World Health Organization

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In reply please refer to: CPH 41/MS/SC/TB168

Your reference:

Digitally signed by Moraru Grigore
Date: 2023.10.17 16:34:13 EEST
Reason: MoldSign Signature
Location: Moldova

Mr Rakesh Chaurasia
Deputy General Manager
- Drug Regulatory Affairs
Macleods Pharmaceuticals Limited
Atlanta Arcade, 3rd Floor, Church Road
near Leela Hotel
Andheri-Kurla Road
Andheri (East)
Mumbai 400 059
Inde

11 April 2008

Dear Mr Chaurasia,

Prequalification Programme: Priority Essential Medicines

Product Reference Number: **TB168** *Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150/75/400/275 mg film-coated Tablets*

This letter is for the **quality** part of the above-mentioned dossier only.

Thank you for submitting the data and information requested for the assessment of the product dossier within the Prequalification Programme of United Nations agencies. A team of evaluators recently assessed the dossier you submitted.

As a result of this assessment, you are kindly requested to submit the following data and information as this was not covered in the product dossier.

The Quality Part of the dossier for **TB168** - Rifampicin/Isoniazid Pyrazinamide/Ethambutol Hydrochloride 150/75/400/275 mg film-coated tablets is prequalified under the following details submitted in the dossier and approved by WHO.

It is important that you note that other parts of the dossier are still under assessment. In particular, the WHOPAR still has to be reviewed, which may result in changes being made to documents such as the Summary of Product Characteristics (SmPC), the Patient Information Leaflet (PIL) and the Label texts. Accordingly, you are strongly advised not to initiate bulk production (printing) of these documents until the remainder of the Prequalification Assessment stages has been completed.

Batch number(s) of the FPPs used in			
Bioequivalence studies (approved batch size)	RF 501		
Stability studies (approved batch size)	RF403, RF404	RF405	RF406
Validation studies (approved batch size):	RF404	RF405	RF406

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Composition of bioequivalence, primary stability and production FPP batches								
Ingredients	Administration Unit		Bioequivalence RF 501		Primary stability RF 405		Production RF 406	
	mg	%*	kg	%*	kg	%*	kg	%*
Core tablet								
Ethambutol Hydrochloride BP	275.0	26.41	130.63	26.41	130.63	26.41	130.63	26.41
Pyrazinamide BP	400.0	38.42	190	38.42	190	38.42	190	38.42
Isoniazid BP	75.0	7.20	35.62	7.20	35.62	7.20	35.62	7.20
Rifampicin BP	150.0	14.41	74.81	14.41	74.81	14.41	74.81	14.41
Shellac (Golden) BP	7.0	0.672	3.33	0.672	3.33	0.672	3.33	0.672
Purified Talc BP	20.0	1.92	9.50	1.92	9.50	1.92	9.50	1.92
Povidone (PVP K-30) BP	2.0	0.192	0.95	0.192	0.95	0.192	0.95	0.192
Disodium Edetate BP	0.5	0.05	0.2375	0.05	0.2375	0.05	0.2375	0.05
Colloidal Silicon Dioxide BP	5.0	0.48	2.38	0.48	2.38	0.480	2.38	0.480
Maize Starch BP	7.0	0.672	3.32	0.672	3.32	0.672	3.32	0.672
Croscarmellose Sodium BP	35.0	3.36	14.25	3.36	14.25	3.36	14.25	3.36
Crospovidone BP	16.0	1.53	6.41	1.53	6.41	1.53	6.41	1.53
Calcium Stearate BP	7.50	0.72	3.56	0.72	3.56	0.72	3.56	0.72
Subtotal 1	**1000**	**96.04**	**475.00**	**96.040**	**475.00**	**96.040**	**475.00**	**96.040**
Purified water BP			Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Isopropyl Alcohol BP			Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Film coat 1*								
Copovidone BP	5.00	0.48	3.56	0.48	3.56	0.48	3.56	0.48
Purified Talc BP	1.00	0.09	0.712	0.09	0.712	0.09	0.712	0.09
Film coat 2*								
Hypromellose BP	12.00	1.15	8.55	1.15	8.55	1.15	8.55	1.15
Castor Oil BP	4.875	0.46	3.48	0.46	3.48	0.46	3.48	0.46
Diethyl Phthalate BP	1.50	0.14	1.07	0.14	1.07	0.14	1.07	0.14
Titanium Dioxide BP	7.50	0.72	5.34	0.72	5.34	0.72	5.34	0.72
Magnesium Stearate BP	0.375	0.03	0.266	0.03	0.266	0.03	0.266	0.03
Purified Talc BP	8.75	0.84	6.22	0.84	6.22	0.84	6.22	0.84
Colour Sunset Yellow	0.22	0.02	0.156	0.02	0.156	0.02	0.156	0.02
Subtotal 2	**41.22**	**3.96**	**29.354**	**3.96**	**29.354**	**3.96**	**29.354**	**3.96**
Grand total	**1041.22**	**100.0**	**494.57**	**100.0**	**494.57**	**100.0**	**494.57**	**100.0**
Isopropyl Alcohol BP			Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Dichloromethane BP			Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Equivalence of compositions or justified differences			The compositions of the bioequivalence, stability and validation batches are the same.					
* Process loss has been disregarded in the calculation of batch quantities of excipients for film coating.								

1. **Labelling for storage**: Do not store above 25 °C, store in a dry place, protect from light.
2. **Nature and contents of container**: Transparent LDPE bag, in a triple laminated aluminium sachet packed in an HDPE and sealed with Aluminium tagger, containing 500 or 1000 tablets.
3. **Shelf life of FPP**: 24 months.
4. **Manufacturing site of FPP**:
   Macleods Pharmaceutical Limited
   Plot No. 25-27, Survey No. 366
   Premier Industrial Estate
   Kachigam, Daman – 396 210 (UT), India
5. **Batch size of FPP**: 475 000 tablets.

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6. Manufacturing site of Ethambutol hydrochloride:

a. Lupin Laboratories Ltd
124, GIDC Estate
Ankeleshwar-393 002
Gujarat, India

b. Themis Medicare Limited
Plot No. 69/A, G.I.D.C.
Industrial Estate, Vapi (District Valsad)
Gujarat, India

Isoniazid:

Amsal Chem Private Limited
A1/410-403, G.I.D.C. Industrial Area
Ankleshwar, District Bharuch-393 002
Gujarat, India

Pyrazinamide:

Calyx Chemicals & Pharmaceuticals Pvt Ltd
N/102, MIDC Tarapur
Boisar, Thane-401 508
India

Rifampicin:

Novartis India Ltd
Sandoz Business Unit
Plot No. L-1, Additional Phase
MIDC, Mahad - 402301
Dist: Raigad, Maharashtra, India

7. Retest period of:

Ethambutol hydrochloride:

60 months (Lupin); 24months (Themis)

Isoniazid: 24 months

Pyrazinamide: 36 months

Rifampicin: 36 months

8. API Specification Reference Number and/or Version:

Ethambutol hydrochloride: SPC/RE-0018-01

Isoniazid: SPC/RI-0011-02

Pyrazinamide: SPC/RP-0028-02

Rifampicin: SPC/RR-0007-04

9. FPP specification Reference Number and/or Version: SPC/FG-0131-05.

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Note: Please consult the "Guidance on variations to a prequalified dossier" before implementation of any changes to the above and other approved parts of the dossier.

Macleods Pharmaceuticals Limited should submit the draft WHOPAR for TB168; rifampicin/isoniazid/pyrazinamide/ethambutol 150/75/400/275 mg tablets as required by the "Guidance note to Applicants (Manufacturers) on the compilation of the WHO Public Assessment Report" at: http://mednet3.who.int/prequal/WHOPAR.htm

You are reminded that only products and manufacturers that meet the recommended norms and standards, as referred to below, will be included on the list.

- Product dossiers, as specified in the relevant guidelines for the submission of product data and information (as found on the prequalification web page www.who.int/prequal);
- Manufacturing Sites: Good Manufacturing Practices;
- Clinical sites (if applicable): Good Clinical Practices.

It is recommended that you submit the requested additional data and information, as listed above, to the UNICEF Supply Division, at your earliest convenience.

Please ensure that your submission contains all the outstanding information and data requested in the addendum. (All outstanding issues should be addressed in one submission and not be presented as separate submissions.) Kindly ensure that all the outstanding points communicated in previous letters and addenda are covered

Submission of the requested additional data and information:

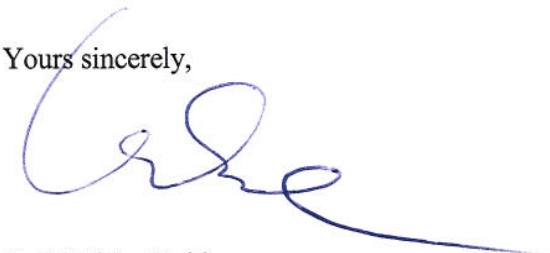
All paper versions of documentation, product samples, CDs and surface mail to the WHO Prequalification Programme should be sent to the following address and all packages/containers should be clearly marked as indicated below.

CONFIDENTIAL
Attention: Dr Matthias Stahl
WHO Prequalification Programme
Product Ref Number:
UNICEF Supply Division
UNICEF Plads – Freeport
2100 Copenhagen
Denmark

For further information regarding the submitted dossier of product **TB168** please use the e-mail address – **prequalassessment@who.int** – and kindly ensure that any such e-mail mentions the corresponding WHO product reference number.

Your cooperation is appreciated.

Yours sincerely,



Dr Matthias Stahl
Quality Assurance and Safety: Medicines
Department of Medicines Policy and Standards