Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name:	Otsuka Pharmaceutical Europe Limited
MHRA Inspection Number:	Insp GPvP 11515/9024085-0006

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
CCDS	Company Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organisation
CSR	Clinical Study Report
DCP	Decentralised Procedure
DHPC	Direct Healthcare Professional Communication
DSUR	Development Safety Update Report
EMA	European Medicines Agency
EU	European Union
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GVP	Good Vigilance Practice
HCP	Healthcare Professional
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
KPI	Key Performance Indicator
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Mutual Recognition Procedure
NAP	Nationally Authorised Product
NCA	National Competent Authority
NIS	Non-Interventional Study
PAES	Post-Authorisation Efficacy Study
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit Risk Evaluation Report

PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreements
QA	Quality Assurance
QMS	Quality Management System
QPPV	Qualified Person responsible for Pharmacovigilance
RMM	Risk Minimisation Measures
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDEA	Safety Data Exchange Agreement
SmPC	EU Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
UK	United Kingdom
XEVMPD	eXtended Eudravigilance Medicinal Product Dictionary

SECTION A: INSPECTION REPORT SUMMARY

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Inspection type:	Statutory National Inspection
System(s) inspected:	Otsuka Pharmaceutical Europe Ltd PSMF MFL2638
Site(s) of inspection:	Remote inspection
Main site contact:	[redacted]
Date(s) of inspection:	19 – 20th May 2020 1st – 2nd June 2020
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	2013: GPvP 11515/285599-0006, 9 – 11th April 2011: GPvP 11515/122759-0003, 2nd – 4th November 2010: GPvP 11515/122759-0002, 16 – 17th June 2008: GPvP 11515/122, 6 – 9th May
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 systems review, risk management activities for [redacted] were examined
Name and location of EU QPPV:	[redacted]
Global PV database (in use at the time of the inspection):	Argus Safety Web version 7.0
Key service provider(s):	No relevant service providers in the context of the inspection scope
Inspection finding summary:	0 Critical findings 1 Major finding 2 Minor findings
Date of first issue of report to MAH:	24 June 2020
Deadline for submission of responses by MAH:	29 July 2020
Date(s) of receipt of responses from MAH:	29 July 2020
Date of final version of report:	3 August 2020
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Otsuka Pharmaceutical Europe Limited 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 Regulation (EC) No 726/2004 as amended, 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.

Otsuka Holdings Ltd is a global organisation with headquarters in Tokyo, Japan. The organisation has business operations in 27 countries and regions worldwide including Asia-Pacific, America, Europe and the Middle East. Otsuka Pharmaceutical Netherlands BV (OPNL) is the MAH for most Otsuka products marketed in the UK and EU and is a wholly owned subsidiary of Otsuka Pharmaceutical Europe Limited (OPEL), which is the European commercial organisation.

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Otsuka has five centrally authorised products for which OPNL is the MAH: [redacted] and [redacted] There is also the centrally authorised product, [redacted] for which Otsuka Novel Products GmbH (ONPG) is the MAH.

The headquarters of Otsuka's global PV organisation is located in New Jersey, US; there are three regional PV centres in New Jersey, US, Asia (Japan and Korea) and Europe (UK and Germany). The EU QPPV and PSMF are located in Germany and BfArM is the supervisory authority responsible for performing pharmacovigilance inspections on behalf of the EU (and the UK during the transition period). Therefore, the scope of the inspection focused on national aspects of the PV system.

B.2 Scope of the inspection

The inspection was focused on routine and additional risk minimisation measures, including the tracking and submission of safety variations, the implementation of updated product information and the implementation of additional risk minimisation measures. Due to the current COVID-19 pandemic, the inspection was performed entirely remotely over four days. The inspection was predominantly performed via document review; however, personnel involved in pharmacovigilance activities were available via videoconference throughout the inspection for ad-hoc queries.

The systems reviewed during the inspection are highlighted in the Pharmacovigilance Inspection Plan (attached as Appendix II).

B.3 Documents submitted prior to the inspection

The company submitted a PSMF (version 91.0, dated 31-Mar-2020) to assist with inspection planning and preparation. Specific documents were requested by the inspection team and

provided by the company prior to the inspection, and these are recorded in document request sheet A. Further documents were requested during the four-day remote inspection.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Inspection Plan and ad hoc interviews with Otsuka personnel are highlighted on the plan in blue text. A closing meeting was held via videoconference on 02-Jun-2020 to review the inspection findings.

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 inspection in April 2013 the company had made the following changes to the pharmacovigilance system:

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- The EU QPPV had changed from [redacted] and is now [redacted]
- Centralised licences were obtained for [redacted] (Nov-2013), [redacted] (Apr-2014), [redacted] (May-2015) and [redacted] (Jul-2018). [redacted] is not currently marketed in the UK.
- [redacted] was withdrawn from the market in October 2019. Residual stock of [redacted] is available to patients until its expiry.

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

No critical findings were identified from the review of pharmacovigilance processes, procedures and documents performed during this inspection.

C.4.2 Major findings

MA.1 Additional risk minimisation measures

Requirements:

Regulation (EC) No. 726/2004 as amended, Article 21(2)

Directive 2001/83/EC as amended

- Article 104(2) *"The marketing authorisation holder shall by means of the pharmacovigilance system referred to in paragraph 1 evaluate all information scientifically, consider options for risk minimisation and prevention and take appropriate measures as necessary."*
- Article 104(3) *"As part of the pharmacovigilance system, the marketing authorisation holder shall:*

  (c) operate a risk management system for each medicinal product;"

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

GVP Module XVI Addendum I – Educational materials

- XVI. Add I.4. *"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 "<month> <year>" should be provided on the first and the last page".*

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 additional risk minimisation measures (aRMMs) may be deemed necessary.

Otsuka had two products for which aRMMs were required:

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- [redacted] is indicated for use as part of an appropriate combination regimen for pulmonary multidrug-resistant tuberculosis (MDR-TB) and has an orphan designation in the EU. The [redacted] aRMMs consisted of an educational programme to manage important identified risks of QT interval prolongation and drug resistance and important potential risks of drug use during pregnancy and breastfeeding. HCP and patient educational materials were distributed electronically via email and as hard-copies to the physician upon receipt of their initial order, and as replacement hard-copies if requested on subsequent orders.

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- [redacted] is indicated for autosomal dominant polycystic kidney disease (ADPKD). The [redacted] aRMMs initially consisted of a training and certification programme for HCPs and a controlled distribution model in the UK that ensured that only trained and certified prescribers could order and receive the product. In early 2020 it was agreed by the MHRA that the controlled distribution model for tolvaptan could cease; however, the prescriber training and certification programme continues.

The following major findings were noted in relation to aRMMs:

Finding MA.1 a)

There were no documented maximum timeframes for updating local additional risk minimisation materials and submitting them to the local health authority following a trigger for update, e.g. an important update to the SmPC such as the additional of a contraindication.

Timelines for updates to local additional risk minimisation materials and submission to the local health authority were determined on a case by case basis, as described in Section 3.4 of [redacted] 'Notification of Changes to SmPC, PL and PI by [redacted] to the [redacted] affiliates and relevant Third Parties' (v1.0, 20-Dec-2019).

There were examples identified during the inspection where the UK additional risk minimisation materials for [redacted] were not updated in a timely fashion to align with the approved updates to the authorised product information:

i. Section 4.3 of the [redacted] EU SmPC was updated to add a contraindication of hypersensitivity to [redacted] derivatives. The licence variation was approved on 29-Jun-2018; however, the [redacted] additional risk minimisation materials, which included an HCP Educational Guide and training slides, were not updated and submitted to the MHRA until 14-Aug-2018, which was 46 days later.

ii. Sections 4.4 and 4.8 of the [redacted] EU SmPC were updated to add a warning and update the safety information on acute liver failure requiring liver transplantation, based on post-marketing experience with tolvaptan in ADPKD. The licence variation was approved on 13-Sep-2018; however, the [redacted] additional risk minimisation materials were not updated and submitted to the MHRA until 05-Nov-2018, which was 53 days later.

As per Directive 2001/83/EC as amended, Article 104(2), MAHs should take appropriate risk minimisation and prevention measures, as necessary.

Root Cause Analysis

[redacted]

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[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 MA.1 b)
Out of a total of nine orders for [redacted] reviewed during the inspection, one shipment did not include the hard-copy [redacted] risk minimisation materials as required. The shipment dated 02-Jan-2018 to [redacted] was a re-supply of [redacted] and educational material was required to be re-supplied to the physician as part of the shipment as per the distribution plan agreed with the MHRA in May 2014. However, the company stated in writing that due to human error at the distributor's site, the materials were not included within the shipment. The physician had received the correct version of the materials via email following their initial order on 27-Jul-2017, but they should have been re-supplied with the later shipment.
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.1 c)
The [redacted] risk minimisation materials current at the time of the inspection were not in full compliance with GVP Module [redacted] – Educational materials.

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i. On the final page of the HCP and patient brochures, a 'Date of preparation' of June 2018 was included; however, the MHRA approval for these materials was provided on 22-Nov-2018. As per GVP Module [redacted] the materials should include the date of last revision of the text (i.e. the approval date of the material by the applicable national competent authority) on the first and the last page.

ii. The materials did not include a unique document identifier on each page.

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]	

C.4.3 Minor findings

MI.1 Maintenance and communication of reference safety information

When new information about the benefits and risks of a product become available it is often appropriate to make changes to reference safety information documents, such as SmPCs and PILs, so that healthcare professionals and patients are able to use the medicinal product correctly on the basis of full and comprehensive information. Communicating safety information to patients and healthcare professionals is a public health responsibility and is essential for achieving the objectives of pharmacovigilance in terms of promoting the rational, safe and effective use of medicines, preventing harm from adverse reactions, minimising risks and contributing to the protection of patients' and public health.

It was noted that Otsuka has had previous issues with the management and communication of updated safety information. There have been numerous complaints raised with the Prescription Medicines Code of Practice Authority (PMCPA) in 2018 and 2019, as well as voluntary admissions submitted by Otsuka in relation to breaches of the ABPI Code of Conduct, specifically in relation to the maintenance of abbreviated prescribing information (API) and educational materials, and maintenance of updated product information on the eMC website. Some of the PMCPA cases remain open pending completion of an audit of the company's procedures in relation to the Code. In addition, an internal audit of the 'End-to-End Product Labelling Management and Implementation' processes [redacted] reported a critical finding in relation to breaches of procedures (audit report date 29-Mar-2019). As a result, Otsuka has updated procedural documents to reflect changes in the Global Regulatory Affairs process for management of labelling updates, performed re-training for relevant staff and established a new workflow within the Regulatory Information Management System used in Europe for distribution of labelling documents. In addition, compliance metrics for the end-to-end label process to support key stakeholders' oversight responsibilities have been improved.

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Based on the actions taken by Otsuka in relation to the PMCPA cases and the internal audit findings, plus the fact that the issues identified by the inspectors appeared to be historic examples rather than more recent systematic issues, the following findings in relation to the maintenance and communication of reference safety information have been graded as minor.

Finding MI.1 a)
Batches of [redacted] tablets were released with a superseded version of the PIL greater than six months after the approval of a variation to add a contraindication of hypersensitivity to [redacted] on 29-Jun-2018. The last batch [redacted] was released on 07-Feb-2019 with PIL component code [redacted] (superseded version). This was over seven months after the variation to add this contraindication was approved. It was noted that the target implementation recorded in the Change Notice form [redacted] for the updated PIL (component code [redacted] was 30-Nov-2018. This has been graded as a minor finding because the MAH was notified by its contract manufacturer for [redacted] in January 2019 that batches had been packed and QP released using a superseded PIL and Otsuka notified the MHRA's Defective Medicines Report Centre and the EMA on 17-Jan-2019. The EMA confirmed that replenishment of stock with the correct PIL should be initiated as soon as possible but an out of stock situation for [redacted] should be avoided as there is no alternative product for the treatment of ADPKD. Batch

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[redacted] was the last batch released with the outdated PIL. The MHRA inspectors did not identify any other issues with release of outdated leaflets.

In addition, Otsuka submitted a voluntary admission to the PMCPA in March 2019 regarding this issue.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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[redacted]

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

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

Finding MI.1 b)

There was evidence of delays in updating the published SmPCs and PILs on the eMC for [redacted]

i. A variation to update sections 4.4 and 4.8 of the [redacted] SmPCs with further information about the risk of impulse control disorders, and section 4.8 of the SmPC to include the new ADRs 'impulse control disorders', 'binge eating', 'compulsive shopping' and 'poriomania' was approved on 26-Oct-2017; however, the updated product information was not sent to Datapharm for upload on the eMC until January 2018. The exact dates are included in the table below.

Product	Date that SmPC was sent	Date that PIL was sent
[redacted]	30-Jan-2018	25-Jan-2018
[redacted]	29-Jan-2018	25-Jan-2018
[redacted]	15-Jan-2018	12-Jan-2018
[redacted]	15-Jan-2018	15-Jan-2018

ii. A variation to update section 4.4 of the [redacted] SmPC to add a statement concerning liver failure requiring liver transplantation and section 4.8 with the addition of acute hepatic failure was approved on 13-Sep-2018; however, the updated product information was not sent to Datapharm for upload on the eMC until 22-Oct-2018.

As described in the company's internal procedure [redacted] 'Notification of Changes to SmPC, PL and PI by [redacted] to the [redacted] affiliates and relevant Third Parties' (v1.0, 20-Dec-2019) section 3.4, internal and external websites should be updated within 10 business days of receiving notification from [redacted] Lead/ONPG Senior Director International Medical and Clinical Operations of the approved product information. Additionally, the MHRA's expectation is that updated SmPCs and PILs should be sent for upload on the eMC within 10 business days from variation approval.

This has been graded as a minor finding because more recent examples reviewed during the inspection of product information updates in 2019 were found to have been sent to Datapharm for upload on the eMC in a timely fashion.

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Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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[redacted]

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

Preventative Action(s)

[redacted]

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

Finding MI.1 c)

There was an example where there was an unacceptable delay in updating the API for [redacted] following an update to the SmPC to add a statement concerning liver failure requiring liver transplantation to section 4.4 and the addition of acute hepatic failure to section 4.8. The variation to update the authorised product information was approved on 13-Sep-2018; however, the API was not updated and made effective until 16-Oct-2018 (item code [redacted], which was 33 days later.

It was also noted that Jinarc promotional material that included the superseded version of the API was not withdrawn until 16-Oct-2018, specifically the online ADPKD Academy: Homepage and Supporting Pages (item code [redacted]

The MHRA expectation is that API is updated and promotional material containing superseded API is withdrawn within 10 business days from variation approval.

This has been graded as a minor finding because other examples of API reviewed during the inspection were updated in a timely fashion.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment
[redacted]

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

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

MI.2 Additional risk minimisation measures

The following minor findings were identified in relation to aRMMs:

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Finding MI.2 a)
[redacted] 'Selection of aRMMs and Evaluation of Effectiveness' (v.1, 29-Mar-19 and v.2, 12-May-2020) described that an 'aRMM evaluation report' would be completed to document the review of effectiveness of risk minimisation measures. However, since this working practice became effective, no aRMM evaluation reports had been completed for [redacted] This has been graded as a minor finding because the latest PSURs for the products (delamanid 28-Oct-2018 to 27-Oct-2019 and tolvaptan 19-Nov-2018 to 18-May-2019) did include an evaluation of the effectiveness of risk minimisation. Otsuka stated that there are plans to document the effectiveness evaluations of the aRMMs for delamanid and tolvaptan in the standalone template coinciding with the timing of the upcoming PSURs for both products.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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[redacted]

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

Preventative Action(s)
[redacted]

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

Finding MI.2 b)

Overall, the inspectors were satisfied that the [redacted] additional risk minimisation materials were being communicated as intended, as there was evidence of electronic and hard-copy dissemination of HCP and patient educational materials for the orders sampled during the inspection and the current versions of the materials were available on the electronic Medicines Compendium (eMC).

However, there were some aspects relating to the initial aRMM implementation plan agreed with the MHRA that had not strictly been adhered to.

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i. In the initial implementation plan agreed with the MHRA in May 2014, Otsuka stated *"we will follow up the pharmacist and/or responsible physician within 10 working days of the date of dispatch by email or phone to confirm that the RMP materials have been reviewed and the necessary risk minimisation actions taken."*

In practice, Otsuka had not followed up with the pharmacist and/or responsible physician within 10 working days of dispatch of the educational materials. In November 2015, the MAH submitted a revised [redacted] order form to the MHRA which included an attestation by the ordering pharmacist that the order complies with the Clinical Commissioning Policy for delamanid [redacted] published July 2015). It was stated during the inspection that this attestation provided the necessary assurance that the physician understood the necessary risk minimisation actions (such as monthly monitoring of ECGs during the treatment). However, it was not made clear in the 2015 correspondence with the MHRA that the company would not fulfil the original commitment to follow-up with the individual physicians.

ii. In addition, the May 2014 correspondence with the MHRA included the statement *"The risk management information will also be made available for download through eMC, in due course via an Otsuka medical-information web-site when available and will be supplied via medical information directly on request."*

Otsuka stated during the inspection that, as there were only a limited number of product orders received following the launch of [redacted] in the EU which enabled the MAH to reply to each request individually, the decision was taken not to implement a medical information website. This was not communicated to the MHRA.

Following the inspection, a discussion was held between the lead inspector and the assigned MHRA assessor for [redacted] to discuss these issues. The assessor's view was that, as [redacted] has been on the UK market since 2014 and the product is prescribed by specialist physicians in [redacted] treatment centres who should have a sound understanding of [redacted] safety profile and risk minimisation measures, it is not considered necessary to have individual follow-up with physicians. The introduction of a medical information website is also not considered necessary as the materials are available online via the eMC. Therefore, Otsuka's response to this inspection finding should focus on preventative actions to ensure that future commitments agreed with regulatory authorities are adequately captured and implemented by the MAH.

Root Cause Analysis

[redacted]

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[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 MI.2 c)

Overall, the inspectors were satisfied that the [redacted] aRMMs were being implemented as intended. The controlled distribution model was not reviewed during this inspection as it was agreed by the MHRA in early 2020 that this could be discontinued, so the focus of review during the inspection was on prescriber training and certification. Based on the documentation reviewed during the inspection, the processes for training and certification appeared to be robust and there was evidence that only certified prescribers were placing orders for [redacted]

One of the requirements of the [redacted] risk management system was that HCPs must complete the RMP educational training and register on the [redacted] prescriber database to become certified prescribers eligible to order and prescribe [redacted] Training and certification can be recorded by one of two ways:

- Online via the [redacted] training portal [redacted] Confirmation of training is captured via completion of an electronic enrolment form by the HCP.
- Face to face training with an Otsuka representative, whereby confirmation of training was entered into the prescriber database by an Otsuka staff member.

For the face to face training, a limitation of the system meant that the date of training was recorded as the date of entry into the system. For example, [redacted] completed face to face training on 18-Jun-2015 and [redacted] completed face to face training on 01-Jul-2015; however, the dates of training in the prescriber database were recorded as 14-Aug-2015, which was the date of entry.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

C.4.4 Comments

1. The delamanid RMP current at the time of the inspection (v.3.2) referred to a 'Healthcare Professional and Patient/Carer Guide' (page 108), which appeared to be in addition to the educational materials for HCPs and patients described on pages 107-108. However, Otsuka confirmed that this was the same material as the HCP and patient educational materials. It is recommended that this is clarified at the next RMP update to avoid confusion.

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

The Lead Inspector has recommended that the next MHRA inspection is performed as part of the routine risk-based national inspection programme.

APPENDIX I REFERENCE TEXTS

- Regulation (EC) No. 726/2004 (Title II, Chapter 3), as amended.
- 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”.

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	Insp GPvP 11515/9024085-0006	**DATES**	Inspection day 1: 19 May 2020 Inspection day 2: 20 May 2020 Inspection day 3: 01 June 2020 Inspection day 4: 02 June 2020
PHARMACOVIGILANCE INSPECTION OF	Otsuka	**START TIME**	09:00 on all days
INSPECTOR	[redacted]		

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

This inspection will be focused on routine and additional risk minimisation measures (including but not limited to the tracking and submission of safety variations, the implementation of updated product information and the implementation of additional risk minimisation measures).

Tuesday 19 May 2020 (day 1)

An opening meeting will be held at the start of the inspection by teleconference (TC) on the morning of day 1 which will be led by the lead inspector. The agenda will be:

- Review of the scope and arrangements for the inspection
- Brief presentation by Otsuka (20 min maximum) with an overview of the company and pharmacovigilance system. The presentation should focus on the topics listed for inspection and any relevant ongoing remediation work in the pharmacovigilance system.

The remainder of the inspection will consist of remote document review. Interview sessions with company personnel are not intended. However, please provide a designated contact point who can assist with any ad hoc questions from the inspector or arrange calls between inspector and subject matter experts if required.

Wednesday 20 May 2020 (day 2)

Day 2 of the inspection will consist of remote document review. Interview sessions with company personnel are not intended. However, please provide a designated contact point who can assist with any ad hoc questions from the inspector or arrange calls between inspector and subject matter experts if required.

Section 43

Interview in relation to [redacted] aRMMs:

Interviewees:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Additional Attendees:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

A TC will be held with the QPPV or delegate on day 2 (time to be confirmed) to indicate the end of the first phase of the inspection and to confirm the plan for inspection day 3.

If required, a second batch of document requests will be submitted at the end of day 2. Documents should be provided by **COB on 29 May 2020**.

Monday 01 June 2020 (day 3)

Review of documents provided for batch 2 and discussion of ad hoc queries from the inspector.

Tuesday 02 June 2020 (day 4)

Review of documents provided for batch 2 and discussion of ad hoc queries from the inspector.

Interview in relation to [redacted] aRMMs:

Interviewees:

- [redacted]
- [redacted]
- [redacted]

Section 43

Additional Attendees:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Interview in relation to UK abbreviated prescribing information & promotional materials:

Interviewees:

- [redacted]
- [redacted]

Additional Attendees:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Interview in relation to [redacted] UK orders:

Interviewees:

- [redacted]
- [redacted]

Additional Attendees:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

The inspection will finish with a closing meeting TC on day 4 (time to be confirmed) when feedback will be provided on the inspection.

Section 43

Otsuka should complete the below with the names and job titles of the designated contact point and those staff who will be dialling into the opening meeting.

Designated contact point:

- [redacted]

Opening meeting attendees:

- [redacted]
- [redacted]
- [redacted]
- Phi[redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]