Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Proveca Limited

MHRA Inspection Number: Insp GPvP 51785/16593606-0004

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ABBREVIATIONS

ADR	Adverse Drug Reaction
CAP	Centrally Authorised Product
CAPA	Corrective and Preventative Action
CHMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
GVP	Good Vigilance Practice
HCP	Healthcare Professional
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
PASS	Post-Authorisation Safety Study
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk Management Plan
SDEA	Safety Data Exchange Agreement
SmPC	EU Summary of Product Characteristics
UK	United Kingdom

SECTION A: INSPECTION REPORT SUMMARY

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Inspection type:	Statutory National Inspection
System(s) inspected:	Proveca Limited, [redacted]
Site(s) of inspection:	NEO, Charlotte Street, Manchester, M1 4ET, UK
Main site contact:	[redacted] Drug Safety Solutions Limited Sleper 11 Brunssum 6446 BW Netherlands [redacted]
Date(s) of inspection:	The inspection was conducted onsite from 01 – 04 July 2019.
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
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 general systems review, specific ADR reports and PSURs were examined for [redacted]
Name and location of EU QPPV:	[redacted] Drug Safety Solutions Limited Sleper 11 Brunssum 6446 BW Netherlands Contact details as above.
Global PV database (in use at the time of the inspection):	Microsoft Excel (commercially available software).
Key service provider(s):	Pharmacovigilance services provided by Drug Safety Solutions Limited. Medical information services provided by ProPharma Group.
Inspection finding summary:	0 Critical finding(s) 6 Major finding(s) 3 Minor finding(s)
Date of first issue of report to MAH:	12 August 2019
Deadline for submission of responses by MAH:	17 September 2019, 28 November 2019, 19 December 2019
Date(s) of receipt of responses from MAH:	16 September 2019, 28 November 2019, 19 December 2019
Date of final version of report:	20 December 2019
Report author:	[redacted]

	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Proveca 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.

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Proveca Limited (hereafter 'Proveca') is a sister company of Irish-based Proveca Pharma Limited, the current MAH of the centrally authorised product [redacted] Proveca was the MAH for [redacted] from EU marketing authorisation approval on 15 September 2016 until 28 March 2019. The product is licensed for the symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders.

At the time of inspection, [redacted] was marketed in the UK, Ireland, Germany, Sweden Norway, Denmark, Iceland and Italy.

At the time of the inspection, the PSMF was located in the Netherlands, therefore the Medicines Evaluation Board was the Supervisory Authority responsible for conducting pharmacovigilance inspections on behalf of the EU.

Pharmacovigilance activities, including the QPPV role, processing and follow-up of adverse event reports, literature searching, signal management and PSUR production are carried out by Drug Safety Solutions Limited (DSSL). Medical information services have been subcontracted to ProPharma Group (PPG).

B.2 Scope of the inspection

The inspection included a review of the global pharmacovigilance system and was performed at Proveca's offices in Manchester. Personnel from the Proveca office in Manchester and DSSL attended the inspection site in order to participate in the inspection. Personnel from PPG participated in the inspection via teleconference.

The inspection was performed using interviews and document review (including outputs from the global safety database and listings of medical information enquiries and product complaints). 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 [redacted] 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. The detail of these requests is contained within document request sheets A and B.

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.

A closing meeting was held to review the inspection findings at the Proveca offices, Manchester on 04 July 2019. Document review was concluded on 09 July 2019 when the last document in response to a follow-up document request was provided.

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

Not applicable as this was the first MHRA pharmacovigilance inspection of the company.

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 Signal Management

Requirements:

Commission Implementing Regulation (EU) No. 520/2012
Article 18(2)
"*Marketing authorisation holders shall monitor the data available in the Eudravigilance database to the extent that they have access to that database.*"

Article 18(3)
"*Marketing authorisation holders, the national competent authorities and the Agency shall ensure the continuous monitoring of the Eudravigilance database with a frequency proportionate to the identified risk, the potential risks and the need for additional information.*"

GVP Module IX – Signal management (Rev 1)
IX.C.3.2. Periodicity of monitoring
"*It is recommended to monitor EudraVigilance data at least every 6 months.*"

MAHs are obliged to ensure that information on the benefits and risks of their products is evaluated on an ongoing basis and appropriate action is taken in response to new information that impacts on the benefit-risk balance.

The following finding was noted in relation to signal detection and management:

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Finding MA.1

Proveca had failed to monitor the data available in EudraVigilance for signal detection purposes for [redacted] even though it was part of the EMA pilot on signal detection in EudraVigilance.

The EMA pilot on signal detection started on 22 February 2018 and the MAHs involved are required to monitor EudraVigilance for signal detection purposes at least every 6 months for all products that are included in the pilot.

It is acknowledged that there was a process in place at DSSL for monitoring EudraVigilance (DSSL GD 11 *How to use retrieve and use data from EudraVigilance*, [redacted] date effective 30 April 2018); however, this had not yet been implemented for [redacted]

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

[redacted]	

MA.2 Additional risk minimisation measures

Requirements:

Commission Implementing Regulation (EU) No. 520/2012
Article 10(3)
"*All personnel involved in the performance of pharmacovigilance activities shall receive initial and continued training in relation to their role and responsibilities. The marketing authorisation holder shall keep training plans and records for documenting, maintaining and developing the competences of personnel and make them available for audit or inspection.*"

GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2)
XVI.B.6. Quality systems of risk minimisation measures
"*The marketing authorisation holder should ensure appropriate version control of the risk minimisation tools in order to ensure that all healthcare professionals and patients receive up-to-date risk minimisation tools in a timely manner and that the tools in circulation are consistent with the approved product information. For this purpose the market authorisation holders are encouraged to keep track of the receipt of any risk minimisation tools by target audience. These records may be subject to audit and inspection.*"

GVP Module XVI Addendum I – Educational materials
XVI. Add I.2. Principles for educational materials
"*The marketing authorisation holder should exercise version control and ensure that only the latest agreed version of the educational material is disseminated.*"

XVI. Add I.3. Submission of educational materials
"*If no other national requirements apply, the draft educational material should be submitted to the competent authorities of Member States as follows:*

- 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; […]."

XVI. Add I.5. Content of educational materials
"*A statement which encourages the reporting of any suspected adverse reaction and information on the modalities how to report in the Member State should be also included.*"

XVI. Add I.6. Assessment and publication of educational materials by the competent authorities of Member States
"*Marketing authorisation holders are solely responsible for the provision, to the competent authorities, of the latest agreed versions of the educational materials.*"

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As part of the conditions of the marketing authorisation for [redacted], the MAH was required to implement a risk management programme, which consisted of educational materials for HCPs and carers to provide information on the administration of [redacted] and to provide information on the management and minimisation of anticholinergic adverse reactions. As per Annex II.D *Conditions Or Restrictions With Regard To The Safe And Effective Use Of The Medicinal Product* of the marketing authorisation, the following elements should be included in the educational materials:

Physician educational materials

- The Summary of Product Characteristics
- Information about the drug utilisation study to monitor and assess effectiveness of additional risk minimisation measures for anticholinergic side effects that may be dose dependent and the importance of contributing to such a study
- Remarks on the importance of reporting on specific adverse drug reactions, namely: urinary retention, constipation, pneumonia, allergic reactions, dental caries, cardiovascular effects, CNS effect and overheating
- The Prescriber checklist, which shall contain the following key messages:
  - Information on the administration of Sialanar
  - Management and minimisation of anticholinergic reactions

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Patient information pack

- Patient information leaflet
- The reminder card for patient's carer, which shall contain the following key messages:
  - Information on the administration of [redacted]
  - Management and minimisation of anticholinergic reactions

The following findings were noted in relation to the educational materials fo[redacted]

Finding MA.2 a)

The UK [redacted] educational materials were submitted to the MHRA on 10 October 2016 and received approval on 11 October 2016. The following deficiencies were identified in relation to the submission of educational materials to MHRA:

i. The MAH did not submit the full educational materials as required per Annex II.D of the marketing authorisation to the MHRA for approval. The prescriber's checklist and reminder card for caregivers were submitted to and approved by MHRA; however, the MAH did not submit any materials which included information about the drug utilisation study. As a result, the hard copy version of the educational packs [redacted] dated May 2017) made no reference to the drug utilisation study.

ii. When the educational materials were submitted to the MHRA for approval in October 2016, no detailed implementation plan, containing the information as per GVP Module XVI Addendum I was provided to assessors. It is acknowledged that none had been requested by the MHRA assessor at the time.

    At the time of the inspection, the UK educational materials were made available on the product website [redacted] and HCPs could either download electronic copies or request paper copies to be sent to them. In addition, paper copies were distributed to paediatricians and paediatric neurologists via key account managers (KAMs), company stands at conferences and in relation to the set-up of study sites for the drug utilisation study. However, this approach had not been agreed with the MHRA.

iii. The MAH had failed to submit an updated version of the educational materials to the MHRA for information following a change in the MAH address in May 2017. This finding is graded minor but has been grouped within the major finding on Additional Risk Minimisation Measures.

Post-inspection request: Proveca are instructed to submit the current educational materials and a detailed implementation plan to the MHRA for approval in line with the requirements of GVP Module [redacted] specifically section XVI. Add I.3. *Submission of educational materials.*

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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.2 b)

In relation to the content of the educational materials, the following deficiencies were noted:

i. At the time of the inspection, the hard copy educational materials [redacted] dated May 2017) and the electronic version accessible at [redacted] (date of last revision 15 February 2017) did not reflect the current MAH name and address (Proveca Pharma Limited, Marine House, Clanwilliam Place, Dublin 2, Ireland) which had been valid since 28 March 2019.

ii. The current hard copy educational materials [redacted] did not include a statement encouraging the reporting of any suspected adverse reaction

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and information on how to report adverse events in the UK.

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.2 c)

There was no system in place to ensure that only the current and up-to-date version of the hard copy educational materials was distributed to HCPs.

i. At the time of inspection, three out of six UK KAMs still held copies of the superseded version of UK educational materials ([redacted] after they had been amended in May 2017 to update the MAH address [redacted] Two of these KAMs also did not hold any hard copies of the updated version.

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[redacted] *Educational Material Creation, Approval and Control* [redacted] stated in section 6.6.(f) that KAMs would receive a notification that the materials had been superseded and that they should be destroyed; however, after version 1 of the materials had been superseded, KAMs were not informed of the change.

In addition, the procedure did not describe how it would be ensured that superseded materials had been destroyed.

ii. A review by inspectors of hard copy educational materials held at the Proveca office identified one example of the superseded version of the materials [redacted] that was stored with the current version of the materials [redacted]

During the inspection, the MAH was unable to retrace which version of the educational materials had been handed out to HCPs by KAMs and which version had been mailed from the Proveca office in the past.

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]	

Finding MA.2 d)

There were no formal training records documenting that UK KAMs had been trained on the educational materials and their content. Training on the risk management programme for [redacted] was important because the KAMs were responsible for distributing paper copies of the materials to paediatricians and paediatric neurologists. During the inspection, the MAH provided a written statement that KAMs had received training on the educational materials and the drug utilisation study on 22 February 2018; however, this had not been captured in training records.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Preventative Action(s)

[redacted]

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

MA.3 Post-Authorisation Safety Studies

Requirements:

Commission Implementing Regulation (EU) No. 520/2012, Article 11(1)(e)

GVP Module I - Pharmacovigilance systems and their quality systems, I.C.1.3. Role of the qualified person responsible for pharmacovigilance in the EU

GVP Module V – Risk management systems (Rev 2)
V.B.10.3.3. RMP annex 3 – part C: Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority
"*Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority should be included in this part C of RMP annex 3, as follows: […]*

- *The final protocols of other category 3 studies: protocols that were not requested to be reviewed by the competent authorities and are submitted by the marketing authorisation holder for information only.*"

V.C.2.1. Risk management plans updates
"*An RMP update is expected to be submitted at any time […] when there is a new or a significant change in the existing additional pharmacovigilance or additional risk minimisation activities. […] For example, a change in study objectives, population or due date of final results, or addition of a new safety concern in the key messages of the educational materials would be expected to be reflected in an updated RMP with the procedure triggering those changes.*" [emphasis added]

GVP Module VIII – Post-authorisation safety studies (Rev 3)
VIII.B.3. Study protocol
"*In order to ensure compliance of the marketing authorisation holder with its pharmacovigilance obligations, the qualified person responsible for pharmacovigilance (QPPV) or his/her delegate should be involved in the review and sign-off of study protocols required in the risk management plan agreed in the EU or conducted voluntarily in the EU […]*".

VIII.B.7. Quality systems, audits and inspections
"*The marketing authorisation holder shall ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified.*"

A PASS is defined in Directive 2001/83/EC as amended as any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

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At the time of inspection, Proveca was conducting a drug utilisation study (category 3 PASS, EUPAS24635) to monitor and assess the effectiveness of [redacted] educational materials. The study had commenced in the UK on 04 December 2018 and at the time of the inspection, two patients had been recruited by participating UK study sites in December 2018 and June 2019, respectively. Both patients had completed the baseline visit, but no further visits had taken place yet. Study set-up and management services were provided by the consultancy David M Projects Ltd.

The following findings were noted in relation to the PASS:

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Finding MA.3 a)

The following deficiencies were noted in relation to the documents and procedures specific to the PASS:

i. The [redacted] had not reviewed and signed off the current approved study protocol [redacted]

ii. The current approved RMP for [redacted] dated 16 December 2016) did not reflect the current status of the PASS and the anticipated date of the final study. In addition, the RMP did not include the current study protocol. [redacted] *Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan* stated that the study was planned and that the final study report would be due in July 2020. In contrast the current approved study protocol [redacted] dated 14 December 2018) stated in section 6. *Milestones* that the final study report would be due in June 2023. The amended study end date should have resulted in a change to the RMP requiring submission to the EMA for approval. As part of the RMP update the current study protocol should also have been appended to the RMP.

iii. Section 6. *Milestones* of the study protocol [redacted] dated 14 December 2018) did not reflect the actual milestones of the PASS. The protocol stated that the start of data collection was April 2018; however, the first patient in the UK was not enrolled until December 2018.

iv. There were no company procedures concerning the management of non-interventional studies, including non-interventional PASS, to ensure compliance of the process in relation to the following activities:
- Involvement of the QPPV in the review and sign-off of PASS protocols or the delegation of this activity (see point i);
- Submission of the final study report to competent authorities of EU Member States in which the study was conducted within 12 months of the end of data collection;
- Registration of the study in, and update of, the EUPAS register. It is acknowledged that the study was registered in the EU PAS Register at the time of inspection.

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]	
[redacted]	

Finding MA.3 b)

The following deficiencies were identified in relation to the management of the PASS:

i. There were examples of missing or incorrect data in the study database. The treating physician had to register participating patients in a web-based study portal which was also used to document the patient's baseline and follow-up visits. The clinical project manager was responsible for remotely performing informed consent form checks and checks for data completeness in the study portal.

a) The informed consent form for patients/ carers for the two enrolled patients in the UK had not yet been uploaded to the study database by investigators despite patients having been enrolled for almost 7 months and 1 month, respectively.

The study protocol [redacted] stated in section 9.1 that "The consent form will be retained at the recruiting physician's site, for 100% remote monitoring of informed consent purposes a copy will be scanned to the study database […]". In addition, the [redacted] Drug Utilisation Study Web Portal Guide (dated May 2019) stated in section 3.2 *Registering a patient* "Before registering a patient please ensure that the Informed Consent Form (ICF) process has taken place. A copy should be: […] 3) Scanned and uploaded to the study portal (see Section 3.3). This final step will enable 100% remote ICF monitoring".

b) The record in the study portal of the baseline visit for patient 0002 at study site #9 in December 2018 contained incorrect dosage information. Each of the three doses administered per day was to be recorded in an individual data field; however, in this instance the total daily dose was recorded in each of the data fields.

At the beginning of 2019 the field to record the total daily dose in the study portal was amended to allow for the recording of each individual dose administered per day. The treating physician of patient 0002 was informed of the change on 09 March 2019 and asked to update the relevant fields for their patient accordingly. A further e-mail was sent by the clinical project manager on 01 April 2019; however, at the time of inspection the dosage had not yet been amended.

ii. The frequency of study monitoring activities was not formally documented. During the inspection, the clinical project manager stated verbally that the study portal would be checked on a monthly basis for completeness of the data.

Root Cause Analysis

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[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]	

MA.4 Auditing of the Pharmacovigilance System

Requirements:

GVP Module II – Pharmacovigilance system master file (Rev 2)
II.B.4.7. PSMF section on quality system
"*A description of the approach used to plan audits of the pharmacovigilance system and the reporting mechanism and timelines should be provided, with a current list of the scheduled and completed audits concerning the pharmacovigilance system maintained in the annex referred to II.B.4.8. [IR Art 3(5)]. This list should describe the date(s) (of conduct and of report), scope and completion status of audits of service providers, specific pharmacovigilance activities or sites undertaking pharmacovigilance and their operational interfaces relevant to the fulfilment of the obligations in the Directive 2001/83/EC, and cover a rolling 5 year period.*"

GVP Module IV – Pharmacovigilance audits (Rev 1)
IV.B.2. The risk-based approach to pharmacovigilance audits
"*Risk can be assessed at the following stages:*
• strategic level audit planning resulting in an audit strategy (long term approach), which should be endorsed by upper management;
• tactical level audit planning resulting in an audit programme, setting audit objectives, and the extent and boundaries, often termed as scope, of the audits in that programme; […]

Risk assessment should be documented appropriately for the strategic, tactical and operational planning of pharmacovigilance audit activity in the organisation […]'.

IV.B.2.1. Strategic level audit planning
"*The audit strategy should cover the governance, risk management and internal controls of all parts of the pharmacovigilance system including:*
• all pharmacovigilance processes and tasks;
• the quality system for pharmacovigilance activities;
• interactions and interfaces with other departments, as appropriate;
• pharmacovigilance activities conducted by affiliated organisations or activities delegated to another organisation (e.g. regional reporting centres, MAH affiliates or third parties, such as contract organisations and other vendors)."

IV.C.1.1.1. The qualified person responsible for pharmacovigilance in the EU (QPPV)
"*Furthermore, the QPPV should receive pharmacovigilance audit reports […].*"

The following findings were noted in relation to quality assurance auditing of the pharmacovigilance system:

Finding MA.4 a)

In relation to the auditing of pharmacovigilance activities conducted by Proveca, the following deficiencies were identified:

i. Pharmacovigilance activities and processes carried out in-house, for example regulatory affairs concerning safety updates to authorised product information, and the implementation of additional risk minimisation measures, such as the development, maintenance and dissemination of educational materials, were not included in the audit strategy and had not been subject to audit since the marketing authorisation for [redacted] had been granted on 15 September 2016.

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Procedure [redacted] *Self-Inspection* [redacted] date effective 03 May 2013) described that "The inspections must be carried out annually". The updated procedure [redacted] titled *Internal Audit* ([redacted] date effective 31 May 2019) stipulated that an annual audit schedule should be created and "that on a Biennial basis the requirements of [...] GPvP as per our requirements as a MAH are maintained."

ii. There was no documented risk assessment which supported the change in audit frequency from every year to once every two years for pharmacovigilance-related audits as described in [redacted]

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

[redacted]	

Finding MA.4 b)

Proveca maintained an Excel spreadsheet of service providers and distributors in which the risk assessment conducted for the purposes of audit planning was captured and which was reviewed monthly on a rolling basis. The following deficiencies were noted in relation to the risk assessment of vendors:

i. There was no procedural documentation supporting the risk assessment of vendors for audit planning. During the inspection, the MAH stated that the risk assessment of service providers and distributors for the purposes of audit planning was conducted in line with [redacted] *Contractor and Vendor Selection* [redacted] date effective 18 February 2019). However, the risk assessment described in the SOP was only applicable to the selection of GMP, GCP and GDP vendors as part of outsourcing activities.

It should be noted that procedure [redacted] *Auditing of Vendors and*

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Contractors ([redacted] date effective 31 May 2019) described that vendors and contractors would be audited every 2 years +/- 6 months "where deemed appropriate through the risk assessment process"; however, this risk assessment was not further defined.

ii. The risk assessment conducted for the purposes of audit planning was incomplete as it did not consider all pharmacovigilance service providers or distributors with whom a pharmacovigilance agreement was in place. The following partners were not included:

- Alliance Healthcare: distributor of [redacted] n the UK;
- Dr. Regenold GmbH: provider of local German pharmacovigilance services, incl. local literature search and screening of German websites for safety data;
- David M Projects Ltd.: study set-up and management of the PASS for [redacted]
- Anthrop Pharmaceuticals AB: distributor in Scandinavia and responsible for local literature monitoring. The partner may also receive adverse event reports and may respond to medical enquiries based on FAQs provided by Proveca;
- Intexo S.r.l: specialist consulting firm that provided patient access in Italy. The partner was responsible for local literature monitoring, may receive adverse event reports and may respond to medical enquiries based on FAQs provided by Proveca.

At the time of the inspection, the risk assessment for the audit plan of the financial year 2019/20 starting in August 2019 was in draft but was not reviewed in detail as part of this inspection. The MAH will therefore review all partners and pharmacovigilance processes as part of the risk assessment to ensure completeness in the future.

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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[redacted]

[redacted]	

Finding MA.4 c)
The medical information service provider ProPharma Group was audited on 10 January 2017 and on 21 January 2019; however, the respective audit reports had not been shared with the QPPV. The supporting procedure [redacted] *Auditing of Vendors and Contractors* [redacted] date effective 31 May 2019) did not contain any provisions regarding with whom the audit report should be shared.
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.4 d)
The following deficiencies were noted in relation to the information provided in PSMF Annex G *Quality system* ([redacted] dated 24 April 2019):

- The audits of DSSL, conducted on 25 January 2019, and of PPG, conducted on 21 January 2019, were incorrectly listed in Annex G1. *Scheduled audits & inspections*.
- Annex G2. *List of completed audits & inspections - Proveca Limited* did not include information on the audit status and on the audit report date.

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Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

[redacted]

Preventative Action(s)

[redacted]

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

MA.5 Management and Reporting of Adverse Reactions

Requirements:

GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)

VI.B.3. Follow-up of reports
"*When first received, the information in suspected adverse reactions reports may be incomplete. These reports should be followed-up as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases. This is particularly relevant for monitored events of special interest, […]. This is in addition to any effort to collect missing minimum criteria for reports validation […].*"

VI.B.4. Data management
"*To ensure pharmacovigilance data security and confidentiality, strict control measures should be in place to provide access to documents and to databases only to authorised personnel. This security measure should be extended to the complete data path. With regard to this, procedures should be implemented to ensure security and non-corruption of data during data transfer. […]*

Electronic data storage should allow traceability (audit trail) of all data entered or modified, including dates and sources of received data, as well as dates and destinations of transmitted data."

The following findings were noted in relation to management and reporting of adverse reactions:

Finding MA.5 a)

The MAH maintained its global safety database in the form of a Microsoft Excel workbook stored on the shared drive at DSSL. The following deficiencies concerning the security and traceability of the database have been identified:

i. There were no control measures to prevent the uncontrolled modification of the data in the Excel workbook. The safety database used Excel data validation for the selection of certain criteria, for example to record case and event seriousness, event outcome, action taken, and route of administration. However, there were no further access controls on the spreadsheet to prevent unauthorised changes of the codes used for these validated fields or to prevent uncontrolled modification of any part of the spreadsheet which may go unnoticed.

   Access to the shared drive, on which the safety database was saved, was password restricted to DSSL employees and it was verbally stated during the inspection that the password for access to the shared drive would be changed on the departure of an employee from DSSL; however, this process was not formally documented.

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ii. There was an example where the update of important case information due to the receipt of follow-up was not visible. Case [redacted] was a spontaneous case reporting the serious event 'seizure accumulation' and was initially received on 12 September 2018 and submitted to EudraVigilance on 24 September 2018. Follow-up information received on 25 September 2018 stated that the event was not considered related to [redacted] A follow-up report with this information was sent to EudraVigilance on 08 October 2018 in accordance with GVP Module VI Appendix 5. The entry in the

database only stated that this was an 'initial' case and, although the updated causality was captured, it was not apparent in the database entry or in the database audit trail that follow-up information had been received and the case entry had been modified.

The audit trail consisted of a separate tab in the workbook which maintained a record of all historical versions of each case row from the database tab. In accordance with DSSL guidance document GD 08 *Conventions for naming emails, electronic documents, cases, etcetera* [redacted] date effective 20 October 2017), the database was version controlled in that modifications to the safety database would be saved under a new file version containing the date of modification in the file name together with the initials of the person modifying the database.

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Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

[redacted]	

Preventative Action(s)

[redacted]

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

Finding MA.5 b)

There was an example of a report on the presumptive off-label use of [redacted] in adult ALS patients for which no follow-up had been conducted to obtain further information.

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The report was sent from the Proveca German Country Manager to [redacted] on 18 June 2018. At the time of report no patient identifiers were available and the report was not classified as a reportable event by [redacted] as it only referred to potential usage in adult patients. It was thus not sent to the MAH for case processing.

Although the MAH queried the case on 28 June 2018 during the weekly review of medical enquiries received by [redacted] no attempt was made by Proveca to confirm the use of [redacted] in adult ALS patients and to request additional information from the reporter.

It should also be noted that PSUR #4 (covering the period from 15 March 2018 to 14 September 2018, dated 20 November 2018) made no reference to this report and incorrectly stated in section 9.2 *Medication errors* that "There were no other reports of overdose, abuse, off label use or use in special populations."

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Preventative Action(s)

[redacted]

MA.6 PSURs

Requirements:

GVP Module VII – Periodic safety update report (Rev 1)
VII.B.5.6.3. PSUR sub-section "Cumulative and interval summary tabulations from post-marketing data sources"
"*This sub-section of the PSUR should provide background for the appendix that provides cumulative and interval summary tabulations of adverse reactions, from the IBD to the data lock point of the current PSUR. These adverse reactions are derived from spontaneous ICSRs including reports from healthcare professionals, consumers, scientific literature, competent authorities (worldwide) and from solicited non-interventional ICSRs including those from non-interventional studies*".

VII.B.5.16.3. PSUR sub-section "Evaluation of risks and new information"
"*This sub-section should provide a critical appraisal of new information relevant to previously recognised risks that is not already included in sub-section 16.2 ("Signal evaluation").*"

PSURs provide analysis of the current understanding of a product. The following finding was noted in relation to PSURs:

Finding MA.6

Adverse reactions from three cases originating from EudraVigilance were erroneously excluded from the entire PSUR #3 (covering the period from 15 September 2017 to 14 March 2018, dated 09 May 2018). These events were epistaxis, complication associated with device and urinary retention; the latter of which was an important identified risk in the risk management plan. The case of urinary retention [redacted] was initially received by Proveca via a regulatory authority on 06 February 2018 and described an elderly patient who was receiving [redacted] brand unspecified).

Under section 16.3 *Evaluation of Risks and New Information* in PSUR #3, it was incorrectly stated that "There was no new information received or identified relevant to previously recognised potential and identified risks, or important missing information during the period of this report."

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]	

C.4.3 Minor findings

MI.1 Collection of Safety Information

Finding MI.1 a)
In relation to the identification of safety information from literature, the following deficiencies had been identified: i. The MAH failed to review a literature article (Parr JR, Todhunter E, Pennington L, et al. *Drooling Reduction Intervention randomised trial (DRI): comparing the efficacy and acceptability of* [redacted] *and* [redacted] *on drooling in children with neurodisability*. Arch Dis Child 2018; 103:371–376) at the time it was identified during the weekly literature search on 03 December 2017 even though the abstract mentioned adverse events as a secondary outcome. As a result, there was potential that reportable ICSRs in the article could have been missed. It is acknowledged that the article was subsequently reviewed during the preparation of PSUR #3 for [redacted] (covering the period from 15 September 2017 to 14 March 2018, report dated 09 May 2018). The article included reports of "One child on [redacted] stopped medication due to hyperactivity." and "One child stopped taking [redacted] at 3 days because her mouth dried and she thought she was going to choke when eating."; however, they were not reportable as the [redacted] used in the trial was manufactured by a hospital pharmacy. ii. Prior to 12 June 2019, the global literature search strategy did not contain the term [redacted] a synonym for [redacted]. The omission was discovered by the MAH during inspection preparation and the search strategy was subsequently updated. As part of the corrective actions taken (CAPA Form 2019-013), a retrospective literature search with the term [redacted] was conducted on 13 June 2019 and no missed articles were identified. The [redacted] guidance document 04 *Setting up and running Literature Searches in PubMed* (version 08, date effective 01 December 2017) described that the literature search strategy for a product should undergo a quality check by a second drug safety officer and that the outcome would be documented in an e-mail that was saved in the client-specific folder. However, no relevant records could be provided by the MAH in relation to the original search strategy.
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]	

Finding MI.1 b)

No reconciliation of safety data had been conducted with Tanner Pharma UK Limited, the distributor for [redacted] in Kuwait and the Republic of South Korea, since the SDEA became effective on 18 July 2017 even though a monthly reconciliation was required as per the agreement.

[redacted] *Data management* describes that when transfer of pharmacovigilance data occurs within an organisation or between organisations, mechanisms should be in place to ensure that all notifications are received and that a confirmation and/or reconciliation process should be undertaken.

This finding has been graded as minor as a statement (dated 02 July 2019) from Tanner Pharma was provided during the inspection affirming that no adverse events, product complaints or medical enquiries had been received since the start of the agreement.

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 MI.1 c)
To retrieve ICSRs from EVWEB, filters were applied in relation to the primary source country based on the countries where [redacted] was marketed. However, the parameters applied did not include Iceland although sales had been made in this territory. This finding is graded as minor as a search conducted by inspectors did not identify any [redacted] cases from Iceland that had been reported to EudraVigilance.
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]	

MI.2 Maintenance of Reference Safety Information

Finding MI.2

The following deficiencies were seen in the procedures governing the submission of safety variations to introduce updates to the authorised product information and their implementation following approval:

i. There were no documented timelines in Proveca written procedures to ensure the timely submission of safety variations by in-house regulatory affairs personnel.

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[redacted] *Safety Monitoring, Signal Detection and Management* ([redacted] date effective 01 August 2018) stated in section 5.8: "The Lead DSO or QPPV will work with the Client to ensure that resulting safety variations are submitted within three months for important risks or six months for non-important risks"; however, there was no equivalent procedure at Proveca.

ii. There was no documented procedure to ensure that approved updates to the product information were implemented in a timely fashion (e.g. on company websites, eMC, medical information FAQs or placing updated PILs into packs). It was verbally described during the inspection that this would be done on a case by case basis and documented through the change control process.

Evidence was seen that following the update to the product information in January 2019 to include a new bottle size and to align product information with EC excipient guidelines, the associated change control [redacted] stipulated that the change should be implemented in packaging components, SmPC text documents, promotional materials, prescribing information and the training manual as applicable within defined deadlines and that these had been met.

It is MHRA expectation that the updated product information should be notified to relevant departments, and, if applicable, updated on company websites and eMC within 10 working days following receipt of the approval of updated product information.

MHRA published guidance (https://www.gov.uk/guidance/medicines-packaging-labelling-and-patient-information-leaflets) states that changes to labels, leaflets and packaging must be introduced within 3 to 6 months of variation approval so that it is ensured that the outdated labelling is not released to the market beyond this time.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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[redacted]

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

MI.3 Contracts & Agreements

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Finding MI.3

Proveca collaborated with several distributors to supply [redacted] inside and outside of the EU. The following deficiencies were noted in relation to the agreements between the MAH and distributors:

i. The distribution agreement with Alliance Healthcare (Distribution) Limited (dated 20 January 2017) did not include any provision for reconciliation to ensure that all reports containing safety information had been sent to Proveca. At the time of inspection, no reconciliation had taken place yet.

ii. The distribution agreement (dated 10 April 2017) and [redacted] (dated 18 July 2017) with Tanner Pharma UK Limited did not include a provision for audit. It is acknowledged that the distributor was included in the risk assessment of vendors used for the purposes of audit planning at the time of inspection.

iii. There was a delay of three months in setting up the [redacted] with Tanner Pharma UK Limited, the distributor in Kuwait and the Republic of South Korea. The distribution agreement became effective on 10 April 2017; however, the [redacted] was only signed on 18 July 2017. Tanner Pharma had received the first supply of [redacted] rom the MAH in April 2017.

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]	

C.4.4 Comments

1. There was no written procedure that described how MedDRA updates would be applied to the data in the safety database. The MAH described verbally that this would be done, if required, when extracting data from the safety database for the 6-monthly PSUR at database lock.

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It is acknowledged that the latest PSUR (covering the period from 15 September 2018 to 14 March 2019, dated 07 May 2019) stated that the latest version of MedDRA had been used [redacted] for the coding of adverse reactions.

2. There was an example of the incorrect classification of a case as 'valid' within the ICSR database. Case [redacted] which described a product quality complaint, had been incorrectly listed as a valid ICSR even though the verbatim text did not mention any presence of an adverse event. This error had not been corrected or picked up during the QC process and as such, the case could have been incorrectly submitted to EudraVigilance. It was confirmed that the case was not erroneously submitted to EudraVigilance.

3. It was noted that the SDEAs with two distributors, Anthrop Pharma and Bifarma, were only implemented with a delay of six and seven months, respectively, after the distribution agreements became effective. It is acknowledged that no sales via these distributors had been made before the relevant SDEAs became effective.

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.
- Guideline on good pharmacovigilance practices (GVP).
- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916).
- EMA/CHMP/ICH/287/1995: ICH guideline E2B (R3) on electronic transmission of individual case safety reports (ICSRs) - data elements and message specification - implementation guide.
- EMA/CHMP/ICH/544553/1998: ICH guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER).
- CPMP/ICH/3945/03: E2D "Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting".
- CPMP/ICH/5716/03: E2E "Pharmacovigilance Planning".
- EMEA/CHMP/PhVWP/235910/2005: "Guideline on conduct of pharmacovigilance for medicines used by the paediatric population".

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	Insp GPvP 51785/16593606-0004	**DAY**	1
PHARMACOVIGILANCE INSPECTION OF	Proveca Limited	**DATE**	01 July 2019
LOCATION	NEO, Charlotte Street, Manchester, M1 4ET	**START TIME**	13:00 arrival for 13:30 start

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Opening Meeting Review of scope of inspection and inspection plan **Company Presentation** Overview of the company, the pharmacovigilance system and the quality system. The presentation may also include information on any relevant ongoing remediation work in the pharmacovigilance system. *(max. 20 minutes)*	[redacted]	All welcome
Document collation and review		
ICSR management, including but not limited to • Data entry, coding assessments and submission to EMA • Follow-up activities	[redacted]	[redacted]

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[redacted]

MHRA INSPECTION NUMBER	Insp GPvP 51785/16593606-0004	**DAY**	2
PHARMACOVIGILANCE INSPECTION OF	Proveca Limited	**DATE**	02 July 2019
LOCATION	NEO, Charlotte Street, Manchester, M1 4ET	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Sources of safety information, including but not limited to • Medical enquiries • Product quality complaints • Literature • EudraVigilance	[redacted]	[redacted]
Post-authorisation safety study	[redacted]	
PSURs	[redacted]	
LUNCH		

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Quality management and oversight of the pharmacovigilance system, including but not limited to • Audits • Management of non-compliance through deviations and CAPA • QPPV and MAH oversight	[redacted]	[redacted]

MHRA INSPECTION NUMBER	Insp GPvP 51785/16593606-0004	**DAY**	3
PHARMACOVIGILANCE INSPECTION OF	Proveca Limited	**DATE**	03 July 2019
LOCATION	NEO, Charlotte Street, Manchester, M1 4ET	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Additional risk management, including but not limited to • Educational materials • Post-authorisation safety study	[redacted]	[redacted]
LUNCH		
Routine risk management, including but not limited to • Signal detection, validation, evaluation and tracking, incl. EudraVigilance monitoring • Identification and submission of safety variations and implementation of approved SmPCs and PILs	[redacted]	[redacted]

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MHRA INSPECTION NUMBER	Insp GPvP 51785/16593606-0004	**DAY**	4
PHARMACOVIGILANCE INSPECTION OF	Proveca Limited	**DATE**	04 July 2019
LOCATION	NEO, Charlotte Street, Manchester, M1 4ET	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Document review and ad-hoc questions	-	As required
Closing meeting	[redacted]	All welcome