Mutual Recognition Procedure

Type IB variation
Final Variation Assessment Report

Lapimyl
Lacidipinum

PL/H/0563/001-003/IB/007/G

Marketing Authorisation Holder: Mylan Ireland Limited

Date: 25.03.2020

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ADMINISTRATIVE INFORMATION

Name of the medicinal product(s) in the RMS	**Lapimyl**
INN (or common name) of the active substance(s)	*Lacidipinum*
Pharmaco-therapeutic group (ATC code)	C08CA09
Pharmaceutical form(s) and strength(s)	Film-coated tablets, 2 mg, 4 mg, 6 mg

Procedure number	PL/H/0563/001-003/IB/007/G
Member States concerned	IT,UK

RMS contact person	**Name: Katarzyna Szymczykiewicz** Tel: (+48) 22 49-21-564 Email: katarzyna.szymczykiewicz@urpl.gov.pl
Name(s) of the assessors	**Quality:** **Name(s):** Paweł Barucki Tel: (+48) 22 49-21-467 Email: pawel.barucki@urpl.gov.pl

Nature of change/s requested	**- Type IB, category B.I.a.1.z** – Change in the manufacturer of a starting material, TBBA, used in the API manufacture. **- Type IB, category B.I.a.2.e** – Minor change to the restricted part of an Active Substance Master File

Active Substance Master File (ASMF) Assessment Report/s	Assessment of the Responses to the Restricted Part (RP) of ASMF. See an attachment to the FVAR.

I. RECOMMENDATION

Based on the review of the data on quality the RMS considers that the variation following application PL/H/0563/001-003/IB/007/G for the following proposed group of changes: *Change in the manufacturer of a starting material, TBBA, used in the API manufacture; Minor change to the restricted part of an Active*
Substance Master File

is approvable

II. EXECUTIVE SUMMARY

II.1 Scope of the variation

- Type IB, category B.I.a.1.z –
Change in the manufacturer of a starting material, TBBA, used in the API manufacture.

- Type IB, category B.I.a.2.e –
Minor change to the restricted part of an Active Substance Master File

III. ASSESSMENT OF THE RESPONSES TO THE MEMBER STATE(S) REQUEST FOR SUPPLEMENTARY INFORMATION

III.1 Quality aspects

III.1.1 Major objections

None.

III.1.1.1 Active substance (related to additional data provided by the applicant only)

N/A.

III.1.1.2 Medicinal product

None.

III.1.2 Other concerns

III.1.2.1 Active substance (related to additional data provided by the applicant only)

N/A

III.1.2.2 Medicinal product

Type IB, category B.I.a.1.z

1. The proposed change relates to the FPM (Finished Product Manufacturer) dossier and the an appropriate modules (**3.2.S.2.1, 3.2.S.4.4**) in sequence 0025 eCTD, have not been found. It should be submitted and the statement that proposed change relates to the FPM dossier only, should be provided as well. In other case, the correctly filled up Annex 3 for the Applicant's Part of ASMF (see CHMP/QWP/227/02 Rev 4 guideline), should be provided by the Drug Substance Manufacturer.

Summary of the Applicant's response

Response:

Applicant acknowledges the agency's comment. We would like to inform agency that 3.2.S.4.4 section of finished product manufacturer with batch analysis data of recent batches from finished product manufacturer has been provided with this response.

Applicant wish to clarify the agency that the proposed changes are related to the key starting material and information related to the key starting materials may be confidential and part of restricted part of ASMF only. Hence, this change doesn't affect 3.2.S.2.1 of finished product manufacturer and also there are no changes related to intermediate manufacturers as well.

Please be informed that the correctly filled up Annex 3 has been submitted by ASMF holder via CESP number - CESP_Submission_1129644.

The Applicant has accepted remark of the Polish authority and explained that section 3.2.S.4.4. of FPM's dossier with test results for drug substance has been amended to the responses. Moreover, the applicant has explained, the following variation relates to the starting materials and an appropriate statement has been provided as well. According to the explanation, section 3.2.S.2.1 has not been affected by the following variation and no other changes have not been introduced.

Assessment of the Applicant's response
The problem has been resolved.

2. QP declaration concerning addition an alternative intermediate (TBBA) manufacturer, should be provided.

Summary of the Applicant's response

Response:

Applicant acknowledges the agency's comment. As per discussions with the agency, requested declarations from drug substance manufacturer are provided along with this response document since TBBA is not an intermediate and it is a Key starting material.

Please find the attached annexure I.

The Applicant has submitted QP declaration from the drug substance manufacturer.

Assessment of the Applicant's response
The problem has been resolved.

3. According to the addition an alternative manufacturer of TBBA intermediate, the compliance of Lapimyl medicinal product with the ICH Q3D Elemental impurities guideline should be confirmed by providing an updated summary of the risk analysis of metal contamination (full assessment should be at the manufacturing site of the medicinal product) and conclusions related to the requirements in the specification of the medicinal product (see also 'Elemental impurities in marketed products Recommendation for implementation "on the EMA website). Please note that the Q3D guideline from 01/01/2018 is a requirement of Ph.Eur. (Supplement 9.3).

Summary of the Applicant's response

Response:

Applicant acknowledges the agency's comment and would like to clarify that TBBA is a key starting material and not an Intermediate. However, the Elemental impurity risk assessment after addition of alternative manufacturer for TBBA which is a Key starting material is provided along with the response package. Elemental impurity risk assessments are provided as annexure - II along with this response. Updated 3.2.P.5.6 also provided along with this.

The Applicant has submitted a Risk Assessment Report of Elemental Impurities in Lacidipine Tablets dated on 29.12.2017 and amended to the responses. Documentation can be accepted.

Assessment of the Applicant's response
The problem has been resolved.

Type IB, category B.I.a.2.e

General notice:

1. The submission letter provided from Dr.Reddy's Laboratories Limited and dated on 20 December 2019, has been filled up incorrectly. The Administrative Details do not cover list of proposed changes in Restricted Part of ASMF from: version EDMF Restricted part number - Dr.Reddy's/Lacidipine/RP/v01-00/2015-07 to: EDMF Restricted part number Dr.Reddy's Lacidipine/RP/v03-00/2019-09. It should be updated and provided to the The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products directly.

Summary of the Applicant's response

Response:

Applicant acknowledges the agency's comment. Applicant would like intimate agency that ASMF holder has responded to the questions provided to them and the CESP number for the same is CESP_Submission_1129644.

See an attachment to the FVAR. An appropriate explanation and justification have been provided by the drug substance manufacturer.

Assessment of the Applicant's response
The problem has been resolved.

3.2.S.2.2 EDMF Restricted part number - Dr.Reddy's/Lacidipine/RP/v03-00/2019-09.

2. According to the EMA/454576/2016 guideline the cases where routine reprocessing is carried out should be identified and justified. Any data to support this justification should be either referenced or presented in 3.2.S.2.5. The reprocessing method should be clearly described and the criteria for deciding when re-processing can be performed, should be provided.

Summary of the Applicant's response

Response:

Applicant acknowledges the agency's comment. Applicant would like intimate agency that ASMF holder has responded to the questions provided to them and the CESP number for the same is CESP_Submission_1129644.

See an attachment to the FVAR. An appropriate explanation and justification have been provided by the drug substance manufacturer.

Assessment of the Applicant's response
The problem has been resolved.

IV. OVERALL CONCLUSION

Based on the review of the data on quality the RMS considers that the variation following application PL/H/0563/001-003/IB/007/G for the following proposed group of changes: *Change in the manufacturer of a starting material, TBBA, used in the API manufacture; Minor change to the restricted part of an Active Substance Master File*

is approvable

V. FURTHER REQUEST FOR SUPPLEMENTARY INFORMATION AS PROPOSED BY THE RMS

V.1 Major objections

None.

V.1.1 Quality aspects

V.1.1.1 Active Substance (related to additional data provided by the applicant only)

N/A

V.1.1.2 Medicinal Product

None.

V.2 Other concerns

V.2.1 Quality aspects

V.2.1.1. Active Substance (related to additional data provided by applicant only)

N/A

V.2.1.2. Medicinal Product

None