RISK MINIMISATION MEASURES EFFECTIVENESS TESTING PROTOCOL

Post-Authorisation Safety Study (PASS) Information

Title	Assessment of the effectiveness of additional Risk Minimisation Measures (aRMMs) among pharmacists for provision of Estradiol hemihydrate 10 micrograms vaginal tablets in a community pharmacy setting
Protocol version identifier	Gina NIS Protocol 270301 Version 6
Date of last version of protocol	Tuesday 21 March 2023 Version 5
EU Post Authorisation Study register number	EUPAS1000000274
Active Substance	Estradiol hemihydrate
Medicinal Product	Estradiol hemihydrate 10 micrograms vaginal tablets
Marketing Authorisation Holder	Novo Nordisk A/S
Joint PASS	No
Research questions and objectives	To evaluate whether the additional risk minimisation measures (Pharmacy Guide, Pharmacy Checklist) are effective in enabling pharmacists to make appropriate decisions to supply Gina to consumers based upon the following criteria: • Age (≥ 50 years old) • Last menstrual period ≥ 1 year ago • Experiencing symptoms of vaginal atrophy (VA) • Contraindications to use of Gina • Special warnings to use of Gina • Dosage instructions • Assessments at 7 weeks and 3 months
Country of Study	UK
Author	[redacted]
Marketing Authorisation Contact	[redacted] [redacted] Novo Nordisk Ltd

Redacted protocol
Includes redaction of personal identifiable information only.

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2. List of Abbreviations

AE	Adverse Event
aRMMs	additional Risk Minimisation Measures
CI	Confidence Intervals
CIG	Communications International Group
DIA	Drug Information Association
EH	Estradiol Hemihydrate
GDPR	General Data Protection Regulation
GP	General Practitioner
GSL	General Sales List medicine
GVP	Guideline on good pharmacovigilance practices
HCP	Healthcare Professional
KPI	Key Performance Indicator
KRMs	Key Risk Messages
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare Products Regulation Agency
MRP	Mutual Recognition Procedure
NIS	Non-Interventional Study
OTC	Over The Counter
P	Pharmacy medicine
PASS	Post-Authorisation Safety Study
PGD	Patient Group Directions
PIL	Patient Information Leaflet
POM	Prescription Only Medicine
PV	Pharmacovigilance
RM	Risk Management
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
URL	Uniform Resource Locator
VA	Vaginal Atrophy

3. Responsible Parties

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4. Abstract

This abstract provides a summary of study objectives and methodology. Detailed descriptions are included in corresponding sections in the main body of the protocol.

Rationale and Background

Estradiol hemihydrate 10 micrograms vaginal tablets (Gina) is a local oestrogen therapy for the treatment of vaginal atrophy (VA) in post-menopausal women.

To support the reclassification of estradiol hemihydrate 10 micrograms vaginal tablets (Gina) from a prescription only medicine to a pharmacy, non-prescription medicine, a number of standard (Summary of Product Characteristics [SmPC], Patient Information Leaflet [PIL], Pack Label) and aRMMs (Pharmacy Guide for the Supply of Gina, Pharmacy Checklist) have been developed for dissemination to pharmacies at launch.

This post-authorisation safety study (PASS) will assess the effectiveness of the agreed aRMMs for Gina (estradiol hemihydrate 10 micrograms vaginal tablets).

Research Questions and Objectives

The overall objective is to evaluate the effectiveness of the aRMMs in mitigating the risks of incorrect supply of Gina to patients in a community pharmacy. Specifically, the goals of the study are to:

- Demonstrate that the training provided by the company is effective in enabling pharmacists to make appropriate decisions to supply Gina based on contraindications and special warnings; this includes awareness and mitigation of safety concerns.
- Identify whether there are particular contraindications or warnings for which pharmacists consistently make the wrong supply decision.
- Establish ease of access to and ease of use of the aRMMs.

Study Design

The study will be a cross sectional, non-interventional web-based survey at approximately six months post the product launch following MHRA approval of the reclassification.

The survey will be distributed across the UK to a representative mix of independent and multiple ownership pharmacies with the aim of achieving a relevant sample size of pharmacists who have read the aRMM materials and conducted at least one consultation during the previous six months.

For this study, it will be important to ensure a representative mix of independent and multiple ownership pharmacies, including those in urban and small-town settings.

The questionnaire has been designed such that all biases in question wording, scale responses and order effect are mitigated. This includes the use of:

- Balanced scales
- Randomisation of response options
- Non-leading question phraseology
- Survey flow, routing and question logic designed to maximise the respondent's efficient and considered response.

A pilot study will run additionally with 20 pharmacists in order to evaluate the quality of the data produced by the respondents and ensure that it will lead to meaningful results.

Study Structure

The pharmacist survey will comprise two main sections, intended to:

1. Understand how the aRMMs are being used in practice. Pharmacists' feedback will be collected and analysed to determine whether changes to the aRMMs are required in order to support pharmacists more effectively when they are supplying Gina.
2. Establish whether pharmacists can answer case study questions correctly and offer the correct advice to patients requesting Gina from a pharmacy. Eight (8) case study scenarios are involved.

Pharmacists will be screened to determine whether they have read the aRMMs and conducted at least one consultation on Gina in the last six months. The scenario section of the questionnaire is designed to mirror real life situations, in which pharmacists may choose to refer to information sources during consultations.

The pharmacist survey will take approximately 20 minutes to complete and will have to be completed in one sitting. However, the survey timer will be set for 60 minutes to allow respondents to take a break if required. During this time, the survey will remain open: respondents will not be able to save it and return to it later. Respondents will be informed about the length of the survey and allocated time to complete.

Data Sources

A structured, self-administered questionnaire comprised of closed questions or statements with multiple response choices (i.e., questions or statements asking the pharmacists to choose from a defined list of responses) will be used to collect the survey data. The questionnaire will collect data on pharmacist characteristics in addition to their responses pertaining to the effectiveness of the aRMMs.

Study Size

The survey will be distributed across the UK to a representative mix of pharmacists working in independent and multiple ownership community pharmacy businesses in city, urban, small town, and rural settings, with the aim of achieving a total sample size of 200 pharmacists who have all read the aRMMs and conducted at least one consultation during the previous six months.

The sample size chosen for this study is dependent on statistical and feasibility considerations. The 200 responses will generate a combined response to 1600 case study scenarios, which will be taken together to measure the proposed success criteria.

Data Analysis

Previous analysis of comparable PASS studies has shown that receipt and use rates for risk management (RM) materials among healthcare professionals (HCPs) rarely exceed 80% (preliminary results of a cumulative systematic review and meta-analysis of risk minimisation survey studies presented at EMA/DIA Information Day, 2017),[3] whereas percentages of correct knowledge of key

safety messages mostly lie between 70% and 90%. On this basis, a threshold of 80% has been set as an average across the eight case study scenarios, rather than on each one individually.

Data segmentation will be generated for key variables e.g., splitting the sample by gender and age, outlet type and job title.

Success Criteria

The aRMMs will be deemed effective if the following criteria are met:

- An average of at least 80% of pharmacists correctly advise whether to supply or not supply for each of the eight case study scenarios. The Key Performance Indicator (KPI) will be deemed achieved at 73.2% plus to allow 6.9% statistical precision (see table 2).
- The total number of correct answers across the scenarios exceeds 80%. The KPI will be deemed achieved at 77.6% plus to allow 2.5% statistical precision (see table 2). This means that 1242 correct answers out of the 1600 answers will be achieved.

Quality Control

The study will be conducted in accordance with all applicable regulatory and privacy requirements.

Documentation of all data management activities will allow step-by-step retrospective assessment of data quality and performance. Management of data will be performed in accordance with applicable standards and data cleaning procedures to ensure its integrity (e.g., removing errors and inconsistencies in the data).

Where the percentage of pharmacists answering a scenario question correctly is below the level defined to represent success, the training materials will be reviewed and improved as appropriate in both sets.

5. Amendments and Updates

This is the second version of the protocol which has been revised to address the MHRA RFI (dated 21/03/2022) received during the application to reclassify legal status of Gina from POM to P.

6. Milestones

Milestone	Timelines
Gina reclassification approval	28th June 2022
Launch of product in pharmacy	September 2022
Roll out of aRMMs	September 2022
MHRA protocol approval	22nd June 2023
User testing	10.04.2023
Registration in the EU PAS Register®	
Pilot study launch	25.07.2023
Pilot study data collection and results reporting	04.08.2023
(If required) Submission of changes made to the protocol and questionnaire to MHRA	22.09.2023
(If required) MHRA updated protocol approval	17.11.2023
Main study launch	20.11.2023
End of data collection	08.12.2023
Publication of final study report	31.01.2024

7. Rationale and Background

Estradiol hemihydrate 10 micrograms vaginal tablets (Gina) is a local oestrogen therapy for the treatment of vaginal atrophy (VA) in post-menopausal women.

To support the reclassification of Gina from a prescription only medicine to a pharmacy, non-prescription medicine, a number of standard RMMs (Summary of Product Characteristics [SmPC], Patient Information Leaflet [PIL], Pack Label) and aRMMs (Pharmacy Guide for the Supply of Gina , Pharmacy Checklist) have been developed for dissemination to pharmacies at launch.

In accordance with the Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk Minimisation Measures, the effectiveness of RMMs should be assessed in relation to stakeholder behaviour. Community pharmacists are key stakeholders in relation to reclassified medicines. They play an important role in moderating access to non-prescription medicines. It is the pharmacist's role to assess customers for suitability to supply non-prescription medicines, ensuring they meet eligibility requirements in terms of indications, contraindications and warnings, in accordance with the SmPC. The pharmacist is also expected to provide directions for use and safe use of non-prescription medicines, including dosing instructions.

The MHRA has asked Novo Nordisk to confirm that the aRMMs for their estradiol hemihydrate 10 micrograms vaginal tablet (Gina) products operate effectively in the community pharmacy setting by conducting a post-authorisation safety study (PASS).

Product information

Gina 10 microgram vaginal tablets[1]
Each vaginal tablet contains: Estradiol hemihydrate equivalent to estradiol 10 micrograms
License holder: Novo Nordisk A/S.

Gina tablets are vaginal tablets used for the treatment of vaginal atrophy due to oestrogen deficiency in postmenopausal women aged 50 years and above, who have not had a period for at least 1 year. Gina tablets contain estradiol hemihydrate, a synthetic oestrogen which is chemically and biologically identical to human estradiol.

Estradiol induces and maintains primary and secondary female sexual characteristics as well as maintaining vaginal pH around normal range which enhances normal bacterial flora and alleviates the symptoms of vaginal atrophy due to oestrogen deficiency in post-menopausal women, when applied vaginally.

Gina is administered intravaginally and must be used initially one tablet every day for two weeks, and then one tablet twice a week. Treatment can be started on any convenient day and a forgotten dose should be used as soon as the patient remembers. However, a double dose should be avoided.

Gina is not indicated during pregnancy. If pregnancy occurs during medication with Gina, treatment should be withdrawn immediately.

Further product information can be found in the Summary of Product Characteristics (SmPCs) for Gina.[1]

[1] Gina Summary of Product Characteristics (SmPC), https://www.medicines.org.uk/emc/product/13930/smpc#ORIGINAL

Pharmacist role and training

Pharmacists have been identified as having an important role in facilitating and counselling patients to determine suitability of use of Gina, and in directing women for whom it is unsuitable to their doctors.

Novo Nordisk Ltd. has produced material consisting of a Pharmacy Guide for the Supply of Gina and a Pharmacy Checklist. The checklist acts as an aide memoire for the pharmacist in determining if the medicine is suitable for supply.

Key Risk Messages for Pharmacists

The Pharmacy Guide for the Supply of Gina and Pharmacy Checklist include risk messages for pharmacists to consider when determining the suitability of a patient for supply of Gina and other important messages for pharmacists to consider during consultations.

Study protocol objective

The objective of this protocol is to describe in detail the methods that will be employed to evaluate the effectiveness of the aRMMs in the UK and to outline the estimated timeline for the major study milestones (Section 6: Milestones). This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is a commitment to the MHRA.

8. Research Questions and Objectives

The overall objective of this study is to evaluate the effectiveness of the aRMMs. Specifically, the primary objectives are to:

- Demonstrate that the training is effective in enabling pharmacists to make appropriate decisions to supply based on contraindications and special warnings; this includes awareness and mitigation of safety concerns;
- Identify whether there are particular contraindications or warnings for which pharmacists consistently make wrong supply decisions;
- Establish ease of access to and ease of use of the aRMMs.

9. Research Methods

This section presents the methods that will be employed to evaluate the effectiveness of the aRMMs in the UK.

9.1 Study Design

The study will be a cross sectional, non-interventional web-based survey that will be conducted in the UK at approximately six months post the product launch for Gina following MHRA approval of the reclassification. The study will be conducted anonymously among pharmacists who have read the aRMMs for Gina and have conducted at least one consultation regarding the supply of Gina during the previous six months.

For this study, it will be important to ensure a representative mix of independent and multiple ownership pharmacies, including those in urban and small-town settings.

The questionnaire has been designed such that all biases in question wording, scale responses and order effect are mitigated. This includes the use of:

- Balanced scales
- Randomisation of response options
- Non-leading question phraseology
- Survey flow, routing and question logic designed to maximise the respondents' efficient and considered responses.

9.1.1 Study Structure

The pharmacist survey will comprise two main sections, intended to:

1. Understand how the aRMMs are being used in practice. Pharmacists' feedback will be collected and analysed to determine whether changes to the aRMMs are required in order to support pharmacists more effectively when they are supplying the products. These questions are based on simple scales, comprising single or multiple choices. They cover the following areas:
    - aRMMs received and read prior to the study
    - Frequency of consultations
    - The setting within the pharmacy used for the consultation
    - aRMMs used during the consultation
    - Ease of access to the aRMMs
    - Level of pharmacist confidence in advising on the use of Gina and correctly supplying.

2. Establish whether the pharmacists can answer questions correctly and offer the correct advice to customers requesting Gina for vaginal atrophy from a community pharmacy. Eight (8) case study scenarios are involved.

Pharmacists will be screened to ensure they have read the Gina aRMMs and conducted a consultation on Gina in the last six months. The scenario section of the questionnaire is designed to mirror the real-life situations, in which pharmacists may choose to refer to information sources during consultations. As the pharmacist may be completing the survey away from their usual place of consultation and may not have access to the materials they would usually use, information on how to access the aRMMs will be provided after the screening process and before the scenario section of the questionnaire.

It will be possible to complete the survey on a desktop, tablet or mobile device. However, pharmacists will be advised to complete the survey on a desktop device for a better user experience.

The pharmacist survey will take approximately 20 minutes to complete and will have to be completed in one sitting. However, a survey timer will be set for 60 minutes to allow respondents to take a break if required. During this time, the survey will remain open: respondents will not be able to save it and return to it later. Respondents will be informed about the length of the survey and that it must be completed within one hour.

Pharmacists invited to participate in the study will agree to abide by the safety reporting requirements of Novo Nordisk Ltd. Participants will also agree to take part in the research voluntarily, supplying their information for the purposes of the study and within the CIG Research privacy rules.

The survey will be conducted online using proprietary market research questionnaire software. The survey has been designed and scripted for completion by community pharmacists. The questionnaire will be accessed by means of a secure URL link, which will be sent in an email invitation to CIG Research's opt-in panel of pharmacists. The sample of 200 respondents to the survey will be quota controlled to be nationally representative of community pharmacists in the UK.

Novo Nordisk Ltd. have provided aRMM tools to all UK pharmacies by post, so participants in the survey will have had access to and will recall reading the material provided during the six months prior to the study. All participants will have conducted at least one consultation with a female customer for the supply of Gina in the six months prior to the survey being conducted.

9.1.2 Success Criteria

The aRMMs will be deemed effective if the following criteria are met:

- An average of at least 80% of pharmacists correctly advise whether to supply or not supply Gina for each of the eight case study scenarios. In order to allow for ±<6.9% statistical precision (see table 2), the KPI will be deemed achieved at 73.2% plus.
- The total number of correct answers across all scenarios should exceed 80%. In order to allow for ±<2.5% statistical precision (see table 2), the KPI will be deemed achieved at 77.6% plus. This means that 1242 correct answers out of the 1600 answers will be achieved.

Table 1. Example of success criteria analysis

	Answered correctly	Answered incorrectly
Scenario 1	170 (85%)	30 (15%)
Scenario 2	190 (95%)	10 (5%)
Scenario 3	150 (75%)	50 (25%)
Scenario 4	180 (90%)	20 (10%)
Scenario 5	160 (80%)	40 (20%)
Scenario 6	200 (100%)	0 (0%)
Scenario 7	140 (70%)	60 (30%)
Scenario 8	190 (95%)	10 (5%)
TOTAL	1380	220
Average	86.25%	13.75%

The above example shows that aRMMs are effective because, on average, 86.25% of the pharmacists provided correct answers across all scenarios, equivalent to 1380 out of 1600 correct answers. While the average correct answer rate is above the 80% (±<2.5%) threshold across the eight scenarios, there is one (scenariob7) which is below the threshold. In this instance, detailed analysis of which segment of pharmacists underperformed will be conducted, including e.g.:

- How many consultations these respondents estimate that they have conducted
- How they differ (if at all) from the main sample in terms of their demography, location, length of service and outlet type. Given that this may be based on small sub-samples (in the above example, at scenario 7, it is 60 respondents), this will be a qualitative analysis
- Level of confidence about advising patients and about supplying Gina relative to the sample average
- Self-rated knowledge of the product
- Usefulness rating of the materials.

Should any scenario fall below the 80% (>-6.9%) answering correctly threshold, appropriate changes will be made to the aRMM tools. In the above example, scenario 7 did not pass the threshold, so the information relating to this scenario in the training materials would be amended. Any changes will take account of which wrong answer is selected by those giving incorrect answers in each scenario where the threshold is not met. Scenario 3 met the criteria as 75% is within the 6.9% statistical error for 80% threshold on 200 sample (73.2% plus).

9.2 Setting

Estradiol hemihydrate 10 micrograms vaginal tablets (Vagifem) received its product licence in the UK in 2010 and has been available as a prescription only (POM) medicine since then. Since September 2022 it has been available as a pharmacy (P) medicine for women to purchase from pharmacies under the brand name Gina. As a P medicine, Gina can only be supplied through registered pharmacies under the personal supervision of a pharmacist. It is the pharmacist's role to help women assess whether Gina is a suitable option for them. Pharmacists are required to check that there are no contraindications to supply and to know when to refer women to their doctor for further advice.

9.2.1. Method of Pharmacist Recruitment for Participation

The study objectives will be accomplished by means of a cross-sectional survey of all targeted pharmacists that received and read the aRMM materials supplied for Gina in the UK. Invitations will

be sent by email to pharmacists from CIG Research's opt-in panel of 12,500 UK community pharmacists. Response rates of 2-3% are typical in studies of this type and length.

Information on this panel is held on CIG's cloud-based servers and updated continuously to ensure all unsubscribes are removed and new participants wishing to join the panel are classified according to their job title, location and outlet type. When invitations are sent to participate in this survey, the panel stratification classification may be used to boost responses from under-represented segments in collected responses, by encouraging pharmacists in those segments to take part.

The respondents' understanding of the appropriate use and risks of Gina will be evaluated using an online survey. Each invitation will include information on how to access the survey online.

CIG Research will compensate pharmacists for their time spent completing the survey in the form of reward points, which can be redeemed for vouchers to the value of £20 per completed response. This remuneration programme is run by CIG Research and is governed by UK laws and regulations.

9.2.2. Inclusion Criteria

All respondents invited to participate will be qualified pharmacists working in community pharmacies in the UK, will have read at least one of the aRMM materials and held at least one consultation with a female customer regarding the supply of Gina in the previous six months. The sample will aim to be representative of community pharmacists by age, gender, outlet size, and by region within the UK, including Northern Ireland.

Respondents will be invited to participate on the basis that they meet and confirm their acceptance of the inclusion criteria:

- Their information will only be used for research purposes and will not be passed to any other organisation without their permission;
- They have the right to refuse to answer questions or withdraw at any time. They consent to CIG Research collecting and using the information that they voluntarily provide for the purposes of research;
- They understand that if they become aware of any safety information during the course of the study, they will spontaneously report these to CIG Research, who will pass their comments to the client . They may choose to have these passed on anonymously or with their contact details, which will be collected at the end of the survey.

9.2.3. Exclusion Criteria

Pharmacists will not be included in the study if they:

- Have not read the aRMM materials supplied for the product in the UK, or do not recall having read them;
- Are employed in full-time research, GP practices or hospitals (i.e., not community-based pharmacists);
- Work only as online pharmacists and do not provide consultations;
- Are in the employment of or are contracted to the Novo Nordisk Ltd., Communications International Group or Consensio LLP.

9.3 Variables

The variables for analyses will be derived from the study data to address the objectives outlined in Section 8: Research Questions and Objectives, as follows:

- Assessment of pharmacists' knowledge/understanding of how to supply Gina to patients
- Utilisation of the aRMM materials during consultations
- Accessibility of each of the aRMMs to the pharmacist
- Confidence about advising customers on the use of Gina
- Usefulness of the aRMMs.

9.4 Data Sources

A structured, self-administered questionnaire comprised of closed questions comprising statements with multiple response choices (i.e. questions or statements asking the pharmacists to choose from a defined list of responses) will be used to collect the survey data. Questions will be asked in an order which provides a 'funnel' from general introductory topics towards the scenario-based questions, which constitute risk knowledge responses, on which KPIs have been set.

The questionnaire will collect data on pharmacist characteristics (i.e., job title, outlet type, region), and their responses to the scenario-based risk knowledge questions. The data collected from the survey will be used to inform the evaluation of the effectiveness of the aRMMs.

The questionnaire will begin with screening questions to confirm eligibility. Depending on the answers to the screening questions, survey participation will either be terminated or continued. If ineligible, the respondent will be immediately notified with a 'thank you' message that survey participation has ended. If eligible, the respondent will be allowed to continue survey participation.

The full questionnaire can be found in **Annex 3**.

9.4.1 Screening questions for pharmacists

The following question types will be used to screen out respondents:

- Consent to participate
- Consent to report safety information
- Job title – to include pharmacists and exclude other roles within community pharmacy
- Whether the pharmacist has had at least one consultation with a female customer about the supply of Gina during the six-month period preceding the study
- Whether the pharmacist recalls reading the aRMMs in the six months prior to the survey
- Whether they are employed by or contracted to Novo Nordisk Ltd., the MHRA, Communications International Group or Consensio LLP.

9.4.2 Data on pharmacist demographic characteristics

The following question types will be used to collect demographic characteristics data:

- Outlet type
- Brand of multiple outlet
- Location of pharmacy
- Job title within the pharmacist cohort – supervisor/manager/proprietor/locum/pharmacist
- Length of time practising as a community pharmacist
- Age of respondent
- Gender of respondent.

9.4.3 Data pertaining to evaluation of the effectiveness of the aRMMs

The questionnaire includes eight case study scenarios in the form of short representations of typical situations in which a patient requests Gina and is either supplied or not supplied, based on their presentation. In each case, the option to "supply" or "do not supply" will be chosen by the respondents and will be correct or incorrect. The number of correct responses to each scenario will assess the knowledge of the pharmacists. The knowledge level analysed using descriptive statistics and confidence intervals will be used to determine the effectiveness of the aRMMs. In the case of incorrect responses to the case study questions, respondents will be provided with the correct response for their information. In the case of correct responses, they will be informed that their response was correct.

Additional evaluation measures will include:

- Reading and utilising of each of the aRMMs among participants
- Ease of access to the aRMMs in the pharmacy during consultations
- Level of confidence in advising patients on the use of Gina and correct supplying
- Self-rated knowledge/comprehension of the use of Gina and correct supplying.

9.4.4 Pilot testing of the survey questions

The pilot study will be run with 20 pharmacists in order to evaluate the quality of data produced by respondents to ensure that it leads to meaningful results. This will include evaluating each of the case study scenarios in terms of the answers given and whether they differentiate clearly between correct and incorrect answers. Given the pilot sample size of 20 responses, the statistical validity of correct answer rates on the scenarios are limited, and only indicate approximate levels of success or failure in each case. The pilot also assesses whether the process runs successfully and that all biases in question wording, scale responses and order effect are mitigated i.e., all questions are answered and not skipped, and the survey flow, routing and question logic ensure efficient and considered responses.

Participants in this this pilot study will be recruited from a random sample of approximately 1000 pharmacists from the CIG Research panel in order to establish response rates based on the inclusion criteria above. The sample of 20 responses is based on the expected response rate of 2% on 1000 targets, assuming a large proportion of pharmacists have read the aRMMs and are eligible to participate. The pilot is used to predict response rates for the full survey. 20 responses allow effective assessment of the value and meaningfulness of responses to the survey. Within a sample of 20 responses, a variety of job titles, genders, ages, and multiple and independent outlet pharmacists would be expected.

The quality of the data collected will be analysed and any issues or shortcomings in the questionnaire design will be reported. Fieldwork and data analysis of the pilot is scheduled to take two weeks from the pilot study launch. A report with results of the pilot study will provided to Novo Nordisk Ltd. and any necessary changes will be suggested for the questionnaire and in the protocol. If the quality of pilot data meets the criteria described above and meaningful results are achieved, no changes to the protocol or questionnaire will be required. In this case, the pilot sample data will be combined with the main study data to produce the final report. It will be acceptable to do this as the pilot study will conducted using the same software, questionnaire and recruitment methods as the main study, with the same high-quality data being collected. The only difference will be that the pilot will be conducted 2 months before the main study, but this is not deemed to be a major limitation. However, if the quality of pilot data does not meet the criteria described above, an

updated protocol will be provided to the MHRA within four weeks and the pilot sample of 20 respondents will not be counted in the main study.

9.4.5 Data collection process

CIG Research will send invitations by email to its opt-in members of its pharmacist panel with a unique URL link to the online survey for each panel member, which will be hosted in the electronic surveying system QuestionPro. Responses may be completed on desktop, tablet or mobile devices, with the survey limited to one response per participant.

The email invitation (example in **Annex 1**) will include an overview of the rationale for the study and a URL link to the survey. Survey data collection will be open for a maximum of 30 days. The survey study date will begin approximately six months after the product launch.

All questions will be validated (compulsory to complete) within the surveying system. This means that respondents will not be able to complete the survey unless they have answered all questions. The survey will have to be completed in one sitting. However, the survey timer will be set for 60 minutes to allow respondents to take a break. The vast majority of surveys are completed 'at one sitting' but given that this questionnaire will be approximately 20 minutes long, it is possible that the break will be required. In this case, the survey will have to remain open as it will not be possible to close the survey and return to it later. All invitees will be notified about the length of the survey in the invitation.

Questions will be programmed to ensure that they are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question once the question has been answered and they cannot skip ahead. Response options will be presented in randomised lists to minimise positional bias. Programming will be reviewed by Quality Control and simulated users (user testers) prior to implementation.

The first invitation will be sent to all panel members whose job title is within the pharmacist cohort. During the fieldwork, it is anticipated that the majority of responses will come in within the first week, and reminders will be sent to pharmacists who have not started the survey after 3-7 days (see section 9.4.6).

Responses will be collated automatically within the survey software and will be monitored throughout the fieldwork process. The CIG Research team will check the flow of responses, any aberrant responses, and the number of minutes each respondent takes to complete the questionnaire. Once the sample has been achieved, with 200 respondents having completed the survey, it will be closed to further respondents.

In the case of potential safety reporting during fieldwork, the survey responses will be checked at least twice daily for AE comments, which will be reported to the client within 24 hours in accordance with the PV reporting requirements.

9.4.6 Follow-up reminder process

It is expected that two reminders will be required to achieve the sample defined above (2-3% response rate), with those who have already responded having been removed from the reminder process. The intervals between reminders will be approximately 3-7 days.

Further reminders to boost sampling will be issued should there be a shortfall in numbers within any segments, where specific sub-samples are under-represented in the collected responses (e.g., certain age groups, regions or outlet types). CIG Research will monitor the responses, and should any segment not achieve a sufficient number of responses, reminder invitations will be sent to

specifically targeted panel members who have not yet started the survey. Filters will be used to target only profiles that match under-represented criteria (e.g., those who are 'female' or 'age 50+'). This is expected to achieve the full sample successfully. If any sample group is still under-represented, CIG Research will explore the remaining of its panel further, in order to get desired results.

9.4.7 Respondent remuneration

CIG Research's panel of opt-in pharmacists are compensated for their time participating in surveys throughout the year. CIG Research funds this programme from its commercial research, and there is no link to individual clients in the process. CIG Research's pharmacist panel receive honoraria for surveys completed, proportionate to the length of the questionnaire and difficulty in obtaining the sample. Honoraria will be £20 in reward points per completed response.

9.5 Study size

This section presents sample size and precision of the estimate calculations for various survey sample sizes. The precision of the estimate calculations is based on the following assumptions:

- The confidence intervals (CIs) around the estimate are two-sided
- The probability of type-I error (alpha) is 5%
- The table below provides precision of the estimate (width of 95% CI around the estimate) for a range of sample sizes at or around the 50% mark, which is the least accurate point in the standard deviation curve.

Table 2. Sample size obtained for various precisions

Sample size	Statistical precision (at 50%)
100	± 9.8%
150	± 8.0%
200	± 6.9%
250	± 6.2%
300	±5.7%
1600 (total case studies)	± 2.5%

The sample size chosen for this study is dependent on statistical and feasibility considerations. On the basis of the maximum feasible sample size achievable within the scope of this study, and the relative precision of this dataset, a sample of 200 pharmacists has been chosen. It may be necessary to over-sample up to 250 in order to achieve the 200, based on 80% having read aRMMs and conducted at least one consultation with a patient on Gina in the six months prior to the survey. This represents a response rate of approximately 2% of the CIG Research panel and is typical of the response rates achieved for questionnaires of 12-20 minutes' length.

Each respondent will be shown eight case study examples of consultations and will answer corresponding questions. The 200 responses will generate a combined response to 1600 case studies, which will be taken together to measure the proposed success criteria, with a variance of ± 2.5% on 1600 responses.

9.6 Data management

All data collected during the study will be held confidentially by CIG Research using an electronic data collection system called QuestionPro. This system encrypts all identifiable information, and respondent identifiers are stored separately from survey responses.

To minimise data entry errors, skip logic for certain questions as well as the ability to mark only one response or multiple responses, as appropriate, form part of the survey programming. There will be no follow-up queries to respondents for this project. Detailed management of data is described in section 9.8 Quality control.

9.7 Data analysis

The threshold of 80% correct answers to supply or not supply Gina in the eight case studies has been set as a KPI on the basis that previous analysis of comparable PASS studies has shown that receipt and use rates for RM tools among HCPs rarely exceed 80%[3], whereas percentages of correct knowledge of key safety messages mostly lie between 70% and 90%. On this basis, a threshold of 80% has been set as an average across the eight case studies, rather than on each case study.

On completion of the fieldwork, all data will be checked and validated to ensure that any erroneous or duplicated responses are excluded. Data extraction for the total sample and for each segment within the sample will be carried out and CIG Research will compile a series of tables and charts for the final report, combining and comparing segments as appropriate. Detailed commentary will be provided for each table and each chart, explaining the data, interpreting it and drawing appropriate conclusions.

Data segmentation will also be generated for key variables, each of which have a minimum sample size of 30 responses (e.g., splitting the sample by gender and age, outlet type and job title). In addition, key segments can be generated against specific answers.

Detailed methodology for summary and statistical analyses of data collected in this study will be included in the report on the survey.

Data collected from the survey will be reported as descriptive statistics. Frequency distributions with 95% CIs will be calculated for pharmacist responses to all questions that address the survey objectives.

CIG Research will apply all appropriate statistical validation to the recommended sampling approach, to the quota setting and recruitment processes. 100% of responses will be validated to ensure quality of completion, non-replication (i.e., ballot-stuffing) and response to all questions by all respondents.

The full study analysis will include the following statistics, including metrics for survey administration:

- The number and percentage of target respondents within the CIG Research opt-in panel who are invited to participate; number of invitations sent in total;
- The number and percentage of invitees who open the invitation but do not proceed to participate in the survey; open and click through rates;

- Reasons for ineligibility – i.e., the number opening the survey and commencing responses but who are ruled ineligible on the grounds of not recalling receiving and reading the aRMMs, job title, outlet type or agreement to have their data included;
- The number and percentage commencing the survey but failing to complete other than through eligibility – drop-outs;
- Final number of survey completions;
- The number and percentage of pharmacists by job title and outlet type who completed the survey;
- The comparative profile of pharmacists who gave correct or incorrect responses to the eight case study scenarios in terms of their demography;
- The demographic characteristics of those participating – e.g., age, gender, years since qualifying;
- Pharmacist responses to questions pertaining to the survey objectives:

    - Pharmacists' knowledge/understanding of the risks associated with the supply of Gina
    - The number and percentage of pharmacists who correctly responded to each scenario about the risks of supplying Gina
    - Recall of reading and utilising the aRMMs
    - Utilisation of the aRMMs during consultations
    - Number of consultations in the last six months
    - Location of consultations within the pharmacy.

Detailed analysis will be carried out for each scenario. Where the percentage of pharmacists answering a scenario question correctly is below the level defined to represent success, the training materials relating to that scenario will be reviewed and improved as appropriate. **Annex 4** includes risks and contraindications that are covered in the scenarios and four corresponding answer options. All scenario answers will be analysed and the percentage proportion of correct versus incorrect answers will be shown. If less than 80% correct answers are provided, the aRMMs have not passed the success criteria and the relevant training materials will be amended. There are three possible incorrect answers for each scenario question. If one incorrect answer is overperforming, related section in training materials will be updated, but if all three incorrect answers over-index to a statistically significant level at the 95% confidence limit applied to all analysis of this data (see table 2), changes will be made in all of them.

The report will include a detailed executive summary, together with conclusions and recommendations in line with the information required for the EMA PASS template for the final study report: Guidance for the format and content of the final study report of non-interventional post-authorisation safety studies.

9.8 Quality control

The study will be conducted in accordance with all applicable regulatory requirements. The testing will also be conducted in accordance with all applicable subject privacy requirements (including UK GDPR), and the guiding principles of the current version of the Declaration of Helsinki.

Documentation of all data management activities will allow step-by-step retrospective assessment of data quality and performance. Management of data will be performed in accordance with applicable standards (including MHRA *'GXP' Data Integrity Guidance and Definitions*[4]) and data

cleaning procedures to ensure the integrity of the data (e.g., removing errors and inconsistencies in the data).

The survey data will be collected using a secure online data entry system. The proposed system has been validated and is secure for receiving and storing survey data. A cloud-based data repository will be used to warehouse survey data and other relevant programme information. This platform ensures compliance with Annex 11 *EudraLex The Rules Governing Medicinal Products in the European Union*[5] for the entry, storage, manipulation, analysis and transmission of electronic information.

The system is integrated with dashboard reporting services to enable real time access to data collected online. All data entered will be single data entered by the respondent. Data will be checked in real time against the programmed edit specifications as they are entered to ensure that data are being entered according to acceptable parameters and requirements. Data exported into Excel for the purposes of generating presentation charts for reporting will be aggregated and not manipulated in any way that alters the results of the survey and will match the data held within the secure online data entry system. All versions generated will be dated, kept with accompanying documentation and archived. This archived data will be available for independent audit throughout the study and retrospectively.

9.9 Limitations of the research methods

It is a limitation that the participating pharmacists will be self-selected since respondents will voluntarily respond to the invitation to participate. However, the survey recruitment strategies are intended to recruit a representative sample. All data from the survey are self-reported and therefore susceptible to possible reporting bias. There could be discrepancies between what pharmacists report about their practices and their actual behaviours. In this case, it would be difficult to validate whether pharmacists' responses to practice-related questions completely concur with their actual behaviours since this is a self-reported survey.

A secondary limitation inherent in survey research is the reliance on the respondent's recall of whether or not the aRMM materials were read and utilised. If respondents say they did not read and utilise the aRMMs, they will be screened out. It is possible that pharmacists may simply not recall the tools that were received and read. It is possible that removing those who do not recall reading the aRMMs will reduce the overall sample size, depending on the proportion of all pharmacists eligible to participate in the survey.

The objective of this PASS is to measure the effectiveness of the pharmacy training materials. This study will look at two process indicators: a) reaching the target population and b) assessing clinical knowledge. These process indicators are intended to provide insight into to what extent the dissemination of pharmacy materials has been executed as planned and whether the intended measures impact on behaviour.

For the switch of estradiol hemihydrate 10 micrograms vaginal tablets from POM to P, where it is not feasible for the applicant to obtain data on outcome indicators for reductions in adverse events, effectiveness evaluation of this PASS is exclusively based on the careful interpretation of data on process indicators. Situations like these are acknowledged in the *Guideline on good pharmacovigilance practices Module XVI*[6], where measurement of effectiveness may need to rely on process indicators instead of outcome indicators.

10. Protection of human subjects

All parties will ensure protection of pharmacists' personal data and will not include names on any client forms, reports, publications, or in any other disclosures, except where required by laws. In the case of data transfer, parties will maintain high standards of confidentiality and protection of pharmacist data. In the specific case of safety reporting, respondents are required to give their permission for information to be passed to Novo Nordisk Ltd. (see Section 11, below).

Due to the nature of the study, informed consent is not required. Participants need to go to the survey website in order to complete the survey. Consent is implied by these actions. Additionally, at the beginning of the survey, the respondent will be asked if they agree to take part in the survey. If yes, the respondent continues with the survey questions. If no, the survey is terminated.

11. Management and safety reporting

This study does not involve data collection on clinical endpoints on individual patients. However, safety information may be identified during the course of data collection (e.g., through an email note to CIG Research). Any safety information for an individual patient that is volunteered by a study participant during the course of this research will be reported to Novo Nordisk Ltd.

12. Plans for disseminating and communicating study results

A final report describing the survey objectives, detailed methods, results, discussion and conclusions will be developed at the end of the survey for submission to the MHRA within the timeframe specified in 'Section 6: Milestones.' In addition, the study results will be posted on the EU PAS register.

13. References

1. Gina Summary of Product Characteristics (SmPC) https://www.medicines.org.uk/emc/product/13930/smpc#ORIGINAL
2. EMA/DIA Information Day, 2017: Preliminary results of a cumulative systematic review and meta-analysis of risk minimisation survey studies Minutes of the PRAC meeting 6-9 March 2017 (europa.eu)
3. MHRA *'GXP' Data Integrity Guidance and Definitions* letter (publishing.service.gov.uk)
4. EudraLex: The Rules Governing Medicinal Products in the European Union, Volume 4 *Good Manufacturing Practice Medicinal Products for Human and Veterinary Use*, Annex 11: Computerised Systems *Annex 11 Final 0910 (europa.eu)*
5. Guideline on good pharmacovigilance practices (GVP) – Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2) (europa.eu)

Annex 1. Example invitation to participate in the survey

Dear Pharmacist,

This survey has been commissioned on behalf of Novo Nordisk to comply with MHRA requirements as part of the study among pharmacists to understand your attitudes and behaviour in relation to the recent switch of estradiol hemihydrate 10 micrograms vaginal tablets from POM to Pharmacy (P). This being a new category of medicine available as a P medicine, as part of the marketing authorisation, the MHRA requested a PASS study to be conducted which they must review and approve. The study reviews the information and training you may have received about the product to enable you to correctly advise patients and mitigate risk, using a series of scenarios for you to consider. The scenarios have been developed to ensure a complete understanding of the product and ability to supply appropriately in different situations. It is important that you take time to answer.

This survey should take approximately 20 minutes to complete and it will have to be completed in one sitting within 60 minutes. Please do not close the survey until you have completed it as you will not be allowed to re-open it. It is possible to complete the survey on a desktop, laptop, tablet or mobile device, but we recommend completing it on your desktop for the best experience.

CIG Research will compensate pharmacists for their time spent completing the survey in the form of reward points, which can be redeemed for vouchers to the value of £20 per completed response. This remuneration programme is run by CIG Research and is governed by UK laws and regulations.

Start survey

Many thanks for your ongoing support.

Your help is greatly appreciated.

Yours faithfully,

[redacted]

Annex 2. ENCePP checklist for study protocols

Study title:
Assessment of the effectiveness of additional Risk Minimisation Measures (aRMMs) among pharmacists for provision of estradiol hemihydrate 10 micrograms vaginal tablets (Gina) in a community pharmacy setting

EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				6
1.1.1 Start of data collection[2]	☒	☐	☐	
1.1.2 End of data collection[3]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results	☒	☐	☐	

Comments:

Section 2: Research questions	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research questions and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is being conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup about whom the study results are intended to be generalised)	☒	☐	☐	9
2.1.4 Which hypothesis(es) is(are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

[2] Date from which information is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[3] Date from which the analytical dataset is completely available.

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	
3.3	Does the protocol specify measures of occurrence? (e.g. rate, risk, prevalence)	☐	☐	☒	
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/ adverse reactions? (e.g. adverse events that will not be collected in the case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9
4.2	Is the planned study population defined in terms of:				9
	4.2.1 Study time period	☒	☐	☐	
	4.2.2 Age and sex	☐	☐	☒	
	4.2.3 Country of origin	☒	☐	☐	
	4.2.4 Disease/indication	☐	☐	☒	
	4.2.5 Duration of follow-up	☒	☐	☐	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYs, healthcare services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview, including scales and questionnaires, vital statistics)	☒	☐	☐	9
9.1.3 Covariates and other characteristics?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.5
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	8.3
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.8
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.8

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have the requirements of the Ethics Committee/ Institutional Review Board been described?	☐	☒	☐	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results? (e.g. to regulatory authorities)	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☐	☐	☒	

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____

Annex 3. Questionnaire design

SURVEY LEGEND

Instructions to the programmer who is tasked with scripting the survey into the survey software.

MULTI CODE is inserted for questions in which respondents may choose more than one option from the pre-defined list of answers.

SINGLE CODE is inserted for questions where only one answer is permitted from the pre-defined list of answers.

Close on codes (x-y) requires that those who choose any of the specified answers denoted by those codes will be redirected to terminate the survey because they are not eligible to continue. These respondents will receive a notification that they are not eligible to continue with the questionnaire.

IF QA code (x or y) denotes that the following question will be filtered (i.e., visible) only to those who answered QA with a pre-defined answer which is attributed with the code (i.e., x or y).

SLIDER less than one to x describes the format for answering a question using a scale with x points, where a score of 0 is entitled 'less than one' and a score of x or more is entitled 'x plus'. A slider is a graphic response option within the survey software allowing respondents to drag their cursor to a specific point on this scale.

RANDOMISE Randomising is an option within survey software to ensure that each respondent sees the list of answers or names in a different (random) order, thus removing Order Effect from the survey. The software automatically re-combines the responses for each answer prior to presenting them for analysis.

QB PIPE FROM QA refers to the process of branching, whereby those who select options in QA are shown options pertaining to QA in QB.

REPEAT FOR X SCENARIOS repeat the same instruction for each of the x scenarios which appear in the survey.

SLIDER SUM 100% This is a feature within the survey software whereby respondents may attribute percentages to each of two or more answers, and the software will require their answers to add up to 100%. This feature uses the same slider visual described above.

SINGLE CODE GRID A single code grid is a matrix of scale questions where a respondent may answer only once per row in the matrix and is required to do so.

INTRODUCTION

Dear Pharmacist,

This survey has been commissioned on behalf of Novo Nordisk to comply with MHRA requirements as part of a study among pharmacists to understand your attitudes and behaviour in relation to the recent switch of estradiol hemihydrate 10 micrograms vaginal tablets from POM to Pharmacy (P). The study reviews the information and training you may have received about the products to enable you to correctly advise patients and mitigate risk, using a series of scenarios for you to consider. The scenarios have been developed to ensure a complete understanding of the product and ability to supply appropriately in different situations. **It is important that you take time to answer.**

This survey should take **approximately 20 minutes** to complete and it will have to be completed in one sitting within 60 minutes. Please do not close the survey until you have completed it as you will not be allowed to re-open it. It is possible to complete the survey on a desktop, laptop, tablet or mobile device, but we recommend completing it on your desktop for the best experience.

CIG Research will compensate pharmacists for their time spent completing the survey in the form of reward points, which can be redeemed for vouchers to the value of £20 per completed response. This remuneration programme is run by CIG Research and is governed by UK laws and regulations.

Any information you provide will be treated as confidential. It will be combined with feedback from others like yourself. You will remain anonymous. Your information will only be used for research purposes, with the requirement that reports on aggregated results will be shared with health authorities and will not be passed to any other organisation without your permission.

You have the right to refuse to answer questions or withdraw at any time. For more information about your rights, please see our privacy notice, available here: Privacy Policy

By proceeding to the next screen:

- I consent to CIG Research collecting and using the information about me that I voluntarily provide for the purposes of research.
- I have read, understand and agree to the terms described above.

a. YES, I am happy to proceed with the research survey on this basis
b. NO, I am not happy to proceed with the research survey on this basis and I do not wish to continue - CLOSE

This survey has been commissioned by a healthcare manufacturer upon request from the MHRA.

We are required to pass on to our client details of adverse events, product complaints, other safety information or pregnancies that are mentioned during the course of market research. Although what you say will, of course, be treated in confidence, should you raise an adverse event, product complaint, other safety information or pregnancy, we will need to report this even if it has already been reported by you directly to the company or the regulatory authorities using the MHRA's 'Yellow Card' system. In such a situation we need to know whether or not you are willing to waive the confidentiality given to you under the Market Research Codes of conduct specifically in relation to any adverse events, product complaints, other safety information or pregnancy.

Do you agree to waive the confidentiality given to you under the Market Research Codes of conduct specifically in relation to any adverse event you report to us?

If you agree to waive confidentiality, your name and contact details will be forwarded to the sponsor's pharmacovigilance department for the express and sole purpose of follow-up of such report(s). All other information that you give us in the context of this study will continue to remain confidential. Are you willing to participate with the survey on this basis?

a. I agree
b. I do not agree

IF AGREEING ABOVE:

Thank you. Please note that if you provide your name during the adverse event reporting, this will not be linked in any way to your responses given during the survey.

We are obligated to share the manner in which your personal information will be handled and stored.

Any safety information we receive will be forwarded to the sponsor of this research for their records.

The sponsor will record any safety information including personal data received in their global Safety database in the interests of patient safety and in compliance with all applicable global laws and regulations and are regularly used to look for overall patterns and trends

During the reporting of safety information, the sponsor will not disclose such personal data to any un-associated third parties with the exception of sharing reported Safety Information with health authorities as mandated by law. However, when sending the Safety Information report personally identifiable details will be pseudonymised

The sponsor will retain the data as long as required by law

Please can you confirm if you agree to your personal details being stored for this purpose?

a. I agree
b. I do not agree

IF NOT AGREEING ABOVE:

If we become aware of a reportable adverse event we are obliged to report this to the pharmaceutical company. We will file this report without giving any of your details, but if the Drug Safety Department requires more information, may we contact you again (without identifying you to the pharmaceutical company)?

a. Yes
b. No

NB: You will still be able to participate in the research regardless of your answer to this question.

Which, if any, of these organisations have you worked for or been contracted to in the last year?

MULTI CODE Close on codes a-d

a. Novo Nordisk Ltd.
b. Communications International Group
c. Consensio LLP
d. MHRA
e. None of these

DEMOGRAPHIC QUESTIONS

QA What is your job title?
SINGLE CODE Close on codes e-m

a. Pharmacist Proprietor
b. Pharmacist Manager / Supervisor
c. Pharmacist
d. Locum Pharmacist
e. Non-pharmacist Manager/Supervisor
f. Non-pharmacist Proprietor
g. Accuracy Checking Technician
h. Pharmacy Technician
i. Dispensing Assistant
j. Medicines Counter Assistant / Pharmacy Assistant / Beauty Counter Assistant
k. Healthy Living Advisor / Champion
l. Healthcare Advisor / Consultant
m. Other

QB. What type of outlet do you work in?
SINGLE CODE Close on codes g-j

a. One shop independent
b. Group branch shop (2 to 5 outlets)
c. Group branch shop (6 to 9 outlets)
d. Group branch shop (10 to 49 outlets)
e. Group branch shop (50 plus outlets)
f. Multiple head office
g. Hospital
h. GP practice pharmacy
i. Exclusively online pharmacy (no consultations)
j. Other

QC. IF QB code e or f Which multiple do you work in?
SINGLE CODE

a. Boots
b. Lloyds Pharmacy
c. Superdrug
d. Rowlands Pharmacy
e. Well Pharmacy
f. Day Lewis
g. Supermarket pharmacy
h. Other

QD. In what type of location is your pharmacy based?
SINGLE CODE

a. City centre
b. Town centre
c. Suburb
d. Village
e. Rural

QE. Where is your pharmacy?
SINGLE CODE

a. Scotland
b. Northern Ireland
c. Wales
d. North East
e. North West
f. Yorkshire and the Humber
g. West Midlands
h. East Midlands
i. South East
j. South West
k. East of England
l. Greater London

QF. What is your gender?
SINGLE CODE

a. Male
b. Female
c. Other
d. Prefer not to say

QG. What is your age?
SINGLE CODE

a. Under 25
b. 25-29
c. 30-34
d. 35-39
e. 40-44
f. 45-49
g. 50-54
h. 55-59
i. 60-64
j. 65 plus
k. Prefer not to say

QH. For how many years have you been qualified as a pharmacist?
SLIDER less than one to 30 plus

STUDY QUESTIONS

Q1. In the last six months, have you held any consultations regarding the supply of Gina (estradiol hemihydrate 10 micrograms vaginal tablets) in the pharmacy?
SINGLE CODE Close on code b

a. Yes
b. No

Q2. In the last six months have you read the Pharmacy Guide for the Supply of Gina and/or pharmacy checklist regarding the supply of Gina to help minimise risk when having consultations?
SINGLE CODE

a. Yes
b. No CLOSE

Q3. Which, if any, of these materials have you read to help minimise risk when having consultations regarding the supply of Gina? **MULTI CODE - RANDOMISE Close if Pharmacy Guide for the supply of Gina or Checklist not selected**

a. Pharmacy guide for the supply of Gina
b. Pharmacy checklist
c. SmPC
d. Pack copy

Q4a. How many consultations do you estimate that you have had with patients about Gina in the pharmacy in the last six months?
SLIDER from 1 to 200 plus (increments of 1)

Q4b What proportion of these consultations have not resulted in the supply of Gina?
Q4c And What proportion have resulted in the supply of Gina?
100% sum

Q5. Where in the pharmacy are these consultations conducted?
SLIDER SUM 100%

a. In a private consultation area
b. At the pharmacy counter
c. Elsewhere

Q6. How confident do you feel about advising patients on the use of Gina?
SINGLE CODE

a. Completely
b. Very
c. Fairly
d. Not very
e. Not at all

Q7. And how confident are you about correctly supplying Gina?
SINGLE CODE

a. Completely
b. Very
c. Fairly
d. Not very
e. Not at all

Q8. How would you rate your own level of knowledge about Gina?

SINGLE CODE GRID

RANDOMISE	Excellent	Good	Fair	Poor	Very Poor	None at all
Its mode of action	o	o	o	o	o	o
Its side effects	o	o	o	o	o	o
Recommended dosage, frequency	o	o	o	o	o	o
Its use with concomitant medication	o	o	o	o	o	o
Red flags/contraindications	o	o	o	o	o	o

Q9. PIPE FROM Q3 Which, if any, of these materials have you used in conjunction with consultations regarding the supply of Gina in the pharmacy? **RANDOMISE MULTI CODE**

a. Pharmacy guide for the supply of Gina
b. Pharmacy checklist
c. SmPC
d. Pack copy
e. Other

Q10. IF Q9 code b. **Which patients do you use the Gina Pharmacy Checklist with?**

a. With every patient
b. Only with new patients
c. Only with a complicated/ complex patients

Q11. How useful do you find each of the following sources in helping you make decisions about the supply of Gina?
Please rate on a 1-5 scale where 1 is not useful at all and 5 is extremely useful. If you do not use a source, please tick the 'not applicable' box.

SINGLE CODE GRID

	Not useful at all	Not very useful	Quite useful	Very useful	Essential	N/A
The Gina Summary of Product Characteristics (SmPC)						
The Pharmacy Guide for the supply of Gina						
The Pharmacy Checklist						

Q12. PIPE FROM Q3 Were the materials easily accessible to you when giving consultations?

SINGLE CODE GRID

RANDOMISE	Yes	No
a. The Pharmacy Guide for the supply of Gina	o	o
b. The Pharmacy Checklist	o	o
c. SmPC	o	o
d. Pack copy	o	o
e. Other	o	o

Q13. Gina SCENARIOS

We would like you to take time reading the following scenarios of typical situations in which a patient requests Gina. Please select one of the two "supply" / "do not supply" options that you believe is a correct course of action, and then choose one of the four answers supporting your decision for supplying or not supplying Gina that is the most accurate in your view.

While considering your answers, you can access any of the support materials you would typically use during this type of consultation, including the training materials for Gina.

Scenario 1

Ms R used Gina for 12 months to treat her vaginal atrophy symptoms. She was pleased with the results as she was able to enjoy intercourse again. As her symptoms had resolved, 6 months ago she decided to stop using Gina. Unfortunately, her symptoms have recently returned and as she is no longer enjoying intercourse and beginning to avoid intimacy with her partner, she wants to start using Gina again. There have been no changes to her health status or her family history.

Select the correct course of action from the following for supplying estradiol hemihydrate 10 micrograms vaginal tablets (Gina):

SINGLE CODE

A. Supply Gina
B. Do not supply Gina

Now please consider the reason for your decision about supplying/not supplying Gina in the above scenario. Which **one** of these actions is correct to your knowledge?

a. Supply Gina as there are no contraindications to restarting Gina.
b. Supply Gina after referring to GP to check Gina is still suitable for her.
c. Do not supply but offer treatment for thrush.
d. Do not supply. A course of Gina can only be used once.

Correct course of action: a. Supply Gina as there are no contraindications to restarting Gina.

Symptoms of vaginal atrophy may return once Gina is stopped. If there are no new contraindications or reasons to refer to GP, Gina may be restarted after a break. Gina may be used as long as she and her pharmacist agree it is suitable. There is no suggestion that Mrs R has thrush.

Scenario 2

Ms E has returned to the pharmacy after finishing her first pack of Gina. She tells you that she hasn't noticed a big improvement in her symptoms, but they definitely haven't got any worse. She hasn't experienced any new symptoms, there have been no changes to her health status or in her family history.

Select the correct course of action from the following:

SINGLE CODE

A. Supply Gina
B. Do not supply Gina

Now please consider the reason for your decision about supplying/not supplying Gina in the above scenario. Which **one** of these actions is correct to your knowledge?

a. Supply but suggest she asks her GP to investigate other causes.
b. Supply. Significant symptom improvement may not be experienced until after the second pack.
c. Do not supply. Refer to GP for a prescription.
d. Do not supply. Refer to GP to change treatment.

Correct course of action: b. Supply. Significant symptom improvement may not be experienced until after the second pack. The first pack of Gina lasts for 7 weeks. Women may not experience a significant improvement in symptoms until after 3 months of treatment.

Scenario 3

Ms G has been purchasing Gina from your pharmacy for 6 months. Recently her symptoms have returned with severe vaginal itching which keeps her awake at night and she has noticed a lump on her vulva.

Select the correct course of action from the following:

SINGLE CODE

A. Supply Gina
B. Do not supply Gina

Now please consider the reason for your decision about supplying/not supplying Gina in the above scenario. Which **one** of these actions is correct to your knowledge?

a. Supply. These symptoms are common in postmenopausal women and do not need additional treatment.
b. Supply. The symptoms will resolve with prolonged use of Gina.
c. Do not supply, refer to GP. These symptoms are probably due to thrush but should be treated by the GP.
d. Do not supply, refer to GP. Red flag symptoms of severe vaginal itching with a vulval lump indicate possible vulval dermatoses.

Correct course of action: d. Do not supply, refer to GP. Red flag symptoms of possible vulval dermatoses. Severe vaginal itching with a vulval lump are red flag symptoms as they could indicate vulval dermatoses.

Scenario 4

Mrs F comes into pharmacy and asks if she would be suitable for Gina. Her GP has been prescribing oestrogen creams for the past 6 months to manage her VA symptoms. She has responded well but finds the creams messy and difficult to use. She tells you she is 60 years old and her health hasn't changed since her last prescription.

Select the correct course of action from the following:

SINGLE CODE

A. Supply Gina
B. Do not supply Gina

Now please consider the reason for your decision about supplying/not supplying Gina in the above scenario. Which **one** of these actions is correct to your knowledge?

a. Supply. Switching from one local oestrogen to another such as Gina is appropriate provided there are no other health considerations.
b. Supply but refer back to GP for a full health check.
c. Do not supply. Gina is not suitable for 60-year-olds.
d. Do not supply. Gina cannot be used by women who have previously used a cream.

Correct course of action: a. Supply. Switching from one local oestrogen to another such as Gina is appropriate provided there are no other health considerations. The GP has already prescribed a local treatment. There have been no changes to her health. Gina is indicated for women over 50 who have not had a period for at least one year.

Scenario 5

Your counter assistant, Jill, refers Mrs C to you. She has been using Gina for 9 months now. She has experienced good results and no problems using Gina, and there have been no changes in her medical health or risk factors. However, she told Jill that despite using the applicator correctly she has recently experienced a lot of discomfort every time she inserts the vaginal applicator. She wants to ask for your advice. She has been using the correct dose of Gina, with no break in treatment. She is not experiencing symptoms of thrush.

Select the correct course of action from the following:

SINGLE CODE

A. Supply Gina
B. Do not supply Gina

Now please consider the reason for your decision about supplying/not supplying Gina in the above scenario. Which **one** of these actions is correct to your knowledge?

a. Supply. Reinforce correct use of the applicator.
b. Supply. The discomfort will go if she continues to use Gina.
c. Do not supply, refer to GP for assessment of other causes.
d. Do not supply. Local oestrogen treatment is not suitable.

Correct course of action: c. Do not supply, refer to GP for assessment of other causes. Discomfort using the applicator after several months of treatment may indicate a new concurrent vaginal condition (e.g., thrush, an STI or vulval dermatoses) or general health changes (e.g., a change in dexterity due to arthritis).

Scenario 6

Mrs W is 55 and has been using Gina for the last 9 months. She went through her menopause at least 4 years ago. She has found that Gina really helps with her vaginal atrophy symptoms and she is feeling almost back to her usual self. She has come into your pharmacy today for her next 3-month supply. On a couple of occasions in the last month she noticed a small amount of bleeding – she describes it as "just some spots of blood" – after sex. She thought it was strange, but it was only a small amount, so she hasn't been to see her GP about it.

Select the correct course of action from the following:

SINGLE CODE

A. Supply Gina
B. Do not supply Gina

Now please consider the reason for your decision about supplying/not supplying Gina in the above scenario. Which **one** of these actions is correct to your knowledge?

a. Supply. Bleeding after sex is normal and will settle after continued use of Gina.
b. Supply. Gina is relieving her vaginal symptoms so she should continue to use it.
c. Do not supply, refer to GP. Red flag symptoms of possible endometrial cancer or hyperplasia.
d. Do not supply, refer to GP. She has a vaginal infection which needs treatment.

Correct course of action: c. Do not supply, refer to GP. Red flag symptoms of possible endometrial cancer or hyperplasia. Any undiagnosed vaginal bleeding is a red flag symptom and should be investigated.

Scenario 7

Miss J had thrush which was treated before starting to use Gina 7 weeks ago which she is happy to continue using. She now has a discharge which is quite smelly and isn't quite like her previous episode of thrush, but she is not sure.

Select the correct course of action from the following:

SINGLE CODE

A. Supply Gina
B. Do not supply Gina

Now please consider the reason for your decision about supplying/not supplying Gina in the above scenario. Which **one** of these actions is correct to your knowledge?

a. Supply. Discharge whilst using a local oestrogen is common.
b. Supply. Provide treatment for thrush as well.
c. Do not supply, refer to GP. Vaginal discharge is a common symptom of fibroids.
d. Do not supply, refer to GP. She could have thrush or a vaginal infection which needs to be evaluated by her GP.

Correct course of action: d. Do not supply, refer to GP. Red flag symptom which needs to be evaluated by her GP. The discharge is not the same as her symptoms of thrush so needs to be investigated.

Scenario 8

When discussing the suitability of Gina for Miss T, she tells you that she had endometrial hyperplasia 2 years ago which was treated by a hysterectomy and she has had no further problems. Otherwise, she is well.

Select the correct course of action from the following:

SINGLE CODE

A. Supply Gina
B. Do not supply Gina

Now please consider the reason for your decision about supplying/not supplying Gina in the above scenario. Which **one** of these actions is correct to your knowledge?

a. Supply. Gina may be used by women who have had a hysterectomy.
b. Supply. Endometrial hyperplasia can be treated with oestrogen.
c. Do not supply. Local oestrogens are contraindicated in women who have had a hysterectomy.
d. Do not supply. Gina is not effective in women who have had a hysterectomy.

Correct course of action: a. Supply. Unopposed local oestrogen may be used by women who have had a hysterectomy. Miss T has had a hysterectomy so will not develop endometrial hyperplasia. Women with symptoms of VA may use Gina regardless of whether they have had a hysterectomy or not.

Annex 4: Risks assessed in case study scenarios

Number	Answer	Risk/contraindication
Scenario 1	a. Correct	Correct understanding that Gina may be restarted after a break
	b. Incorrect	There is no need to refer back to GP unless there are other reasons such as contraindications
	c. Incorrect	The symptoms are those of vaginal atrophy not thrush as there is no discharge present
	d. Incorrect	Gina may be used after a break in treatment and as often as required
Scenario 2	a. Incorrect	Significant improvement in symptoms may not be experienced until after the second pack
	b. Correct	Correct understanding that significant improvement in symptoms may not be experienced until after the second pack
	c. Incorrect	GP referral is not required after the first pack if symptoms have not worsened
	d. Incorrect	GP referral or a change in treatment is not required after the first pack if symptoms have not worsened
Scenario 3	a. Incorrect	These are red flag symptoms which require referral to GP. Gina will not relieve the symptoms
	b. Incorrect	These are red flag symptoms which require referral to GP. Gina will not relieve the symptoms
	c. Incorrect	These are red flag symptoms which require referral to GP. There is no discharge present, so thrush is unlikely
	d. Correct	Correct understanding of red flag symptoms which require referral to GP
Scenario 4	a. Correct	Correct understanding that women may switch from a prescribed cream to Gina
	b. Incorrect	GP referral is not required as there have been no changes in health status
	c. Incorrect	Gina may be used by women over 50
	d. Incorrect	Gina may be used by women who have previously been prescribed a cream by their GP

Scenario 5	a. Incorrect	The applicator is being used correctly. The reason for the discomfort should be investigated
	b. Incorrect	Gina has already been used for 9 months. The reason for the discomfort should be investigated
	c. Correct	Correct understanding that the reason for the discomfort should be investigated
	d. Incorrect	A local oestrogen is not contraindicated but the reason for the discomfort should be investigated
Scenario 6	a. Incorrect	Any undiagnosed vaginal bleeding is a red flag symptom and should be investigated
	b. Incorrect	Any undiagnosed vaginal bleeding is a red flag symptom and should be investigated, regardless of symptom relief
	c. Correct	Correct understanding of red flag symptoms which require referral to GP
	d. Incorrect	Bleeding after sex is a red flag symptom not a sign of thrush
Scenario 7	a. Incorrect	An unusual discharge is a red flag symptom ad should be investigated
	b. Incorrect	An unusual discharge is a red flag symptom ad should be investigated
	c. Incorrect	Vaginal discharge is not a common symptom of fibroids
	d. Correct	Correct understanding that an unusual discharge is a red flag symptom ad should be investigated
Scenario 8	a. Correct	Correct understanding that Gina may be used by women who have had hysterectomy
	b. Incorrect	Endometrial hyperplasia should never be treated with oestrogen
	c. Incorrect	Local oestrogen is not contraindicated in women who have had a hysterectomy
	d. Incorrect	Women who have had a hysterectomy may use Gina