des irritablen Kolons. Jatros Gastroenterol. 2/4

(1993)).
The protocol for this study included insufficient determinations of major features such as the definition of the primary evaluation and the statistical methods. In addition, major deviations from the study protocol were also identified. Study participants were included outside the protocol defined "Kruis criteria". The protocol itself defined about 20 clinical endpoints consisting of all sorts of gastrointestinal symptoms, physical examination results, and global scores of well-being. A hierarchy of the endpoints, and statistical methods for evaluation were not defined. Most of the evaluations presented in the study report did not show relevant differences between the active treatment group and placebo. The claim for efficacy was mainly based on the global score for efficacy as of the physician, for which a statistically significant result was achieved.
The results of the study were rejected based on these major deviations with the protocol which does not allow relying on the study, in particular due to unclear patient population with a doubtful presence of IBS, and unclear statistical methods used, unclear evaluation strategy and the poor overall results achieved.
A complete re-evaluation of this study was presented by the applicant, which allegedly had fully considered the CHMP points to consider (on IBS) (defining "responder criteria"), and which for the first time defined statistical methods and described the evaluation strategy properly. Statistically significant differences in the majority of the newly defined efficacy parameters were postulated.
The main reasons for the rejection of this re-evaluation were the following: the re-evaluation was regarded to represent a post-hoc evaluation under knowledge of the results of the study, which could have substantially biased the results. Moreover, significant irregularities in the conduct of the clinical trial were identified which casts doubts on the GCP compliance and therefore the use of these data to support the application In addition, the study showed statistically significant center effects, with a high dependency of the overall results on the results in one of the centers involved.

2. The treatment of IBS (and the total entity of functional gastrointestinal disorders) with a potentially non-efficacious medication leads to potential clinically relevant risks that could result in a persistence of disability or incapacity. In particular:

- IBS is associated with a reduction of Quality of Life which shows relevant deteriorations in all domains of Quality of Life compared to healthy individuals and shows lower scores in part of the domains compared to patients with diabetes mellitus, end-stage renal disease, COPD, congestive heart failure, or ischemic heart disease (Lea R and PJ Whorwell: Quality of Life in Irritable Bowel Syndrome. Pharmacoeconomics 2001; 19: 643-653; ten Berg MJ et al: Quality of life of patients with irritable bowel syndrome is low compared to others with chronic diseases. Eur J Gastroenterol Hepatol 2006; 18: 787-792)
- The high impact of IBS on patients' daily life is further illustrated by the finding that IBS is the most common cause for absenteeism from work after the common cold and leads to a significant loss of working days, time off from work in order to seek health services, and days with early termination of work. A relevant loss of productivity has been associated with IBS. (Drossman DA et al: U:S: householder survey of functional gastrointestinal disorders Dig Dis Sci 1993; 38: 1569-1580; Spinelli A : Irritable Bowel Syndrome. Clin Drug Invest 2007; 27: 15-33.)
- IBS has also been associated with increased rates of surgery of the gut, female reproductive organs and others. Compared to a healthy control population, IBS-

patients have a 2-3-times increased rate of cholecystectomies, 1.5-times increased rate of appendectomy, a 1.6-1.7-times increased rate of hysterectomies, and a 22% increase in surgery of the spine. (Longstreth, G Fand JF Yao: Gastroenterology 2004; 126: 1665-1673; Haler W Land P Schooenfeld: Aliment Pharmacol Ther 2003; 17: 997-1005).

- "Undertreatment" or non-treatment with a medicinal product with non-established efficacy will therefore lead to prolonged incapacity with a significant impact on the quality of life of the patients as well as potential unnecessary surgical intervention.

Following the rejection of the application, the applicant filed a legal action against the BfArM administrative decision. Of note, the applicant reiterated its claim to be granted a German National marketing authorisation based on the first renewal of the medicinal product allegedly in line with the Acquis Communautaire in Austria in 2012.

In view of the abovementioned concerns and considering that the medicinal product is authorised in other Member States, it is in the interest of the Union to protect patients from the above described risks which cannot be justified by an adequate benefit and to refer the matter to the CHMP requesting its opinion under Article 31 of Directive 2001/83/EC as to whether the benefit-risk balance of this medicinal product is favourable and whether the marketing authorisations should be maintained, varied, suspended, or revoked.

Signed

30.3.2016

Date [redacted]