Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Morningside Healthcare Limited

MHRA Inspection Number: Insp GPvP 20117/18351580-0001

10 South Colonnade, Canary Wharf, London E14 4PU **T** 020 3080 6000 **E** gpvpinspectors@mhra.gov.uk
www.gov.uk/mhra

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAP	Centrally Authorised Product
CAPA	Corrective and Preventative Action
CHMP	Committee for Medicinal Products for Human Use
CMDh	Co-ordination group for Mutual recognition and Decentralised procedures – human
CMS	Concerned Member States
DCP	Decentralised Procedure
EMA	European Medicines Agency
EU	European Union
GVP	Good Vigilance Practice
HCP	Healthcare Professional
ICH	International Conference on Harmonisation
MAH	Marketing Authorisation Holder
MRP	Mutual Recognition Procedure
NAP	Nationally Authorised Product
NCA	National Competent Authority
PIL	Patient Information Leaflet
PIQU	Product Information Quality Unit
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
QMS	Quality Management System
QPPV	Qualified Person responsible for Pharmacovigilance
aRMM	Additional Risk Minimisation Measures
RMM	Risk Minimisation Measures
RMP	Risk Management Plan
RMS	Reference Member State
SPC	EU Summary of Product Characteristics
SOP	Standard Operating Procedure

UK	United Kingdom

SECTION A: INSPECTION REPORT SUMMARY

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Inspection type:	Statutory National Inspection
System(s) inspected:	Morningside Healthcare Limited [redacted]
Site(s) of inspection:	Remote inspection
Main site contact:	[redacted]
Date(s) of inspection:	20 April – 08 June 2020 The inspection was conducted remotely with document review completed by inspectors on: 11 – 13 May 2020 27 – 28 May 2020 08 June 2020
Lead Inspector: **Accompanying Inspector(s):**	[redacted]
Previous inspection date(s):	N/A
Purpose of inspection:	Inspection of pharmacovigilance systems to review compliance with UK and EU requirements.
Products selected to provide system examples:	As part of the review of additional risk management, [redacted] RMPs and RMMs were reviewed.
Name and location of EU QPPV:	[redacted]
Global PV database (in use at the time of the inspection):	ARISg version 7.4.5.2 (commercially available).
Key service provider(s):	Pharmacovigilance services (including role of EU QPPV) provided by APCER Life Sciences.
Inspection finding summary:	1 Critical finding 4 Major findings
Date of first issue of report to MAH:	10 July 2020

Deadline for submission of responses by MAH:	14 August 2020 25 September 2020
Date(s) of receipt of responses from MAH:	13 August 2020 18 September 2020
Date of final version of report:	21 September 2020
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Morningside Healthcare Limited (hereafter referred to as Morningside) was selected for routine inspection as part of the MHRA's statutory, national pharmacovigilance inspection programme. The purpose of the inspection was to review compliance with currently applicable EU and UK pharmacovigilance regulations and guidelines. In particular, reference was made to Directive 2001/83/EC as amended, Commission Implementing Regulation (EU) No 520/2012 and the adopted good pharmacovigilance practices (GVP) Modules.

A list of reference texts is provided at Appendix I.

Morningside is a global pharmaceutical company, manufacturing and distributing generic and branded medicinal products worldwide with headquarters located in Leicester, UK. Selected PV activities have been outsourced to APCER Life Sciences Ltd. (APCER), with headquarters in Uxbridge, London and also has offices based in India. PV activities outsourced to APCER include the role of the QPPV, ISCR management, PSUR management and signal detection and analysis.

At the time of inspection, Morningside held 199 medicinal product licences in the UK which covered 91 active substances, of which 124 products were currently marketed. 51 products had been licensed via the DCP, 25 through MRP and 123 via UK national procedures.

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One product, [redacted] was subject to additional monitoring, with the implementation of additional risk minimisation measures (aRMMs) for the product being led by [redacted] through a collaboration agreement. Three other products had aRMMs: [redacted] and [redacted]

B.2 Scope of the inspection

The inspection included a review of the local (UK) pharmacovigilance systems and was performed remotely due to the COVID-19 pandemic.

The remote inspection was performed over several weeks using a series of document requests followed by a period of document review by inspectors. Further detail can be found in the remote inspection plan (Appendix II).

The scope of the inspection focused on specific areas of risk management, covering maintenance of reference safety information (from identification of updates to product information, submission of variations and implementation of updated product information) and a review of aRMMs for [redacted], [redacted] The CAPA developed in response to a request from the MHRA's Product Information Quality Unit (PIQU) sent in November 2019, which instructed the MAH to update the product information for [redacted] and [redacted] in line with the outcome of an Article 31 referral for combined hormonal contraceptives (CHC) (EMEA/H/A-31/1356, adopted on 16 January 2014), was also reviewed.

Due to the limited scope, other critical pharmacovigilance activities not covered during this inspection should be subject to review at a subsequent pharmacovigilance inspection.

B.3 Documents submitted prior to the inspection

The company submitted a PSMF (version 8, effective 28 February 2020) to assist with inspection planning and preparation. Specific additional documents were also requested by the inspection team and provided by the company prior to the inspection as part of an initial document request. This included all documented procedures governing the inspected topics, additional risk minimisation materials and evidence of implementation, a list of safety variations for UK authorised products and a list of PILs updated with safety related information since 01 January 2017, and CAPA related documentation.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Inspection Plan. Minor amendments to the Inspection Plan that occurred during the inspection are highlighted using italic text in Appendix II.

Due to the remote nature of the inspection, once responses to the three rounds of document requests were submitted, a period of document review was scheduled and completed on the following dates:

- 11 – 13 May 2020 (to review documents from request sheet A)
- 27 – 28 May 2020 (to review documents from request sheets B and C)
- 08 June 2020 (to review documents from request sheet D)

A remote closing meeting was held to review the inspection findings at 3.30 pm GMT on Monday 08 June 2020.

A list of the personnel who attended the closing meeting is contained in the Closing Meeting Attendance Record, which will be archived together with the inspection notes, a list of the documents requested during the inspection and the inspection report.

SECTION C: INSPECTION FINDINGS

C.1 Summary of significant changes and action taken since the last inspection

Since the previous MHRA inspection in 2009 the company had made the following changes to the pharmacovigilance system:

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- The QPPV provided by APCER (previously [redacted] had changed from [redacted] located in the UK) to [redacted] (located in Germany).

C.2 Definitions of inspection finding gradings

Critical (CR): a deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

Major (MA): a deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

Minor (MI): a deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

Comment: the observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

The factual matter contained in the Inspection Report relates only to those things that the inspection team saw and heard during the inspection process. The inspection report is not to be taken as implying a satisfactory state of affairs in documentation, premises, equipment, personnel or procedures not examined during the inspection.

Findings from any inspection which are graded as critical or major will be shared with the EMA, other EU competent authorities and the European Commission.

C.3 Guidance for responding to inspection findings

Responses to inspection findings should be clear, concise and include proposed actions to address both the identified deficiency and the root cause of the deficiency. Consideration should also be given to identifying and preventing other potential similar deficiencies within the pharmacovigilance system.

Responses should be entered directly into the table(s) in section C.4. The following text is intended as guidance when considering the information that should be entered into each of the fields within the table(s). 'Not applicable' should be entered into the relevant field if the requested information is not appropriate for the finding in question.

Root Cause Analysis Identify the root cause(s) which, if adequately addressed, will prevent recurrence of the deficiency. There may be more than one root cause for any given deficiency.
Further Assessment Assess the extent to which the deficiency exists within the pharmacovigilance system and what impact it may have for all products. Where applicable, describe what further assessment has been performed or may be required to fully evaluate the impact of the deficiency e.g. retrospective analysis of data may be required to fully assess the impact.
Corrective Action(s) Detail the action(s) taken / proposed to correct the identified deficiency.
Preventative Action(s) Detail the action(s) taken / proposed to eliminate the root cause of the deficiency, in order to prevent recurrence. Action(s) to identify and prevent other potential similar deficiencies should also be considered.
Deliverable(s) Detail the specific outputs from the proposed / completed corrective and preventative action(s). For example, updated procedure/work instruction, record of re-training, IT solution.
Due Date(s) Specify the actual / proposed date(s) for completion of each action. Indicate when an action is completed.

Further information relating to inspection responses can be found under 'Inspection outcomes' at: https://www.gov.uk/guidance/good-pharmacovigilance-practice-gpvp

C.4 Inspection findings

C.4.1 Critical findings

CR.1 Additional risk minimisation measures

Requirements:

Commission Implementation Regulation 520/2012, Article 11

'1. 1. Specific quality system procedures and processes shall be in place in order to ensure the following:
…
(g) appropriate communication by the marketing authorisation holder of relevant safety information to healthcare professionals and patients.'

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance, Regulation 182

'The holder must (as part of its pharmacovigilance system) –
…
(c) operate a risk management system for the product in accordance with the risk management plan (if any) for the product'

GVP Module XVI addendum I: Educational Materials

XVI. Add I.3. Submission of educational material
'…the draft educational material should be submitted to the competent authorities of Member States as follows:
• with a cover letter and/or request form including the following information…
- a detailed implementation plan for the educational material with the following information:
- target population(s);
- dissemination method (e.g. paper, e-mail, via social media, learned societies and/or patient associations, publication on websites);
- time point when dissemination is anticipated to start and frequency of further disseminations;
- estimated date of launch or date of start of the marketing of the product (in the case of a new marketing authorisation)'

Risk minimisation measures are interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur. The majority of safety concerns are addressed by routine risk minimisation measures. Exceptionally, for selected important risks, routine risk minimisation may be considered insufficient and aRMMs may be deemed necessary.

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At the time of inspection, Morningside had four products [redacted] and [redacted] for which aRMMs were required in the EU RMP and these were reviewed during the inspection.

Finding CR.1 a)
Significant deficiencies were identified in the implementation of the aRMMs for three of the

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products reviewed during the inspection:

1. [redacted]
The RMP [redacted] was approved on 06 February 2015 and the product had been marketed in the UK since 02 October 2015. The aRMMs in the approved RMP included the following educational materials for HCPs and patients around the risk of venous and arterial thromboembolism:

- Checklist for prescribers – combined hormonal contraceptives (CHCs)
- CHCs: important information for women (including information about the recommendations coming from the Europe-wide review of the safety of CHCs)
- Information for women about risk of blood clots with CHCs (including information of at-risk individuals and symptoms of blood clots).

i. The aRMMs were not implemented prior to 28 February 2020, following notification of this inspection, and the MAH only identified this non-compliance in February 2020. The RMP stated that "The educational material will be made available to HCPs through sales representatives and website" but the materials had not been made available via any channel prior to this date, when these materials were uploaded to the Electronic Medicines Compendium (EMC).
ii. The materials and associated implementation plan for [redacted] had not been submitted to the MHRA for approval prior to implementation on 28 February 2020.
iii. The materials had not been uploaded on the dedicated website: www.morningsidecontraceptives.com, as specified in the RMP [redacted]

2. [redacted]
The RMP [redacted] was approved on 01 October 2014 and the product had been marketed in the UK since 18 May 2016. The aRMMs in the approved RMP included the following educational materials for HCPs and patients around the risk of venous and arterial thromboembolism:

- Checklist for prescribers – [redacted]
- Important information for women: about risk of blood clots with [redacted] (including information of at-risk individuals, symptoms of blood clots and use of CHCs)

i. The aRMMs were not implemented prior to 28 February 2020, following notification of this inspection, and the MAH only identified this non-compliance in February 2020. The materials had not been made available via any channel prior to this date, when these materials were uploaded to the EMC.
ii. The materials and associated implementation plan for [redacted] had not been submitted to the MHRA for approval prior to implementation on 28 February 2020.

3. [redacted]
The RMP [redacted] was approved on 30 March 2015 and was effective until 22 April 2020 when RMP [redacted] was approved. The aRMMs in the approved RMP [redacted] included educational materials for HCPs and patients around the following risks: ectopic pregnancy, spontaneous abortion, contraceptive failure, drug exposure during pregnancy and breast feeding, conditions and drug interactions associated with loss of efficacy, use of the product beyond 72 hours since unprotected sex and use in women under 16 years of age. The educational materials required in the RMP to inform patients and HCPs of these risks were:

- A patient questionnaire for use by HCPs
- A patient advice leaflet

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- An e-learning module accessible from www.morningsidecontraceptives.com.

i. The e-learning module had not been implemented. This was missed due to a lack of a formal process and had not been identified prior to the inspection. The intention of the e-learning module was not included in RMP [redacted] and so the level of risk and potential impact on patients is not known.

This has been graded as a critical finding because it undermines the rights, safety and well-being of patients, and it represents a serious breach of legislation. It also undermines the approval of these products as they are approved on the basis that the identified and potential risks of the products will be managed by the MAH.

Actions to be taken by the MAH
The educational materials and implementation plan for [redacted] should be submitted as soon as possible for approval by the MHRA, in line with the requirements laid out in GVP Module XVI. Addendum I.3. Submission of education materials. Once approval has been received, the subsequent versions of the materials should be uploaded to the EMC immediately.

For the [redacted] e-learning module, as the RMP [redacted] removed this requirement no further action is required with regard to this aRMM.

Root Cause Analysis
[redacted]

Further Assessment
[redacted]

Corrective Action(s)
[redacted]

Deliverable(s)	**Due Date(s)**
[redacted]	

Preventative Action(s)
[redacted]

Deliverable(s)	**Due Date(s)**
[redacted]	

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Finding CR.1 b)
There were no documented procedures which detailed how Morningside would ensure that aRMMs would be implemented in accordance with agreed RMPs. [redacted] 'Generation, Submission and maintenance of Risk Management Plan (RMP)' had been in effect since 25 September 2017 and governed RMP processes but this did not include detail on how aRMMs would be managed and implemented.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Preventative Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]

C.4.2 Major findings

MA.1 Additional risk minimisation measures

Requirements:

GVP Module XVI addendum I: Educational Materials

XVI. Add I.4. Format and layout of educational materials
'for version control, a unique document identifier should be used on each sheet of the educational material, and the date of last revision of the text (i.e. the approval date of the material by the applicable national competent authority) in the format of " " should be provided on the first and the last page…'

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Finding MA.1 a)
The risk minimisation materials for [redacted], accessible from the EMC, did not include a unique document identifier on each page of the material to support version control. Additionally, the [redacted] 'Combined hormonal contraceptives: important information for women' included the date "January 2014", but the material had not been submitted to the MHRA for approval. This should be updated with the future approval date and the approval date included on all other risk minimisation materials for these products.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
[redacted]
Preventative Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]

MA.2 Reference safety information

Requirements:

Commission Implementation Regulation 520/2012, Article 11

'1. Specific quality system procedures and processes shall be in place in order to ensure the following:
...
(f) the update of product information by the marketing authorisation holder in the light of scientific knowledge, including the assessments and recommendations made public via the European medicines web-portal, and on the basis of a continuous monitoring by the marketing authorisation holder of information published on the European medicines web-portal'

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 5 Pharmacovigilance, Regulation 76(1)

'The holder of a UK marketing authorisation or parallel import licence for a medicinal product must ensure that the product information relating to the product is kept up to date with current scientific knowledge'

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Finding MA.2 a)
There were examples of delays of over six months taken to submit safety variations following identification of the need to update product information. 1. The MAH identified the need to update the SPC and PIL for [redacted] in line with the reference product on 10 December 2018, and this included an update to sections 5.1 and 5.2 of the SPC to describe the relative bioavailability of the product within plasma concentrations. However, submission was not made until 02 April 2020, 477 days since the identification date, significantly over the MHRA expected six-month timeframe from identification to submission. 2. The MAH identified the need to update the SPC and PIL for [redacted] on 13 August 2019 following a recommendation from the 8 - 11 July 2019 PRAC meeting. The PRAC recommended that product information should be updated to include safety information on the risk of nephrolithiasis with [redacted] and gave a submission deadline of 05 October 2019. However, the MAH did not submit a variation to the MHRA until 06 March 2020. 3. The MAH identified the need to update the SPC and PIL for [redacted] following PRAC and CMDh recommendations published on 22 April 2018, which included an update to section 4 of the SPC to revise the wording on overdose, pregnancy, contraception and fertility, and include information on increased toxicity through concomitant use of [redacted] and [redacted] However, submission was not made until 26 October 2018, over the MHRA expected six-month timeframe from identification to submission. The MAH stated that several variation submissions had been delayed in order to avoid multiple versions of SPCs and PILs due to ongoing variation applications at the same time. Morningside should discuss possible methods to manage multiple variation applications with the MHRA PIQU (Patient.Information@mhra.gov.uk).
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]
Preventative Action(s)
[redacted]

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Deliverable(s)	Due Date(s)
[redacted]	

Finding MA.2 b)

Prior to April 2020, there was no process in place to ensure that product information published on the EMC was kept up to date and, as a result, out of date or delayed uploads of SPCs were observed.

During the inspection it was found that, for two products, outdated SPCs were published on the EMC:

- [redacted] current approved version dated 04 December 2019, EMC SPC dated 13 February 2019. The current version of the SPC included updates to sections 4.4 and 4.8 to bring the SPC in line with the reference product. These updates included the addition of the following serious adverse events: deterioration of conditions with use of combined oral contraceptives (such as epilepsy and porphyria), chloasma, disturbances of liver function and induced or exacerbated symptoms of angioedema in women with hereditary angioedema exogenous oestrogens.
- [redacted] current approved version 16 December 2019, EMC SPC dated 26 September 2019. The current version of the SPC included updates to section 4.4 to bring the SPC in line with the reference product so that the correct graph of the number of VTE per 10,000 women in one year for [redacted] containing CHCs was included.

Furthermore, the MAH had not uploaded the current approved versions of SPCs for the below products within the expected 10-day timeframe following MHRA approval:

- [redacted] MHRA approval 05 February 2018, EMC updated 17 October 2020. The SPC section 4 had been updated to align with the reference product to include several new contraindications, special warnings and precautions for use, further information on use during pregnancy and interactions with other medicinal products, new information on the management of overdose and advice on reporting suspected adverse reactions.
- [redacted] MHRA approval 03 March 2020, EMC updated 22 April 2020. The SPC sections 4 and 5 had been updated to align with the reference product to add further information on interactions with other medicinal products, include more information on overdose and update the pharmacokinetic properties.

The new company procedure [redacted] 'Updates to external sites following approvals to artworks and SPCs', effective from April 2020, which detailed how product information on EMC would be maintained, also described a monthly check to ensure materials on EMC are up to date. Evidence was provided of the first monthly review completed in April 2020 but three products were not included in this first review: [redacted]

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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Corrective Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	
Preventative Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	

MA.3 Quality management systems

Requirements:

Commission Implementation Regulation 520/2012, Article 8

'2. The quality system shall cover organisational structure, responsibilities, procedures, processes and resources, appropriate resource management, compliance management and record management.

3. The quality system shall be based on all of the following activities:
…
(d) quality improvements: correcting and improving the structures and processes where necessary.'

GVP Module I.B.6. Responsibilities for the quality system within an organisation

'For the purpose of a systematic approach towards quality in accordance with the quality cycle (see I.B.3.), managerial staff (i.e. staff with management responsibilities) in any organisation should be responsible for:
…
identifying and investigating concerns arising within an organisation regarding suspected nonadherence to the requirements of the quality and pharmacovigilance systems and taking corrective, preventive and escalation action as necessary;'

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Finding MA.3 a)

There were no formal procedures in place to ensure the appropriate management of non-compliance and deviations identified in the pharmacovigilance system before March 2020.

The SOP titled: [redacted]-Deviations and CAPA process' had been in effect since 10 March 2020, just prior to the inspection.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)

[redacted]

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Deliverable(s)	Due Date(s)
[redacted]	

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Finding MA.3 b)
The MAH identified the lack of aRMM implementation outlined in CR.1.a) in February 2020 but there was a two-month delay to investigate the non-compliance and documenting corrective and preventative actions. CAPA [redacted] was raised 30 April 2020 and documented the root causes analysis as a 'lack of procedure on aRMM implementation' and 'delayed implementation of aRMMs'. The resulting corrective actions (to assign preparation of an effectiveness assessment and to conduct a gap analysis on approved RMPs/aRMMs) were also included with deliverables aimed for June 2020. These deliverables could have been addressed earlier if there had not been a delay in investigating and documenting the corrective and preventative actions.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)
[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Finding MA.3 c)
The SPC Gap Analysis created as part of CAPA [redacted] which was raised in response to the MHRA PIQU request to update product information for [redacted], did not include an entry for [redacted] As the product was not marketed at the time of inspection, this omission has minimum impact, yet the company should ensure that all MAs have been included in this analysis.
Root Cause Analysis
[redacted]
Further Assessment

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[redacted]	
Corrective Action(s)	
[redacted]	
[redacted]	
[redacted]	
Preventative Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	

MA.4 Regulatory affairs

Requirements:

Eudralex Volume 2A, Chapter 5 – Guidelines of 16 May 2013 on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008

'C.I.11 Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan'

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Finding MA.4 a)

The [redacted] RMP [redacted] was approved when the UK licence [redacted], was granted on 10 November 2014. Subsequently, when the UK licence [redacted] was granted on 30 March 2015, the RMP approved was [redacted] and this version included aRMMs which were not present in RMP [redacted]

The MAH did not submit a variation to update the dossier for [redacted] following the approval of version 2.1 of the [redacted] RMP.

Version 3.1 of the [redacted] RMP was approved on 22 April 2020 and was submitted for both licences, with the summary of revision of changes (Annex 8) including a statement that the RMP had been prepared for all licences of [redacted] (POM and P medicines).

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

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Preventative Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	

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C.4.4 Comments

[redacted]RMP: Morningside should check with MHRA assessors that Version 2.0 of the [redacted]RMP has been approved, as this was submitted alongside a [redacted] variation, instead of as a type II variation.

Morningside should note that with regard to RMS and CMS procedures, in the UK, MAHs can implement [redacted] variations based on the RMS approval date. Therefore, any changes to product packaging associated with such variations should be implemented within 3 – 6 months from receipt of variation approval from the RMS.

SECTION D: CONCLUSIONS AND RECOMMENDATIONS

D.1 Conclusions

The factual matter contained in the Inspection Report relates only to those things that the inspection team saw and heard during the inspection process. The Inspection Report is not to be taken as implying a satisfactory state of affairs in documentation, premises, equipment, personnel or procedures not examined during the inspection. It is recommended that you review whether the inspection findings also apply to areas not examined during the inspection and take appropriate action, as necessary.

The responses to the inspection findings, which include proposed corrective and preventative actions, do appear to adequately address the issues identified. No additional responses are required at this time. When the company has adequately implemented the proposed corrective and preventative actions, the pharmacovigilance system will be considered to be in general compliance with applicable legislation.

D.2 Recommendations

Given the seriousness of the inspection findings, the Inspection Action Group for GCP and Pharmacovigilance (IAG) has recommended that the next MHRA pharmacovigilance inspection is performed within the next 12 months, to review the impact of the actions taken in response to the inspection findings. Please note that this inspection may be conducted unannounced or at short notice.

IAG have also agreed that every 6 months from the date of issue of the final inspection report, Morningside must submit to the lead inspector a list of new MAs and new or updated RMPs which include aRMMs.

In addition, Morningside should submit to the lead inspector the full Gap report from MA.4 a) (Corrective Action Deliverable 13) upon completion, but no later than 16 November 2020.

APPENDIX I REFERENCE TEXTS

- Directive 2001/83/EC, as amended.
- Commission Implementing Regulation (EU) No 520/2012.
- Commission Implementing Regulation (EU) No 198/2013.
- Guideline on good pharmacovigilance practices (GVP).
- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916).
- CPMP/ICH/5716/03: E2E "Pharmacovigilance Planning".
- Eudralex Volume 2A, Chapter 5 – Guidelines of 16 May 2013 on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures - C (2013) 2804 (OJ C 223, 2.8.2013, p. 1–79).

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	TBC		
PHARMACOVIGILANCE INSPECTION OF	Morningside	**DATES**	20 April until ~ 12 June 2020
LOCATION	Office-based inspection		

Inspection plan

This inspection will focus on the following topics:

1. **Maintenance of Reference Safety Information**
   - Pre-submission processes
   - Post-approval processes
   - Implementation of updated RSI
2. **Risk Management**
   - Routine and additional risk minimisation measures
   - Additional pharmacovigilance activities

Inspection timetable

Thursday 7 May

Initial document requests made on 20 April should be submitted via the agreed platform by COB Thursday 7 May.

Monday 11 May – Friday 15 May

Inspectors will complete a review of the documents provided. If required, the Lead inspector will communicate any queries that arise from this review which can be addressed via telephone interviews with relevant SMEs or through written communication.

A further set of document requests will be made by the inspection team by COB Friday 15 May.

Tuesday 26 May

Documents from the second set of requests should be submitted by COB Tuesday 26 May.

Wednesday 27 May until – Tuesday 2 June

Inspectors will complete a review of the documents provided. If required, the Lead inspector will communicate any queries that arise from this review which can be addressed via telephone interviews with relevant SMEs or through written communication.

It is anticipated a further set of document requests will be made by the inspection team by COB Tuesday 2 June.

Tuesday 9 June

If required, documents from the third set of requests should be submitted by COB Tuesday 9 June.

Documents were provided Wednesday 03 June

~~**Wednesday 10 June until ~ Friday 12 June**~~ ***Monday 08 June***

Inspectors will complete a review of the documents provided.

If any further document requests are required, Morningside will have a period of 7 calendar days to provide the information.

The Lead Inspector will notify the company once the office-based inspection is complete and will request a teleconference to provide feedback on any non-compliance identified.

N.B. the plan may be subject to change in the lead-up to, or during, the inspection.

Inspection team: [redacted]