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

E-mail: ReferralNotifications@ema.europa.eu

Details on the draft list of products concerned (pending and finalised) are annexed to this notification.

The Austrian Federal Office for Safety in Healthcare (BASG) and the Health Care Inspectorate of the Netherlands (IGZ) performed a joint GCP inspection from 8-12 February 2016 at Micro Therapeutic Research Labs Pvt. Ltd Rajam Bhavanam, No. 6 , Kamarajar Salai, Selaiyur, East Tambaram, Chennai - 600 059, India.

In addition, a study performed at the Micro Therapeutic Research Labs Pvt. Ltd site in Coimbatore (No. 29 A, Krishna Madhuravanam, Vellokinar Pirivu, Thudiyalur, Coimbatore-641029, Tamil Nadu, India) was inspected. Both the Chennai site and the Coimbatore site follow the same provisions and QA activities and are headed by the same supervisor.

The findings reported during the inspection cast serious doubts on the reliability of the data of bioequivalence studies (clinical and bioanalytical part) conducted at the sites inspected:

- The ECG-recordings in a number of independent studies showed inconsistencies which are concluded to be intentional misrepresentation of (study) data (critical finding).
- GCP non-compliant documentation practises have been observed for different study data including the practise to generate source data retrospectively, documentation of incorrect information, overwriting and changing raw data without ensuring the readability of the initial entry and the practise to apply implausible changes without giving a sound justification.
- Other aspects on which GCP non-compliant issues were detected included the procedures on verification of subject identity, the insufficient validation of the computerised system used by the site to capture volunteer information, non-completeness of the TMF/SMF, IMP (shipped to site before approval) and the QMS e.g. standard procedures on (re-)archiving and the process of reconciliation of (QA-issued) study forms, leading to used forms ending up in the unused-forms section and thus not taken into account in CSR writing.

The findings raise serious concerns related to the suitability of the quality management system at both sites and of the reliability of data submitted in applications for marketing authorisations in EU Member States in the time period from June 2012 (date of the oldest study inspected) to June 2016 (submission of Corrective and Preventive Actions (CAPAs)).

In view of the findings described above and the necessity to take an action at EU level, Germany considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it assesses the impact of the findings mentioned above on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of relevant trials performed at these two sites as well as for pending procedures based on trials in the period between June 2012 to June 2016.
The CHMP is requested in particular to provide its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

The CHMP may consider if the scope of this referral should be extended to studies conducted before June 2012.

Signed <name> Date <date>

[redacted] 7.12.16

Prof. Dr. Karl Broich

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

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In addition, a study performed at the Micro Therapeutic Research Labs Pvt. Ltd site in Coimbatore (No. 29 A, Krishna Madhuravanam, Vellokinar Pirivu, Thudiyalur, Coimbatore-641029, Tamil Nadu, India) was inspected. Both the Chennai site and the Coimbatore site follow the same provisions and QA activities and are headed by the same supervisor.

The findings reported during the inspection cast serious doubts on the reliability of the data of bioequivalence studies (clinical and bioanalytical part) conducted at the sites inspected:

- The ECG-recordings in a number of independent studies showed inconsistencies which are concluded to be intentional misrepresentation of (study) data (critical finding).
- GCP non-compliant documentation practises have been observed for different study data including the practise to generate source data retrospectively, documentation of incorrect information, overwriting and changing raw data without ensuring the readability of the initial entry and the practise to apply implausible changes without giving a sound justification.
- Other aspects on which GCP non-compliant issues were detected included the procedures on verification of subject identity, the insufficient validation of the computerised system used by the site to capture volunteer information, non-completeness of the TMF/SMF, IMP (shipped to site before approval) and the QMS e.g. standard procedures on (re-)archiving and the process of reconciliation of (QA-issued) study forms, leading to used forms ending up in the unused-forms section and thus not taken into account in CSR writing.

The findings raise serious concerns related to the suitability of the quality management system at both sites and of the reliability of data submitted in applications for marketing authorisations in EU Member States in the time period from June 2012 (date of the oldest study inspected) to June 2016 (submission of Corrective and Preventive Actions (CAPAs)).

In view of the findings described above and the necessity to take an action at EU level, Slovenia considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it assesses the impact of the findings mentioned above on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of relevant trials performed at these two sites as well as for pending procedures based on trials in the period between June 2012 to June 2016.
The CHMP is requested in particular to provide its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

The CHMP may consider if the scope of this referral should be extended to studies conducted before June 2012.

Signed: [redacted]
Andreja Čufar, MPharm, PhD
Director

Date:
December 12, 2016

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

E-mail: ReferralNotifications@ema.europa.eu

Details on the draft list of products concerned (pending and finalised) are annexed to this notification.

The Austrian Federal Office for Safety in Healthcare (BASG) and the Health Care Inspectorate of the Netherlands (IGZ) performed a joint GCP inspection from 8-12 February 2016 at Micro Therapeutic Research Labs Pvt. Ltd Rajam Bhavanam, No. 6 , Kamarajar Salai, Selaiyur, East Tambaram, Chennai - 600 059, India.

In addition, a study performed at the Micro Therapeutic Research Labs Pvt. Ltd site in Coimbatore (No. 29 A, Krishna Madhuravanam, Vellokinar Pirivu, Thudiyalur, Coimbatore-641029, Tamil Nadu, India) was inspected. Both the Chennai site and the Coimbatore site follow the same provisions and QA activities and are headed by the same supervisor.

The findings reported during the inspection cast serious doubts on the reliability of the data of bioequivalence studies (clinical and bioanalytical part) conducted at the sites inspected:

- The ECG-recordings in a number of independent studies showed inconsistencies which are concluded to be intentional misrepresentation of (study) data (critical finding).
- GCP non-compliant documentation practises have been observed for different study data including the practise to generate source data retrospectively, documentation of incorrect information, overwriting and changing raw data without ensuring the readability of the initial entry and the practise to apply implausible changes without giving a sound justification.
- Other aspects on which GCP non-compliant issues were detected included the procedures on verification of subject identity, the insufficient validation of the computerised system used by the site to capture volunteer information, non-completeness of the TMF/SMF, IMP (shipped to site before approval) and the QMS e.g. standard procedures on (re-)archiving and the process of reconciliation of (QA-issued) study forms, leading to used forms ending up in the unused-forms section and thus not taken into account in CSR writing.

The findings raise serious concerns related to the suitability of the quality management system at both sites and of the reliability of data submitted in applications for marketing authorisations in EU Member States in the time period from June 2012 (date of the oldest study inspected) to June 2016 (submission of Corrective and Preventive Actions (CAPAs)).

In view of the findings described above and the necessity to take an action at EU level, Bulgaria, considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it assesses the impact of the findings mentioned above on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of relevant trials performed at these two sites as well as for pending procedures based on trials in the period between June 2012 to June 2016.
The CHMP is requested in particular to provide its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

The CHMP may consider if the scope of this referral should be extended to studies conducted before June 2012.

Signed: Assoc. Prof. Assena Stoimenova [redacted] Date 14.Dec.2016

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

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The Austrian Federal Office for Safety in Healthcare (BASG) and the Health Care Inspectorate of the Netherlands (IGZ) performed a joint GCP inspection from 8-12 February 2016 at Micro Therapeutic Research Labs Pvt. Ltd Rajam Bhavanam, No. 6 , Kamarajar Salai, Selaiyur, East Tambaram, Chennai - 600 059, India.

In addition, a study performed at the Micro Therapeutic Research Labs Pvt. Ltd site in Coimbatore (No. 29 A, Krishna Madhuravanam, Vellokinar Pirivu, Thudiyalur, Coimbatore-641029, Tamil Nadu, India) was inspected. Both the Chennai site and the Coimbatore site follow the same provisions and QA activities and are headed by the same supervisor.

The findings reported during the inspection cast serious doubts on the reliability of the data of bioequivalence studies (clinical and bioanalytical part) conducted at the sites inspected:

- The ECG-recordings in a number of independent studies showed inconsistencies which are concluded to be intentional misrepresentation of (study) data (critical finding).
- GCP non-compliant documentation practises have been observed for different study data including the practise to generate source data retrospectively, documentation of incorrect information, overwriting and changing raw data without ensuring the readability of the initial entry and the practise to apply implausible changes without giving a sound justification.
- Other aspects on which GCP non-compliant issues were detected included the procedures on verification of subject identity, the insufficient validation of the computerised system used by the site to capture volunteer information, non-completeness of the TMF/SMF, IMP (shipped to site before approval) and the QMS e.g. standard procedures on (re-)archiving and the process of reconciliation of (QA-issued) study forms, leading to used forms ending up in the unused-forms section and thus not taken into account in CSR writing.

The findings raise serious concerns related to the suitability of the quality management system at both sites and of the reliability of data submitted in applications for marketing authorisations in EU Member States in the time period from June 2012 (date of the oldest study inspected) to June 2016 (submission of Corrective and Preventive Actions (CAPAs)).

In view of the findings described above and the necessity to take an action at EU level, Spain considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it assesses the impact of the findings mentioned above on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of relevant trials performed at these two sites as well as for pending procedures based on trials in the period between June 2012 to June 2016.
The CHMP is requested in particular to provide its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

The CHMP may consider if the scope of this referral should be extended to studies conducted before June 2012.

Belén Crespo Sánchez-Eznarriaga 7 of December 2016

[redacted]

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The Austrian Federal Office for Safety in Healthcare (BASG) and the Health Care Inspectorate of the Netherlands (IGZ) performed a joint GCP inspection from 8-12 February 2016 at Micro Therapeutic Research Labs Pvt. Ltd Rajam Bhavanam, No. 6 , Kamarajar Salai, Selaiyur, East Tambaram, Chennai - 600 059, India.

In addition, a study performed at the Micro Therapeutic Research Labs Pvt. Ltd site in Coimbatore (No. 29 A, Krishna Madhuravanam, Vellokinar Pirivu, Thudiyalur, Coimbatore-641029, Tamil Nadu, India) was inspected. Both the Chennai site and the Coimbatore site follow the same provisions and QA activities and are headed by the same supervisor.

The findings reported during the inspection cast serious doubts on the reliability of the data of bioequivalence studies (clinical and bioanalytical part) conducted at the sites inspected:

- The ECG-recordings in a number of independent studies showed inconsistencies which are concluded to be intentional misrepresentation of (study) data (critical finding).
- GCP non-compliant documentation practises have been observed for different study data including the practise to generate source data retrospectively, documentation of incorrect information, overwriting and changing raw data without ensuring the readability of the initial entry and the practise to apply implausible changes without giving a sound justification.
- Other aspects on which GCP non-compliant issues were detected included the procedures on verification of subject identity, the insufficient validation of the computerised system used by the site to capture volunteer information, non-completeness of the TMF/SMF, IMP (shipped to site before approval) and the QMS e.g. standard procedures on (re-)archiving and the process of reconciliation of (QA-issued) study forms, leading to used forms ending up in the unused-forms section and thus not taken into account in CSR writing.

The findings raise serious concerns related to the suitability of the quality management system at both sites and of the reliability of data submitted in applications for marketing authorisations in EU Member States in the time period from June 2012 (date of the oldest study inspected) to June 2016 (submission of Corrective and Preventive Actions (CAPAs)).

In view of the findings described above and the necessity to take an action at EU level, Finland considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it assesses the impact of the findings mentioned above on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of relevant trials performed at these two sites as well as for pending procedures based on trials in the period between June 2012 to June 2016.
The CHMP is requested in particular to provide its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

The CHMP may consider if the scope of this referral should be extended to studies conducted before June 2012.

[redacted]

Signed Sinikka Rajaniemi
Director General

Date 14.12.2016

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

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In addition, a study performed at the Micro Therapeutic Research Labs Pvt. Ltd site in Coimbatore (No. 29 A, Krishna Madhuravanam, Vellokinar Pirivu, Thudiyalur, Coimbatore-641029, Tamil Nadu, India) was inspected. Both the Chennai site and the Coimbatore site follow the same provisions and QA activities and are headed by the same supervisor.

The findings reported during the inspection cast serious doubts on the reliability of the data of bioequivalence studies (clinical and bioanalytical part) conducted at the sites inspected:

- The ECG-recordings in a number of independent studies showed inconsistencies which are concluded to be intentional misrepresentation of (study) data (critical finding).
- GCP non-compliant documentation practises have been observed for different study data including the practise to generate source data retrospectively, documentation of incorrect information, overwriting and changing raw data without ensuring the readability of the initial entry and the practise to apply implausible changes without giving a sound justification.
- Other aspects on which GCP non-compliant issues were detected included the procedures on verification of subject identity, the insufficient validation of the computerised system used by the site to capture volunteer information, non-completeness of the TMF/SMF, IMP (shipped to site before approval) and the QMS e.g. standard procedures on (re-)archiving and the process of reconciliation of (QA-issued) study forms, leading to used forms ending up in the unused-forms section and thus not taken into account in CSR writing.

The findings raise serious concerns related to the suitability of the quality management system at both sites and of the reliability of data submitted in applications for marketing authorisations in EU Member States in the time period from June 2012 (date of the oldest study inspected) to June 2016 (submission of Corrective and Preventive Actions (CAPAs)).

In view of the findings described above and the necessity to take an action at EU level, Hungary considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it assesses the impact of the findings mentioned above on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of relevant trials performed at these two sites as well as for pending procedures based on trials in the period between June 2012 to June 2016.
The CHMP is requested in particular to provide its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

The CHMP may consider if the scope of this referral should be extended to studies conducted before June 2012.

Signed

[redacted]

Csilla Pozsgay MD.
Director General
12/12/2016

NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
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The findings reported during the inspection cast serious doubts on the reliability of the data of bioequivalence studies (clinical and bioanalytical part) conducted at the sites inspected:

- The ECG-recordings in a number of independent studies showed inconsistencies which are concluded to be intentional misrepresentation of (study) data (critical finding).
- GCP non-compliant documentation practises have been observed for different study data including the practise to generate source data retrospectively, documentation of incorrect information, overwriting and changing raw data without ensuring the readability of the initial entry and the practise to apply implausible changes without giving a sound justification.
- Other aspects on which GCP non-compliant issues were detected included the procedures on verification of subject identity, the insufficient validation of the computerised system used by the site to capture volunteer information, non-completeness of the TMF/SMF, IMP (shipped to site before approval) and the QMS e.g. standard procedures on (re-)archiving and the process of reconciliation of (QA-issued) study forms, leading to used forms ending up in the unused-forms section and thus not taken into account in CSR writing.

The findings raise serious concerns related to the suitability of the quality management system at both sites and of the reliability of data submitted in applications for marketing authorisations in EU Member States in the time period from June 2012 (date of the oldest study inspected) to June 2016 (submission of Corrective and Preventive Actions (CAPAs)).

In view of the findings described above and the necessity to take an action at EU level, Iceland considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it assesses the impact of the findings mentioned above on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of relevant trials performed at these two sites as well as for pending procedures based on trials in the period between June 2012 to June 2016.
The CHMP is requested in particular to provide its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

The CHMP may consider if the scope of this referral should be extended to studies conducted before June 2012.

Signed Runa Hauksdóttir Hvannberg [redacted]

Date 5.12.2016

NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
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In addition, a study performed at the Micro Therapeutic Research Labs Pvt. Ltd site in Coimbatore (No. 29 A, Krishna Madhuravanam, Vellokinar Pirivu, Thudiyalur, Coimbatore-641029, Tamil Nadu, India) was inspected. Both the Chennai site and the Coimbatore site follow the same provisions and QA activities and are headed by the same supervisor.

The findings reported during the inspection cast serious doubts on the reliability of the data of bioequivalence studies (clinical and bioanalytical part) conducted at the sites inspected:

- The ECG-recordings in a number of independent studies showed inconsistencies which are concluded to be intentional misrepresentation of (study) data (critical finding).
- GCP non-compliant documentation practises have been observed for different study data including the practise to generate source data retrospectively, documentation of incorrect information, overwriting and changing raw data without ensuring the readability of the initial entry and the practise to apply implausible changes without giving a sound justification.
- Other aspects on which GCP non-compliant issues were detected included the procedures on verification of subject identity, the insufficient validation of the computerised system used by the site to capture volunteer information, non-completeness of the TMF/SMF, IMP (shipped to site before approval) and the QMS e.g. standard procedures on (re-)archiving and the process of reconciliation of (QA-issued) study forms, leading to used forms ending up in the unused-forms section and thus not taken into account in CSR writing.

The findings raise serious concerns related to the suitability of the quality management system at both sites and of the reliability of data submitted in applications for marketing authorisations in EU Member States in the time period from June 2012 (date of the oldest study inspected) to June 2016 (submission of Corrective and Preventive Actions (CAPAs)).

In view of the findings described above and the necessity to take an action at EU level, Latvia considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it assesses the impact of the findings mentioned above on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of relevant trials performed at these two sites as well as for pending procedures based on trials in the period between June 2012 to June 2016.
The CHMP is requested in particular to provide its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

The CHMP may consider if the scope of this referral should be extended to studies conducted before June 2012.

[redacted] S.Henkuzens Date 05.12.2016.

MINISTERUL SĂNĂTĂȚII
AGENȚIA NAȚIONALĂ A MEDICAMENTULUI
ȘI DISPOZITIVELOR MEDICALE
INTRARE Nr. 51838
IEȘIRE
Ziua 05 Luna 12 Anul 2016

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

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In addition, a study performed at the Micro Therapeutic Research Labs Pvt. Ltd site in Coimbatore (No. 29 A, Krishna Madhuravanam, Vellokinar Pirivu, Thudiyalur, Coimbatore-641029, Tamil Nadu, India) was inspected. Both the Chennai site and the Coimbatore site follow the same provisions and QA activities and are headed by the same supervisor.

The findings reported during the inspection cast serious doubts on the reliability of the data of bioequivalence studies (clinical and bioanalytical part) conducted at the sites inspected:

- The ECG-recordings in a number of independent studies showed inconsistencies which are concluded to be intentional misrepresentation of (study) data (critical finding).
- GCP non-compliant documentation practises have been observed for different study data including the practise to generate source data retrospectively, documentation of incorrect information, overwriting and changing raw data without ensuring the readability of the initial entry and the practise to apply implausible changes without giving a sound justification.
- Other aspects on which GCP non-compliant issues were detected included the procedures on verification of subject identity, the insufficient validation of the computerised system used by the site to capture volunteer information, non-completeness of the TMF/SMF, IMP (shipped to site before approval) and the QMS e.g. standard procedures on (re-)archiving and the process of reconciliation of (QA-issued) study forms, leading to used forms ending up in the unused-forms section and thus not taken into account in CSR writing.

The findings raise serious concerns related to the suitability of the quality management system at both sites and of the reliability of data submitted in applications for marketing authorisations in EU Member States in the time period from June 2012 (date of the oldest study inspected) to June 2016 (submission of Corrective and Preventive Actions (CAPAs)).

In view of the findings described above and the necessity to take an action at EU level, National Agency for Medicines and Medical Devices, Romania considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it assesses the impact of the findings mentioned above on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of relevant trials performed at these two sites as well as for pending procedures based on trials in the period between June 2012 to June 2016.
The CHMP is requested in particular to provide its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

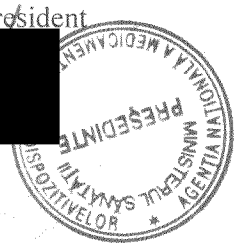
The CHMP may consider if the scope of this referral should be extended to studies conducted before June 2012.

Dr. Nicolae FOTIN

Date 07.12.2016

NAMMD (Romania) President

[redacted]



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The findings reported during the inspection cast serious doubts on the reliability of the data of bioequivalence studies (clinical and bioanalytical part) conducted at the sites inspected:

- The ECG-recordings in a number of independent studies showed inconsistencies which are concluded to be intentional misrepresentation of (study) data (critical finding).
- GCP non-compliant documentation practises have been observed for different study data including the practise to generate source data retrospectively, documentation of incorrect information, overwriting and changing raw data without ensuring the readability of the initial entry and the practise to apply implausible changes without giving a sound justification.
- Other aspects on which GCP non-compliant issues were detected included the procedures on verification of subject identity, the insufficient validation of the computerised system used by the site to capture volunteer information, non-completeness of the TMF/SMF, IMP (shipped to site before approval) and the QMS e.g. standard procedures on (re-)archiving and the process of reconciliation of (QA-issued) study forms, leading to used forms ending up in the unused-forms section and thus not taken into account in CSR writing.

The findings raise serious concerns related to the suitability of the quality management system at both sites and of the reliability of data submitted in applications for marketing authorisations in EU Member States in the time period from June 2012 (date of the oldest study inspected) to June 2016 (submission of Corrective and Preventive Actions (CAPAs)).

In view of the findings described above and the necessity to take an action at EU level, Slovakia considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it assesses the impact of the findings mentioned above on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of relevant trials performed at these two sites as well as for pending procedures based on trials in the period between June 2012 to June 2016.
The CHMP is requested in particular to provide its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

The CHMP may consider if the scope of this referral should be extended to studies conducted before June 2012.

Signed Zuzana Batova

[redacted]

Date 7.12.2016

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The Austrian Federal Office for Safety in Healthcare (BASG) and the Health Care Inspectorate of the Netherlands (IGZ) performed a joint GCP inspection from 8-12 February 2016 at Micro Therapeutic Research Labs Pvt. Ltd Rajam Bhavanam, No. 6 , Kamarajar Salai, Selaiyur, East Tambaram, Chennai - 600 059, India.

In addition, a study performed at the Micro Therapeutic Research Labs Pvt. Ltd site in Coimbatore (No. 29 A, Krishna Madhuravanam, Vellokinar Pirivu, Thudiyalur, Coimbatore-641029, Tamil Nadu, India) was inspected. Both the Chennai site and the Coimbatore site follow the same provisions and QA activities and are headed by the same supervisor.

The findings reported during the inspection cast serious doubts on the reliability of the data of bioequivalence studies (clinical and bioanalytical part) conducted at the sites inspected:

- The ECG-recordings in a number of independent studies showed inconsistencies which are concluded to be intentional misrepresentation of (study) data (critical finding).
- GCP non-compliant documentation practises have been observed for different study data including the practise to generate source data retrospectively, documentation of incorrect information, overwriting and changing raw data without ensuring the readability of the initial entry and the practise to apply implausible changes without giving a sound justification.
- Other aspects on which GCP non-compliant issues were detected included the procedures on verification of subject identity, the insufficient validation of the computerised system used by the site to capture volunteer information, non-completeness of the TMF/SMF, IMP (shipped to site before approval) and the QMS e.g. standard procedures on (re-)archiving and the process of reconciliation of (QA-issued) study forms, leading to used forms ending up in the unused-forms section and thus not taken into account in CSR writing.

The findings raise serious concerns related to the suitability of the quality management system at both sites and of the reliability of data submitted in applications for marketing authorisations in EU Member States in the time period from June 2012 (date of the oldest study inspected) to June 2016 (submission of Corrective and Preventive Actions (CAPAs)).

In view of the findings described above and the necessity to take an action at EU level, AUSTRIA considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it assesses the impact of the findings mentioned above on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of relevant trials performed at these two sites as well as for pending procedures based on trials in the period between June 2012 to June 2016.
The CHMP is requested in particular to provide its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

The CHMP may consider if the scope of this referral should be extended to studies conducted before June 2012

[redacted]

Signed DI Dr Christa Wirthumer-Hoche

Date 05.12.2016

NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
E-mail: ReferralNotifications@ema.europa.eu

Details on the draft list of products concerned (pending and finalised) are annexed to this notification.

The Austrian Federal Office for Safety in Healthcare (BASG) and the Health Care Inspectorate of the Netherlands (IGZ) performed a joint GCP inspection from 8-12 February 2016 at Micro Therapeutic Research Labs Pvt. Ltd Rajam Bhavanam, No. 6 , Kamarajar Salai, Selaiyur, East Tambaram, Chennai - 600 059, India.

In addition, a study performed at the Micro Therapeutic Research Labs Pvt. Ltd site in Coimbatore (No. 29 A, Krishna Madhuravanam, Vellokinar Pirivu, Thudiyalur, Coimbatore-641029, Tamil Nadu, India) was inspected. Both the Chennai site and the Coimbatore site follow the same provisions and QA activities and are headed by the same supervisor.

The findings reported during the inspection cast serious doubts on the reliability of the data of bioequivalence studies (clinical and bioanalytical part) conducted at the sites inspected:

- The ECG-recordings in a number of independent studies showed inconsistencies which are concluded to be intentional misrepresentation of (study) data (critical finding).
- GCP non-compliant documentation practises have been observed for different study data including the practise to generate source data retrospectively, documentation of incorrect information, overwriting and changing raw data without ensuring the readability of the initial entry and the practise to apply implausible changes without giving a sound justification.
- Other aspects on which GCP non-compliant issues were detected included the procedures on verification of subject identity, the insufficient validation of the computerised system used by the site to capture volunteer information, non-completeness of the TMF/SMF, IMP (shipped to site before approval) and the QMS e.g. standard procedures on (re-)archiving and the process of reconciliation of (QA-issued) study forms, leading to used forms ending up in the unused-forms section and thus not taken into account in CSR writing.

The findings raise serious concerns related to the suitability of the quality management system at both sites and of the reliability of data submitted in applications for marketing authorisations in EU Member States in the time period from June 2012 (date of the oldest study inspected) to June 2016 (submission of Corrective and Preventive Actions (CAPAs)).

In view of the findings described above and the necessity to take an action at EU level, Denmark considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it assesses the impact of the findings mentioned above on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of relevant trials performed at these two sites as well as for pending procedures based on trials in the period between June 2012 to June 2016.
The CHMP is requested in particular to provide its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

The CHMP may consider if the scope of this referral should be extended to studies conducted before June 2012

[redacted]

Signed Thomas Senderovitz

Date 5 December 2016

NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
E-mail: ReferralNotifications@ema.europa.eu

Details on the draft list of products concerned (pending and finalised) are annexed to this notification.

The Austrian Federal Office for Safety in Healthcare (BASG) and the Health Care Inspectorate of the Netherlands (IGZ) performed a joint GCP inspection from 8-12 February 2016 at Micro Therapeutic Research Labs Pvt. Ltd Rajam Bhavanam, No. 6 , Kamarajar Salai, Selaiyur, East Tambaram, Chennai - 600 059, India.

In addition, a study performed at the Micro Therapeutic Research Labs Pvt. Ltd site in Coimbatore (No. 29 A, Krishna Madhuravanam, Vellokinar Pirivu, Thudiyalur, Coimbatore-641029, Tamil Nadu, India) was inspected. Both the Chennai site and the Coimbatore site follow the same provisions and QA activities and are headed by the same supervisor.

The findings reported during the inspection cast serious doubts on the reliability of the data of bioequivalence studies (clinical and bioanalytical part) conducted at the sites inspected:

- The ECG-recordings in a number of independent studies showed inconsistencies which are concluded to be intentional misrepresentation of (study) data (critical finding).
- GCP non-compliant documentation practises have been observed for different study data including the practise to generate source data retrospectively, documentation of incorrect information, overwriting and changing raw data without ensuring the readability of the initial entry and the practise to apply implausible changes without giving a sound justification.
- Other aspects on which GCP non-compliant issues were detected included the procedures on verification of subject identity, the insufficient validation of the computerised system used by the site to capture volunteer information, non-completeness of the TMF/SMF, IMP (shipped to site before approval) and the QMS e.g. standard procedures on (re-)archiving and the process of reconciliation of (QA-issued) study forms, leading to used forms ending up in the unused-forms section and thus not taken into account in CSR writing.

The findings raise serious concerns related to the suitability of the quality management system at both sites and of the reliability of data submitted in applications for marketing authorisations in EU Member States in the time period from June 2012 (date of the oldest study inspected) to June 2016 (submission of Corrective and Preventive Actions (CAPAs)).

In view of the findings described above and the necessity to take an action at EU level, Estonia considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it assesses the impact of the findings mentioned above on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of relevant trials performed at these two sites as well as for pending procedures based on trials in the period between June 2012 to June 2016.
The CHMP is requested in particular to provide its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

The CHMP may consider if the scope of this referral should be extended to studies conducted before June 2012.

Signed [redacted] Date 07.12.2016

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

E-mail: ReferralNotifications@ema.europa.eu

Details on the draft list of products concerned (pending and finalised) are annexed to this notification.

The Austrian Federal Office for Safety in Healthcare (BASG) and the Health Care Inspectorate of the Netherlands (IGZ) performed a joint GCP inspection from 8-12 February 2016 at Micro Therapeutic Research Labs Pvt. Ltd Rajam Bhavanam, No. 6 , Kamarajar Salai, Selaiyur, East Tambaram, Chennai - 600 059, India.

In addition, a study performed at the Micro Therapeutic Research Labs Pvt. Ltd site in Coimbatore (No. 29 A, Krishna Madhuravanam, Vellokinar Pirivu, Thudiyalur, Coimbatore-641029, Tamil Nadu, India) was inspected. Both the Chennai site and the Coimbatore site follow the same provisions and QA activities and are headed by the same supervisor.

The findings reported during the inspection cast serious doubts on the reliability of the data of bioequivalence studies (clinical and bioanalytical part) conducted at the sites inspected:

- The ECG-recordings in a number of independent studies showed inconsistencies which are concluded to be intentional misrepresentation of (study) data (critical finding).
- GCP non-compliant documentation practises have been observed for different study data including the practise to generate source data retrospectively, documentation of incorrect information, overwriting and changing raw data without ensuring the readability of the initial entry and the practise to apply implausible changes without giving a sound justification.
- Other aspects on which GCP non-compliant issues were detected included the procedures on verification of subject identity, the insufficient validation of the computerised system used by the site to capture volunteer information, non-completeness of the TMF/SMF, IMP (shipped to site before approval) and the QMS e.g. standard procedures on (re-)archiving and the process of reconciliation of (QA-issued) study forms, leading to used forms ending up in the unused-forms section and thus not taken into account in CSR writing.

The findings raise serious concerns related to the suitability of the quality management system at both sites and of the reliability of data submitted in applications for marketing authorisations in EU Member States in the time period from June 2012 (date of the oldest study inspected) to June 2016 (submission of Corrective and Preventive Actions (CAPAs)).

In view of the findings described above and the necessity to take an action at EU level, Croatia considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it assesses the impact of the findings mentioned above on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of relevant trials performed at these two sites as well as for pending procedures based on trials in the period between June 2012 to June 2016.
The CHMP is requested in particular to provide its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

The CHMP may consider if the scope of this referral should be extended to studies conducted before June 2012.

[redacted]

Signed: Siniša Tomić, PhD, Associate Professor Date: 02/12/2016

Head of Agency for Medicinal Products and Medical Devices
(HALMED)

NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
E-mail: ReferralNotifications@ema.europa.eu

Details on the draft list of products concerned (pending and finalised) are annexed to this notification.

The Austrian Federal Office for Safety in Healthcare (BASG) and the Health Care Inspectorate of the Netherlands (IGZ) performed a joint GCP inspection from 8-12 February 2016 at Micro Therapeutic Research Labs Pvt. Ltd Rajam Bhavanam, No. 6 , Kamarajar Salai, Selaiyur, East Tambaram, Chennai - 600 059, India.

In addition, a study performed at the Micro Therapeutic Research Labs Pvt. Ltd site in Coimbatore (No. 29 A, Krishna Madhuravanam, Vellokinar Pirivu, Thudiyalur, Coimbatore-641029, Tamil Nadu, India) was inspected. Both the Chennai site and the Coimbatore site follow the same provisions and QA activities and are headed by the same supervisor.

The findings reported during the inspection cast serious doubts on the reliability of the data of bioequivalence studies (clinical and bioanalytical part) conducted at the sites inspected:

- The ECG-recordings in a number of independent studies showed inconsistencies which are concluded to be intentional misrepresentation of (study) data (critical finding).
- GCP non-compliant documentation practises have been observed for different study data including the practise to generate source data retrospectively, documentation of incorrect information, overwriting and changing raw data without ensuring the readability of the initial entry and the practise to apply implausible changes without giving a sound justification.
- Other aspects on which GCP non-compliant issues were detected included the procedures on verification of subject identity, the insufficient validation of the computerised system used by the site to capture volunteer information, non-completeness of the TMF/SMF, IMP (shipped to site before approval) and the QMS e.g. standard procedures on (re-)archiving and the process of reconciliation of (QA-issued) study forms, leading to used forms ending up in the unused-forms section and thus not taken into account in CSR writing.

The findings raise serious concerns related to the suitability of the quality management system at both sites and of the reliability of data submitted in applications for marketing authorisations in EU Member States in the time period from June 2012 (date of the oldest study inspected) to June 2016 (submission of Corrective and Preventive Actions (CAPAs)).

In view of the findings described above and the necessity to take an action at EU level, Norway considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it assesses the impact of the findings mentioned above on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of relevant trials performed at these two sites as well as for pending procedures based on trials in the period between June 2012 to June 2016.
The CHMP is requested in particular to provide its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

The CHMP may consider if the scope of this referral should be extended to studies conducted before June 2012.

Signed
Audun Hågå
Director General

Date 02.12.2016

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

E-mail: ReferralNotifications@ema.europa.eu

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The Austrian Federal Office for Safety in Healthcare (BASG) and the Health Care Inspectorate of the Netherlands (IGZ) performed a joint GCP inspection from 8-12 February 2016 at Micro Therapeutic Research Labs Pvt. Ltd Rajam Bhavanam, No. 6 , Kamarajar Salai, Selaiyur, East Tambaram, Chennai - 600 059, India.

In addition, a study performed at the Micro Therapeutic Research Labs Pvt. Ltd site in Coimbatore (No. 29 A, Krishna Madhuravanam, Vellokinar Pirivu, Thudiyalur, Coimbatore-641029, Tamil Nadu, India) was inspected. Both the Chennai site and the Coimbatore site follow the same provisions and QA activities and are headed by the same supervisor.

The findings reported during the inspection cast serious doubts on the reliability of the data of bioequivalence studies (clinical and bioanalytical part) conducted at the sites inspected:

- The ECG-recordings in a number of independent studies showed inconsistencies which are concluded to be intentional misrepresentation of (study) data (critical finding).
- GCP non-compliant documentation practises have been observed for different study data including the practise to generate source data retrospectively, documentation of incorrect information, overwriting and changing raw data without ensuring the readability of the initial entry and the practise to apply implausible changes without giving a sound justification.
- Other aspects on which GCP non-compliant issues were detected included the procedures on verification of subject identity, the insufficient validation of the computerised system used by the site to capture volunteer information, non-completeness of the TMF/SMF, IMP (shipped to site before approval) and the QMS e.g. standard procedures on (re-)archiving and the process of reconciliation of (QA-issued) study forms, leading to used forms ending up in the unused-forms section and thus not taken into account in CSR writing.

The findings raise serious concerns related to the suitability of the quality management system at both sites and of the reliability of data submitted in applications for marketing authorisations in EU Member States in the time period from June 2012 (date of the oldest study inspected) to June 2016 (submission of Corrective and Preventive Actions (CAPAs)).

In view of the findings described above and the necessity to take an action at EU level, Sweden considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it assesses the impact of the findings mentioned above on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of relevant trials performed at these two sites as well as for pending procedures based on trials in the period between June 2012 to June 2016.

The CHMP is requested in particular to provide its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

The CHMP may consider if the scope of this referral should be extended to studies conducted before June 2012.

Signed: [redacted] Date: 2016-12-05

Marie Gårdmark

NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
E-mail: ReferralNotifications@ema.europa.eu

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The Austrian Federal Office for Safety in Healthcare (BASG) and the Health Care Inspectorate of the Netherlands (IGZ) performed a joint GCP inspection from 8-12 February 2016 at Micro Therapeutic Research Labs Pvt. Ltd Rajam Bhavanam, No. 6 , Kamarajar Salai, Selaiyur, East Tambaram, Chennai - 600 059, India.

In addition, a study performed at the Micro Therapeutic Research Labs Pvt. Ltd site in Coimbatore (No. 29 A, Krishna Madhuravanam, Vellokinar Pirivu, Thudiyalur, Coimbatore-641029, Tamil Nadu, India) was inspected. Both the Chennai site and the Coimbatore site follow the same provisions and QA activities and are headed by the same supervisor.

The findings reported during the inspection cast serious doubts on the reliability of the data of bioequivalence studies (clinical and bioanalytical part) conducted at the sites inspected:

- The ECG-recordings in a number of independent studies showed inconsistencies which are concluded to be intentional misrepresentation of (study) data (critical finding).
- GCP non-compliant documentation practises have been observed for different study data including the practise to generate source data retrospectively, documentation of incorrect information, overwriting and changing raw data without ensuring the readability of the initial entry and the practise to apply implausible changes without giving a sound justification.
- Other aspects on which GCP non-compliant issues were detected included the procedures on verification of subject identity, the insufficient validation of the computerised system used by the site to capture volunteer information, non-completeness of the TMF/SMF, IMP (shipped to site before approval) and the QMS e.g. standard procedures on (re-)archiving and the process of reconciliation of (QA-issued) study forms, leading to used forms ending up in the unused-forms section and thus not taken into account in CSR writing.

The findings raise serious concerns related to the suitability of the quality management system at both sites and of the reliability of data submitted in applications for marketing authorisations in EU Member States in the time period from June 2012 (date of the oldest study inspected) to June 2016 (submission of Corrective and Preventive Actions (CAPAs)).

In view of the findings described above and the necessity to take an action at EU level, The Netherlands considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it assesses the impact of the findings mentioned above on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of relevant trials performed at these two sites as well as for pending procedures based on trials in the period between June 2012 to June 2016.
The CHMP is requested in particular to provide its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

The CHMP may consider if the scope of this referral should be extended to studies conducted before June 2012.

Signed Hugo R. Hurts Date 01-12-2017

H.R. Hurts
Executive director
Medicines Evaluation Board
The Netherlands

NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
E-mail: ReferralNotifications@ema.europa.eu

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The Austrian Federal Office for Safety in Healthcare (BASG) and the Health Care Inspectorate of the Netherlands (IGZ) performed a joint GCP inspection from 8-12 February 2016 at Micro Therapeutic Research Labs Pvt. Ltd Rajam Bhavanam, No. 6 , Kamarajar Salai, Selaiyur, East Tambaram, Chennai - 600 059, India.

In addition, a study performed at the Micro Therapeutic Research Labs Pvt. Ltd site in Coimbatore (No. 29 A, Krishna Madhuravanam, Vellokinar Pirivu, Thudiyalur, Coimbatore-641029, Tamil Nadu, India) was inspected. Both the Chennai site and the Coimbatore site follow the same provisions and QA activities and are headed by the same supervisor.

The findings reported during the inspection cast serious doubts on the reliability of the data of bioequivalence studies (clinical and bioanalytical part) conducted at the sites inspected:

- The ECG-recordings in a number of independent studies showed inconsistencies which are concluded to be intentional misrepresentation of (study) data (critical finding).
- GCP non-compliant documentation practises have been observed for different study data including the practise to generate source data retrospectively, documentation of incorrect information, overwriting and changing raw data without ensuring the readability of the initial entry and the practise to apply implausible changes without giving a sound justification.
- Other aspects on which GCP non-compliant issues were detected included the procedures on verification of subject identity, the insufficient validation of the computerised system used by the site to capture volunteer information, non-completeness of the TMF/SMF, IMP (shipped to site before approval) and the QMS e.g. standard procedures on (re-)archiving and the process of reconciliation of (QA-issued) study forms, leading to used forms ending up in the unused-forms section and thus not taken into account in CSR writing.

The findings raise serious concerns related to the suitability of the quality management system at both sites and of the reliability of data submitted in applications for marketing authorisations in EU Member States in the time period from June 2012 (date of the oldest study inspected) to June 2016 (submission of Corrective and Preventive Actions (CAPAs)).

In view of the findings described above and the necessity to take an action at EU level, the UK considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it assesses the impact of the findings mentioned above on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of relevant trials performed at these two sites as well as for pending procedures based on trials in the period between June 2012 to June 2016.
The CHMP is requested in particular to provide its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

The CHMP may consider if the scope of this referral should be extended to studies conducted before June 2012.

Signed [redacted] Date 7 December 2016

Dr Ian Hudson