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To whom it may concern

EXPERT JUSTIFICATION
on the classification of the medicinal product for medical use

1. Introduction

The following expert justification was performed in order to justify the innovative (original) status of medicinal product Monural®, INN: Fosfomycin, granules for preparation of solution for oral administration 2 g, 3 g Registration Certificate П N012976/01 (hereinafter referred to as "MP"), Marketing Authorization Holder (hereinafter referred to as "MAH") Zambon Switzerland Ltd, Switzerland (hereinafter referred to as "Zambon").

2. Legal basis

The review is performed in frames on the current legislation of the Eurasian Economic Union (hereinafter referred to as "Union") in part of the Union's legislation on medicinal drugs, namely the Decision of the Eurasian Economic Commission (EEC) Council № 78 dated 21.11.2016 with actual amendments in force as of March 2024; current legislation of the Russian Federation on the medicinal drugs, namely the Federal Law № 61-FZ "On Circulation of Medicines" dated 12.04.2010 with actual amendments in force as of February 2024. The list of key references of the legal basis is presented below:

1) Decision of EEC Council № 78 dated 21.11.2016. "On the Rules of Registration and Examination of Medicinal Products for Medical Use", Sect. II p.19
2) Federal Law № 61-FZ "On Circulation of Medicines" dated 12.04.2010 as amended by the Federal Law № 475-FZ dated 27.12.2019, Art.4, p.10.1

3. Review of the available data

3.1. Original medicinal product: definition and criteria

As per the applicable legal references listed above:

Original medicinal product - medicinal product having new active substance, which was registered and entered the global pharmaceutical market for the first time, based on the dossier containing results of full preclinical (non-clinical) and clinical studies confirming the quality, safety, and efficacy of the product (Decision of EEC Council № 78 dated 21.11.2016. "On the Rules of Registration and Examination of Medicinal Products for Medical Use", Sect. II p.19). Original medicinal product is medicinal product with a new active substance, which was first registered in the Russian Federation or in foreign countries based on the results of preclinical studies of medicinal products and clinical studies of medicinal products confirming its quality,

efficacy and safety (Federal Law № 61-FZ "On Circulation of Medicines" dated 12.04.2010 as amended by the Federal Law № 475-FZ dated 27.12.2019, Art.4, p.10.1).
As per the definitions provided above, a medicinal product corresponding to the following criteria fall into the category of original medicinal products:

1) First registration of a medicinal product with new active substance in the world.
2) Existence of complete preclinical and clinical studies that confirm the quality, efficacy and safety of the medicinal product. The results of the studies should support the first registration.
3) In case of the national registration in Russia as per the Federal Law № 61-FZ "On Circulation of Medicines" - first registration of the medicinal product with new active substance in Russia (that can replace the criterion 1)

3.2. Criteria of original medicinal product applicable to the MP

3.2.1. First registration of a medicinal product with new active substance in the world.

Dates of first registrations in the world for medicinal products are recorded using term “International Birth (Registration) Date” (IBD). European Medicines Agency has the registry of validated IBD records for all medicinal products that were registered in the world.

The above-mentioned MP is the medicinal product with new active substance, which was the first registered in the world and entered pharmaceutical market under the trade name "Monuril®" (INN: Fosfomycin, new active substance - Fosfomycin trometamol), having International Registration Date (IBD) on **August, 27th, 1986**, as per the official record of the European Medical Agency.

3.2.2. Existence of complete preclinical and clinical studies that confirm the quality, efficacy and safety of the medicinal product, supporting the first registration.

The medicinal product was registered on the basis of the dossier containing the results of full preclinical and clinical studies of the originator of the medicine (Zambon S.p.A., Italy) confirming the quality, safety and efficacy of the first registered medicinal product with new active substance, which is confirmed by the relevant reports of the originator of this medicine, as well as by the data of published research results, which are the property of the originator of the MP for the purpose of the first registration in the world and subsequent extensions of the registration of the MP containing new active substance.

The holder of the Registration Certificate in the Russian Federation for the MP (Zambon) is the legal successor of the originator acting on behalf of the originator in the Russian Federation, also being a member of Zambon Group of companies.

As per the dossier provided by the MAH, full set of preclinical and clinical studies were performed/sponsored by the originator of the MP to confirm its quality, safety and efficacy. The studies reports were used for the first registration of the medicinal product with new active substance in the world.

As per the dossier several key studies from both preclinical and clinical parts were chosen and are listed below.

The references for main preclinical studies performed by the originator of the MP for the first registration and its extension, as well as follow-up studies during the product life cycle are presented below:

Pharmacology

Primary Pharmacodynamics

- Stapley et al., 1970 [4.3.44];
- Kahan et al. 1974 [4.3.28];
- Albini et al., 1988 [4.3.3];
- Carlone et al., 1987 [4.3.13].

Antimicrobial Activity

- Pinasi et al. 1987a [4.3.37];
- Reeves et al. 1988a [4.3.39];
- Wise and Andrews 1988 [4.3.48];
- King and Phillips 1988 [4.3.30];
- Barry and Fuchs 1991 [4.3.8];

Bactericidal Activity

- Albini *et al.*, 1986a [4.3.1];
- Albini *et al.*, 1986b [4.3.2];
- Cornaglia *et al.*, 1988 [4.3.14];
- Gismondo *et al.*, 1986 [4.3.20];
- Greenwood 1986a [4.3.22];
- Lerner *et al.*, 1988 [4.3.31];
- Pinasi *et al.*, 1987a [4.3.37];
- Ravizzola *et al.*, 1987 [4.3.38];
- Reeves *et al.* 1988a [4.3.39];
- Rossi *et al.*, 1988 [4.3.41];
- Wiedemann and Groos, 1987 [4.3.47]);

Assessment of resistance

- Naber and Thyroff-Friesinger, 1992) [4.3.36];
- Schito et al., 1993 [4.3.42];
- Barry and Fuchs, 1991 [4.3.8];
- Greenwood et al. 1992b [4.3.26];

Pharmacokinetics

Absorption

- Albini, 1985b [4.2.2.2.1 Study # RT 4/85];
- Albini, 1985c [4.2.2.2.2 Study # RT 11/85];
- Bergan *et al.*,1993 [4.3.10];
- Kleeman and James, 1994a [4.2.2.2.4 Study # 6277-123];
- Shimizu et al., 1977 [4.3.43].

Distribution

- Fornasini *et al.*, 1992 [4.2.2.3.1 Study # 8001];
- Fornasini *et al.*, 1991 [4.2.2.3.2 Study # 8002];
- Longo *et al.*, 1981 [4.3.34].

Metabolism

- Fornasini et al., 1991 [4.2.2.3.2 Study # 8002];
- Longo et al., 1981 [4.3.34].

Excretion

- Albini, 1985b [4.2.2.2.1 Study # RT 4/85];
- Albini, 1985c [4.2.2.2.2 Study # RT 11/85];
- Fornasini et al., 1992 [4.2.2.3.1 Study # 8001];
- Longo et al., 1981 [4.3.34];
- Shimizu et al., 1977 [4.3.43].

Safety Pharmacology

- Carenzi *et al.*, 1991a [4.2.1.3.1 Carenzi 1991a].

Drug Interactions

Interaction studies with antibacterial drugs

- Albini and Schioppacassi, 1991a [4.2.1.4.1 Albini 1991a];
- Albini and Schioppacassi, 1991c [4.2.1.4.3 Albini 1991c];
- Albini and Schioppacassi, 1991g [4.2.1.4.7 Albini 1991g];
- Albini and Schioppacassi, 1992c [4.2.1.4.10 Albini 1992c].

Effect of fosfomycin trometamol on commonly used drugs

- Carenzi *et al.*, 1991b [4.2.1.4.11 Carenzi 1991b].

Effect of commonly used drugs on fosfomycin trometamol

- Albini and Schioppacassi, 1991b [4.2.1.4.2 Albini 1991b];
- Albini and Schioppacassi, 1991d [4.2.1.4.4 Albini 1991d];
- Albini and Schioppacassi, 1991e [4.2.1.4.5 Albini 1991e];
- Albini and Schioppacassi, 1991f [4.2.1.4.6 Albini 1991f];
- Albini and Schioppacassi, 1992a [4.2.1.4.8 Albini 1992a];
- Albini and Schioppacassi, 1992b [4.2.1.4.9 Albini 1992b].

Toxicology

Single-dose toxicity

- Ornaghi and Ferrini, 1989a [4.2.3.1.1 Study # 1217];
- Ornaghi and Ferrini, 1989b [4.2.3.1.2 Study # 1216];
- Ornaghi and Ferrini, 1989c [4.2.3.1.3 Study # 1215];
- Ornaghi and Ferrini, 1989d [4.2.3.1.4 Study # 1213];
- Ornaghi and Ferrini, 1989e [4.2.3.1.5 Study # 1214];
- Marubini and Ferrini, 1989 [4.2.3.1.6 Study # 1218];

Repeated-dose toxicity

- Auletta and Carol, 1994 [4.2.3.2.5 Study # 93-3181];
- Bonanomi, 1982 [4.2.3.2.6 Study # 8];
- Kelly, 1989 [4.2.3.2.2 Study # 88-3324];
- Kleeman and James, 1994b [4.2.3.2.3 Study # HW1 6277-124];

Genotoxicity

- Pinasi, 1989 [4.2.3.3.1.1 Study # 1212];
- Seeberg, 1989 [4.2.3.3.1.3 Study # 116020-M-07688];

- Mosesso, 1989 [4.2.3.3.1.2 Study # 116022-M-07888];
- Pinasi, 1987b [4.2.3.3.2.1 Study # 1159];

Reproductive and development toxicity

- Hoberman, 1994a [4.2.3.5.1.2 Study #T/3700/0002];
- Bonanomi, 1993a [4.2.3.5.1.1 Study TR36];
- Hoberman, 1994b [4.2.3.5.2.2 Study #T/3700/003];
- Bonanomi, 1993b [4.2.3.5.2.1 Study TR 28];
- Hoberman, 1994c [4.2.3.5.2.4 Study #T/3700/0004];
- Bonanomi, 1993c [4.2.3.5.2.3 Study TR 37];
- Hoberman, 1994d [4.2.3.5.3.2 Study #T/3700/0005];
- Bonanomi, 1993d [4.2.3.5.3.1 Study TR 32];

Local tolerance

- MacRae 1985 [4.2.3.2.4 Study # 52/55-0-116-003/T/023/85];

Main/pivotal clinical studies of the originator of the MP for the first registration and its extensions:

Clinical efficacy

Table 1: Bacteriological efficacy of fosfomycin trometamol given as a single dose for urinary infection in open studies.

Study	Condition	N° patients	Follow-up	Bacteriological eradication. Patient number (%)
Bailey, 1988	Uncomplicated UTI	25	7 days	14/18 (78%)
Neumann et al. 1985	Uncomplicated UTI	48	3 weeks	46/48 (96%)
Neumann et al. 1987; published in Neumann and Rufin, 1987	Uncomplicated UTI with less sensitive bacteria	18	4 weeks	12/18 (66%)
Moroni et al. 1987	Uncomplicated UTI	91	4 weeks	72/91 (79%)
Swiss Multicenter Trial	Uncomplicated UTI	2,158	7 days	1,141/1,268 (90%)

Clinical safety

The clinical safety profile of fosfomycin trometamol in the treatment or prophylaxis of UTI was evaluated in 1,760 patients in double-blind, double-dummy controlled studies (Selvaggi et al. 1990, Boerema and Willems 1988, Richaud 1989, Asscher et al. 1991, Van Pienbroex et al. 1993, Boerema et al. 1987, MON-US1 - Kraus 1994; MON-US 2- Harnack 1994; MON-US 3 - Bowman, 1994; Rudenko et al. 2005; Baert et al. 1990); 1,480 in open controlled stud-ies (Jardin 1987; Reynaert 1988; Pontonnier 1988; Neu 1990; Naber and Thyroff-Friesinger 1990; Cooper at al. 1990; Crocchiolo 1990; Gianella et al. 1991; Elhanan et al. 1984; Dejonck-heere

et al. 1988; Zinner 1990; de Jong et al. 1991; Bayrak et al. 2007; Estebanez et al. 2009; Usta et al. 2011; Palmieri et al. 1988; Ferraro et al. 1990; Mozdzan et al. 2007; Periti et al. 1988); 5,580in non-controlled studies (Bailey et al. 1988; Moroni 1987; Moroni 1987a; Neu-mann et al. 1985; Neumann and Rufin 1987; Bonfiglio et al. 2005; Ferreira 2003; Pullucku 2007; Reid 2013, Qiao 2013; Mac Gowan et al. 1990; Di Silverio 1988; Di Silverio 1990). Among all the above-mentioned patients, 133 were elderly (Palmieri et al. 1988; Ferraro et al. 1990; Mozdzan et al. 2007; Mac Gowan et al. 1990), 1,278 treated prophylactically (Baert et al. 1990; Periti et al. 1988; Di Silverio et al. 1988; Di Silverio et al. 1990; Rudenko et al. 2005; Monuril™ Study Group Switzerland, 1989) and 1,335 pregnant women (Moroni 1987; Zinner 1990; Krcmery et al. 2001; Bayrak et al. 2007; Estebanez et al. 2009; Usta et al. 2011; Ferreira 2003) .

As per the registration rules that were in place of 35-40 years ago in the originator's country of origin (Italy) and the country of the first registration, the dossier requirements were different in comparison to the actual ones. That fact does not prevent to consider that the results of the studies provided by MAH confirming the quality, safety and efficacy of the new medicinal product for the first registration in the world were sufficient and appropriate, resulting in successful registration expertise performed by the authorized regulatory body of the country of the first registration.

The publications of some studies that were performed to support the first registration are chronologically dated post-registration, that does not contradict to the fact that corresponding studies were performed and used by MAH (before the publication in scientific literature) to proof the quality, efficacy and safety of the MP for its first registration in the world.

3.2.3. First registration of the medicinal product with new active substance in Russia

Monural®, powder for preparation of oral suspension 3 g (sachets), was the first registered medicinal product in the Russian Federation having the new active substance (INN: Fosfomycin), that is confirmed by the registry entry №005945 dated 11.04.1995 presented in the State Register of Medicines (ГРЛС), of 01.11.1998 edition.

4. Conclusion

The data reviewed above allow to unambiguously state that medicinal product Monural®, INN: Fosfomycin, granules for preparation of solution for oral administration 2 g, 3 g, Registration Certificate П N012976/01 fully corresponds to the criteria of original medicinal product and therefore should be categorized as original medicinal product.

5. References

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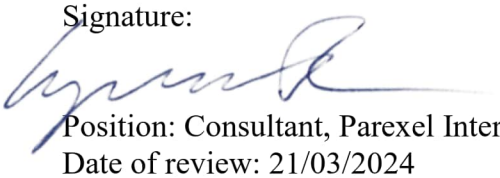

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