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
Version identifier of the final study report	Version 2.0
Date of last version of the final study report	02 January 2024
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
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Redacted report
includes redaction of personal identifiable information only.

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1. Abstract

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.

Name and affiliation of the main author:

Keywords:

Estradiol, menopause, Gina

Rationale and background:

Estradiol hemihydrate 10 micrograms vaginal tablets (Gina) were reclassified to a pharmacy only (P) medicine in the UK in 2022. To support the safe supply of the product via pharmacy, Novo Nordisk developed a Pharmacy Guide for the Supply of Gina and an optional Pharmacy Checklist as additional Risk Minimisation Measures (aRMMs). The content of the materials has been aligned and approved by the MHRA .

This post-authorisation safety study (PASS) sets out to assess the effectiveness of the approved aRMMs for estradiol hemihydrate 10 micrograms vaginal tablets (Gina) as a P medicine, 14 months after the UK market launch.

The research was carried out among UK community pharmacists who had conducted consultations on Gina in the last six months, and had 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. The PASS used a series of patient scenarios designed to test the knowledge of pharmacists about when to supply or not supply the product, and for what reason. Key performance indicators (KPIs) were set at 'best in class' levels of 80% giving correct answers regarding the decision to supply or not supply estradiol in eight scenarios (Table 9-3) to adjudge the target audience who were adequately trained on risk minimisation measures.

Research question and objectives:

The overall objective of the study was 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 were to:

1. Demonstrate that the training provided by Novo Nordisk 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.
2. Identify whether there are particular contraindications or warnings for which pharmacists consistently make the wrong supply decision.

3. Establish ease of access to and ease of use of the aRMMs.

Study design:

The study was a cross sectional, non-interventional web-based survey at twelve months post the first product launch following MHRA approval of the reclassification.

Setting:

The survey was distributed across the United Kingdom (UK) to a representative mix of independent and multiple ownership pharmacies.

Subjects and study size, including dropouts:

Pharmacists who had read the aRMM materials and had conducted at least one consultation during the previous six months were eligible to participate. To ensure representative data, a mix of independent and multiple ownership pharmacies, including those in urban, small town and rural settings were recruited to participate. The target sample size was 200 completed surveys. The sample size chosen for this study was dependent on statistical and feasibility considerations.

Variables and data sources:

The survey collected information about pharmacists' understanding of the key safety messages in the risk minimisation measures using eight multi-parameter scenarios. The scenarios were designed to evaluate pharmacists' ability to make correct supply/do not supply decisions, and as a secondary measure, through multiple safety parameters, to establish their level of understanding of the reasons behind the correct decision.

It also collected information about potential pharmacist behaviour with regard to communicating important safety information to patients, as well as their demographic characteristics and clinical experience.

The KPI was set at 80% for those making appropriate decisions to supply or not supply Gina and also for pharmacists giving the right reason for their decision in each of the eight scenarios. The key objective of this study (objective 1) was satisfied by the supply/not supply question in each scenario. The measure of choice of reason for the decision was a secondary objective (objective 2). This very high bar was set as a 'best in class' objective, and was well above the 70% target set in many PASS studies.

In this survey, the data source was a panel of 35,175 UK retail pharmacy staff who had previously opted-in to participate in research with CIG Research.

Results

1. Discussion

The materials most likely to have been read to help minimise risk when having consultations regarding the supply of Gina were the Pharmacy Guide for the supply of Gina and the Pharmacy Checklist (Table 10-7). In terms of the usefulness of these materials used in consultations, 83% rated the Pharmacy Guide as essential or very useful, and 89% rated the Checklist as essential or very useful.

The research demonstrated that the pharmacy training material provided was effective in enabling pharmacists to make correct decisions to supply or not supply estradiol and consequently the materials have adequately minimised the risk of inappropriate supply.

The materials were rated as easily accessible to pharmacists when having consultations, for all four of the materials included (the Pharmacy Guide, The Pharmacy Checklist, SmPC and Pack Copy).

Across the total sample, in seven of the eight scenarios, the option to supply or not supply estradiol reached the threshold of 80% set as a KPI within the margin of error at 95% confidence.

Regarding secondary consideration of the reason to supply or not supply Gina, it fell short of the high KPI objective that 80% of pharmacists would select the correct reason for their decision in two of the eight scenarios. This was primarily due to the complexity of the multi-parameter scenarios, and particularly these two scenarios, where an incorrect reason was selected by 29.0% of respondents in one case and 29.5% in the other. When all eight scenarios are taken into consideration, the supply/do not supply KPI was exceeded (86.4% +/-1.68%) and the reason for the decision to supply/not supply also exceeded the KPI at 81.4% +/- 1.91%.

The level of pharmacist confidence in providing correct advice and making the right decision about supplying the product was very high. 98.0% of all pharmacists were at least fairly confident about advising patients and 60.5% were very or completely confident. It was also important that the level of confidence increased with the number of consultations pharmacists had given in the first fourteen months since the launch of Gina. Despite their reported confidence, pharmacists, when unsure, tended to become conservative, recommending not to supply Gina and to refer patients to their GP – effectively a low risk option (see scenario 6, Table 10-13).

Pharmacists participating in this study had conducted at least one consultation on Gina in the last six months, and on average had only conducted 15 consultations over the time period. Given that the research took place fourteen months after the launch of the product, the level of appropriate decision-making was relatively high. It is fair to assume that increased experience of consultations, and use of the aRMMs, will improve the proportion of pharmacists giving the correct reason for supply or not to supply, rather than referring to a GP, even in the complex multi-parameter situations presented in these scenarios.

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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 10 micrograms vaginal tablets (Gina)
GDPR	General Data Protection Regulation
GP	General Practitioner
GSL	General Sales List medicine
GXP	Good Practice
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 Direction
POM	Prescription Only Medicine
RM	Risk Management
RMP	Risk Management Plan
SAP	Survey Analysis Plan
SmPC	Summary of Product Characteristics
URL	Uniform Resource Locator

3. Investigators

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Responsibility statement

In the course of this study, no adverse events were reported by pharmacists in relation to Gina.

5. Milestones

Milestone	**Timelines**
Gina reclassification approval	28.06.2022
Launch of product in pharmacy	09.2022
Roll out of aRMMs	09.2022
MHRA protocol approval	31.08.2023
Pilot study launch	17.08.2023
Pilot study data collection and results reporting	31.08.2023
Submission of changes made to the protocol and questionnaire to MHRA	14.09.2023
MHRA updated protocol approval	16.11.2023
Main study launch	22.11.2023
End of data collection	27.11.2023
Publication of final study report	31.01.2024

6. Rationale and background

Estradiol hemihydrate 10 micrograms vaginal tablets (Gina) (EH) was reclassified from a prescription only (POM) to a pharmacy only (P) medicine in the UK in June 2022.

To support the safe supply of the product via pharmacies and ensure correct advice is provided by pharmacists, Novo Nordisk Ltd developed a Pharmacy Guide for the supply of Gina and an optional Pharmacy Checklist as additional Risk Minimisation Measures (aRMMs). The content of the aRMMs was aligned and approved by the MHRA.

This survey was designed to assess pharmacists' understanding of the aRMMs (Pharmacy Guide and Pharmacy Checklist) with respect to potential risks in the supply and use of Gina, and in directing women for whom it is unsuitable to their doctors.

7. Research questions and objectives

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

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

8. Amendments and updates

Number	Date	Section of study report	Amendment or update	Reason
None				

9. Research methods

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

9.1. Study design

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

For this study a representative mix of independent and multiple ownership pharmacies, including those in urban and small-town settings was sampled.

The questionnaire was designed such that all biases in question wording, scale responses and order effect were mitigated. This included 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.

9.2. Setting

The survey was conducted in the UK fourteen months post product launch of Gina, following MHRA approval of the reclassification.

Pharmacists who had read the aRMMs for Gina and had conducted at least one consultation regarding the supply of Gina during the six months prior to the survey were eligible to participate. A mix of independent and multiple ownership pharmacies, including those in urban, small town and rural settings were recruited to participate in the survey from CIG Research's opt-in panel of 35,175 UK community pharmacists.

Table 9-1: Sample quotas set, and quotas achieved

The distribution of pharmacists in the UK formed the basis of quotas set for this survey for geographical distribution and outlet type, and was based on CIG Research's database of UK community pharmacies and staff. Classification by neighbourhood type is not a standard classification variable and quotas were set based on a series of previous surveys conducted by CIG Research in the UK between 2015 and 2023.

	Quotas set proportion (+/-5%)	Quotas achieved
Single outlet independent	15%	15%
Group branch independents 2-49 outlets	35%	34%
Multiples (50 plus outlets)	50%	51%
Pharmacist Proprietor	10%	4%

Pharmacist Manager / Supervisor	30%	17%
Pharmacist	40%	47%
Locum Pharmacist	20%	32%
Urban	50%	58%
Suburban	35%	32%
Rural	15%	11%
London and South East/South West	45%	37%
Midlands and East of England	20%	29%
North East/North West	25%	12%
Scotland, Wales, Northern Ireland	10%	12%

The study was conducted as a non-interventional web-based survey, which allowed respondents to participate at a time and location that was convenient to them. The research panel was used to completing surveys in this environment and no other data collection method was necessary to facilitate acceptable completion rates.

Invitations

Pharmacists based in community pharmacies across the UK were invited to participate in this survey in November 2023. A total of 35,175 pharmacy staff were invited to take part. Invitations were sent in three stages to randomly selected members of the CIG Research panel:

1. Soft launch to established CIG Research panel members (six months-plus membership)

- 21.11.2023: initial invitation sent to 2,069 CIG Research panel members
- 22.11.2023: first reminder sent to 1,980 members from the first group
- 24.11.2023: second reminder sent to 1,945 members from the first group

2. Full launch to total list of 33,060 opt-in research participants (excluding soft launch sample)

- 26.11.2023: initial invitation to 33,060 pharmacists
- No reminder was sent to the full list as the quotas had been met.

9.3. Subjects

Eligible UK-registered pharmacists from CIG Research's opt-in panel who responded to the survey invitation made up the study population.

9.3.1. Inclusion criteria

Pharmacists were required to meet the following criteria for inclusion in the survey:

- Qualified pharmacist working in a community pharmacy in the UK
- 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 six months prior to the study

The sample also aimed to be representative of community pharmacists by age, gender, outlet size, and by region within the UK, including Northern Ireland.

9.3.2. Exclusion criteria

Pharmacists meeting the following criteria were not permitted to take part in the survey:

- Have not read the aRMM materials supplied for the product in the UK, or do not recall having read them
- Have participated in the pilot for the survey (described in Section 9.4.4 of the PASS Protocol: Pilot testing of the survey questions)
- Are employed in full-time research, GP practices or hospitals (i.e., not community-based pharmacists)
- Have been in the employment of or contracted to Novo Nordisk Ltd, the MHRA, Communications International Group or Consensio LLP in the last 12 months.

9.4. Variables

The survey contained a total of 44 questions relating to: agreement to participate (4), eligibility (5), demographics (6), awareness and behaviours pertaining to pharmacist consultations and use of educational materials (5), knowledge of Gina (6), confidence in recommending and supplying Gina (2), attitudes towards the educational materials and their use (2), questions assessing pharmacists' knowledge of the correct decision to supply or not supply Gina (16).

The questionnaire is provided in Annex 3 of the protocol [Appendix 1.1 of this document].

The following survey questions provided the variables needed to address the study objectives:

- Q3, Q11, Q12, Q13 Scenarios 1-8: Demonstrate that the aRMMs are effective in enabling pharmacists to make appropriate decisions to supply based on contraindications and special warnings; this includes awareness and mitigation of safety concerns
- Q13 Scenarios 1-8: Identify whether there are particular contraindications or warnings for which pharmacists consistently make inaccurate supply decisions
- Q11, Q12: Establish ease of access to and ease of use of the aRMMs.

9.5. Data sources and measurement

In order to target the desired population, invitations were sent by email to pharmacists from CIG Research's opt-in panel of 35,175 UK community pharmacy staff. Response rates of 2-3% are typical in studies of this type and length, which would have returned between 704 and 1,055 responses. For this survey, a response rate of 1.16% was achieved within the 7 days of fieldwork (407 started the survey); eligibility among those starting the survey was 52.33%, and completion rate 49.14%.

Respondents accessed the survey by means of a secure URL link provided in the email invitation. Each respondent could access the survey only once, which was controlled by unique account identifiers within the survey software. The sample of 200 respondents to the survey was quota controlled to be nationally representative of community pharmacists in the UK.

Pharmacists were screened to ensure they had read the aRMMs and conducted at least one consultation on Gina in the last six months (Q1, Q2, Q3). The scenario section of the questionnaire was designed to present multi-safety scenarios, even though these would not be typical of most consultations, in which pharmacists could choose to refer to information sources during consultations. As the pharmacist might be completing the survey away from their usual place of consultation and might not have access to the materials they would usually use, an instruction was

given that they could make use of any of the aRMMs they would normally use to help them complete the survey. The decision was taken not to provide a direct electronic link to these materials during the survey, as this would be unlikely to happen in real-life.

Information on the CIG Research opt-in 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 were sent out for this survey, the panel stratification classification was used to boost responses from under-represented segments in collected responses, by encouraging pharmacists in those segments to take part. CIG Research compensated pharmacists for their time spent completing the survey in the form of reward points, which can be redeemed for vouchers. This remuneration programme is independent of Novo Nordisk and is governed by UK laws and regulations.

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) was used to collect the survey data.

The PASS protocol was subject to the following amendments before the launch of the main study:

The survey was piloted with 20 pharmacists from the CIG Research panel who met the inclusion criteria. This was conducted between 17th and 20th August 2023 and the report was appended to the PASS Protocol submitted to the MHRA on 14th September 2023.

The pilot assessed both the flow of the questionnaire and the meaningfulness of the results from this sample.

It concluded that:

- Eligible completions represented one in three of those commencing the survey, leading to a forecast of the requirement for 600 respondents to achieve a 200 sample in the full survey
- At Q4, three slider scales were replaced by a 100% sum question to ensure that the number of consultations resulting in supply of Gina and the number of them resulting in no supply of Gina would total the number of consultations conducted.
- The level of correct responses to the scenarios was short of the 80% KPI target, but not at a statistically significant level, and the target was kept, given that this pilot took place eleven months after the product launch. Amendments were made to the wording of four scenarios.

The full report from the pilot is available in Appendix 1.2 of this document.

The PASS Protocol was amended and re-submitted to the MHRA. It was approved by the MHRA on 16th November 2023.

- A two-step process for answering each scenario was agreed – supply/do not supply, and then reasons for this decision
- A balance of two 'supply' reasons and two 'do not supply' reasons was made for each scenario.

The final questionnaire is available in Annex 3, Appendix 1.1 of this document.

Participation in this study was voluntary. The questionnaire collected 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 was used to evaluate the effectiveness of the aRMMs. Any personal, identifying information used for processing compensation had previously been provided to CIG Research by pharmacy panellists for this purpose and was not collected within this survey.

The collection of any personal, identifying information (e.g., first name, last name, email address) from respondents was only used for processing of compensation, as allowed by local laws and country regulations, and such information was stored in a separate database.

9.6. Bias

A number of controls were in place to ensure that the survey was conducted in a professional manner and to minimise bias, including the following:

The questionnaire was designed such that all biases in question wording, scale responses and order effect were mitigated. This included 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.

The internet survey was programmed to ensure that questions were asked in the appropriate sequence, and all questions were presented in a standard order to reduce exposure bias.

Respondents could not skip ahead or go back to a question once it was answered. All questions presented were required to be answered in order to complete the survey.

Respondents were only allowed to complete the survey once, as controlled by the survey software and panel management system, QuestionPro, to minimise exposure bias and fraud.

9.7. Study size

The sample size chosen for this study was 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 was chosen. For 200 completed surveys, results would be precise to within ±6.9%, based on confidence intervals around a 50% estimate with 95% confidence limits, and ±5.5% at the 80% KPI level. For 1,600 responses (200 sample x 8 case studies per respondent), results would be precise to within ±2.5% at the 50% mark, and ±1.96% at the 80% mark.

Because precision varies based on the proportion who respond correctly, Table 9-2 provides a range of expected precision, based on the normal approximation of the binomial CI, for several proportions as well as sample sizes. The greatest variance and, therefore, the least precision, occurs when the observed proportion of responses is 50%

$P(-1.96 < Z < 1.96) = 0.95$, i.e., there is a 95% probability that a standard normal variable, Z, will fall between -1.96 and 1.96.

The margin of error is 1.96 times the standard error (the standard deviation of the point estimate from the sample), and 1.96 reflects the fact that a 95% confidence level was selected. So, the general form of a confidence interval is:

point estimate + Z SE (point estimate)

where Z is the value from the standard normal distribution for the selected confidence level (e.g., for a 95% confidence level, Z=1.96).

In practice, we often do not know the value of the population standard deviation (σ). However, if the sample size is large (n > 30), then the sample standard deviations can be used to estimate the population standard deviation.

For the 200 completed surveys, results are precise to within ±6.9% at the 50% mark. Note that although the sample size is based on the requirements set in the study, the proportion of correct responses cannot be known ahead of time. Since precision depends on both the sample size and the proportion of correct responses, a range of possible precision is presented for different proportions at relevant sample sizes below. For analyses by segment, where around 100 pharmacists are included, the precision of results lies within ±10% at worst. In the full tables appended, margins of error are quoted for individual percentages within the total sample and for individual sub-sample sizes, but not for individual percentages within segments, where samples are too small to compare statistically.

The precision of the estimate calculations is based on the following assumptions:

- The confidence intervals (CIs), also referred to as margins of error, around the estimate are two-sided
- The probability of type-I error (alpha) is 5%
- The table below provides precision of the estimate (with 95% CI around the estimate) for a range of sample sizes and percentages.

Table 9-2: Estimated precision by sample size

Sample size	Proportion of correct responses observed (%)	Statistical precision/margin of error (+/-%)*
40	20	12.4
40	50	15.5
40	70	14.2
80	20	8.8
80	50	11.0
80	70	10.0
100	20	7.8
100	50	9.8
100	70	9.0
200	10	4.2
200	20	5.5
200	50	6.9
200	80	5.5
1,600 (total case studies)	80	± 1.96

*95% confidence interval, 2-sided.

9.8. Data transformation

All data collected during the study is 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 and skip logic for certain questions as well as the ability to mark only one response or multiple responses as appropriate forms part of the survey programming. There were no follow-up queries to respondents for this project.

9.9. Statistical methods

9.9.1. Main summary measures

Statistical analyses were descriptive i.e., no formal hypothesis was tested. Counts and percentages of the correct responses were calculated for each question/item in the questionnaire. All CIs around the percentages are exact two-sided 95% CIs calculated according to the method of Clopper-Pearson (Clopper and Pearson, 1934[1]). The survey contained skip patterns i.e., some questions were skipped depending on the answer to a previous question. Percentages were based on the population to whom a specific question was presented.

The analysis populations included:

All Respondents – The All Respondents population consisted of respondents who had accessed the survey and started it. These respondents were used as the denominator for percentages in survey administration statistics, unless otherwise specified, and in the survey eligibility results analysis.

Completed Surveys (Primary Population) – The population for all remaining analyses included only those with completed surveys. “Completed” was defined as an eligible respondent who had no missing data, with the exception of data from skip patterns. An eligible respondent was defined as one who completed all eligibility questions and met all inclusion criteria and none of the exclusion criteria.

9.9.2. Main statistical methods

Analysis of the primary objectives:

All responses to questions around the primary objectives were summarised by counts and percentages. Exact binomial two-sided 95% CIs (margins of error) were calculated for the proportion of respondents who gave the correct or desired responses. The primary objectives of the study are listed in Section 7.

The relevant questions to define success of understanding important safety information were combined into eight scenarios (Table 9-3). To be counted as demonstrating understanding of a specific scenario, pharmacists were required to answer two questions correctly – the supply/do not supply question followed by the correct reason for their choice out of four options. The number and percentages, including exact binomial two-sided 95% CIs, of respondents demonstrating understanding were calculated for each individual scenario and for all eight scenarios in aggregate.

The aRMMs were considered effective if at least 80% of respondents demonstrated understanding of each scenario by answering it correctly and if 80% of the total number of responses to the scenarios (i.e., 1,280 out of a possible 1,600) were correct. These KPIs were subject to margin of error validation.

Table 9-3: aRMMs Informing Understanding of Important Safety Messages

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

Analysis of additional survey questions:

Additional questions in the survey included questions to determine respondent eligibility, prescribing status, demographic information, and clinical experience. The number and percentage of respondents were summarised by their responses to each question.

Subgroup analysis:
The following subgroup analyses were performed for each of the questions related to the primary objectives of the study for all completed surveys, as applicable:

Outlet type

- Independents (pharmacists working in small chains of 1-49 outlets)
- Multiples (pharmacists working in chains of 50+ outlets)

Location

- Urban (pharmacists working in city or town centre pharmacies)
- Suburban/Rural (pharmacists in suburbs, villages or rural locations)

Age

- Pharmacists aged under 40 years
- Pharmacists aged 40 plus

Gender (excluding those choosing ‘other’ or ‘prefer not to say’)

- Male pharmacists
- Female pharmacists

Job title

- Pharmacists (those with title Proprietor, Manager or Pharmacist)
- Locums (those with title Locum Pharmacist)

Consultation status

- High consultations (11 plus patients in last 6 months)
- Medium consultations (5-10 patients in the last 6 months)
- Low consultations (1-4 patients in the last 6 months)

Note that the cut-off between low, medium and high consultations was not determined a priori and was instead based on the distribution of consultation frequency in the completed surveys. The goal was to have similar sample sizes in all subgroups.

9.9.3. Missing values

In order to minimise bias, the survey was programmed to ensure respondents could not skip ahead and only allowed for missing data caused by skip patterns. In instances where there was missing data not due to skip patterns (i.e., the respondent did not complete the survey), the respondent was not considered in the analysis.

9.9.4. Sensitivity analyses

All percentages based on the total sample and the totals for segments were sensitivity tested to establish margins of error at each percentage level. These are presented in the tables, as exact binomial two-sided 95% CIs.

9.9.5. Amendments to the Survey Analysis Plan

There were no unforeseen analyses or deviations from the Survey Analysis Plan (SAP). No analysis was completed until survey collection had ended.

9.10. Quality control

The study was conducted in accordance with all applicable regulatory requirements. The testing was also conducted in accordance with all applicable subject privacy requirements (including European General Data Protection Regulation - GDPR), and the guiding principles of the current version of the Declaration of Helsinki.

Documentation of all data management activities allowed step-by-step retrospective assessment of data quality and performance. Management of data was performed in accordance with applicable standards (including MHRA *'Good Practice - GXP' Data Integrity Guidance and Definitions*[2]) and data cleaning procedures to ensure the integrity of the data (e.g., removing errors and inconsistencies in the data).

The survey data was collected using a secure online data entry system. The proposed system was validated as secure for receiving and storing survey data. A cloud-based data repository was used to

warehouse survey data and other relevant programme information. This platform ensured compliance with Annex 11 *EudraLex The Rules Governing Medicinal Products in the European Union*[3] for the entry, storage, manipulation, analysis and transmission of electronic information.

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

10. Results

10.1. Participants

Survey administration statistics for pharmacists invited to participate in the survey are presented in Table 10-1.

Table 10-1: Survey administration statistics

	Number	%
Universe (CIG Research pharmacy staff database)	35,175	100.0
Viewed the invitation during the fieldwork period	1,438	4.1
Eligible to take part based on demography	407	1.2
Those who had held at least one consultation regarding the supply of estradiol hemihydrate 10 micrograms vaginal tablets (Gina) (DSG) in the last 6 months	216	0.61
Those who had read training materials or consultation checklists regarding the supply of estradiol hemihydrate 10 micrograms vaginal tablets (Gina) (EH) without a prescription to help minimise risk when having consultations	213	0.61
Completed the survey (and passed all quality control checks)	200	0.6

In order to achieve 200 responses, 35,175 pharmacy staff were invited to take part and received two reminder invitations over the course of one week (see Appendix 1.3 table 1.1.1). Fieldwork was completed between 22.11.2023 and 27.11.2023, during which 1,438 pharmacy staff opened the invitation and 407 began the survey, 391 agreed to take part and 16 immediately dropped out, stating that they did not want to proceed.

362 (88.9% of those starting the survey) agreed to report any AEs (although in the event, none were reported), and 87.5% had not in the last year worked with any of the four organisations chosen for elimination. 76.7% were eligible on job title, while the remainder were eliminated as non-pharmacist staff. 69.3% were eligible on the basis of their outlet type (excluded were those working in GP Pharmacies, hospitals and non-community pharmacies or online only).

216 (76.7%) of those 282 pharmacists eligible on demographic grounds had held at least one consultation regarding the supply of Gina in the last six months. This was a substantially higher number than had been predicted at the time of submission of the Protocol, based on the pilot (33%).

213 (98.6%) of those eligible as having conducted consultations had read training materials or consultation checklists regarding the supply of Gina (EH) to help minimise risk when having consultations. A further 1.4% had not read them.

13 respondents, having qualified for the survey on all quotas, dropped out before completing the questionnaire. Given that the requirement was for the survey to be completed within one hour, and that many community pharmacists complete surveys while at work in busy pharmacies, this was not unexpected.

10.1.1. Length of survey

The invitation to the survey indicated that respondents should take their time to respond, and that the survey would take in the region of 20 minutes. This was based on the average length of response during the Pilot study of 20 pharmacists. The average length of time taken among the 200 respondents completing this survey was 16.0 minutes, with the range from 308 seconds to 3479 seconds.

Time taken (seconds)	Number	%
Up to 540 (5-9 mins)	68	34.0
541-720 (9-12 mins)	37	18.5
721-900 (12-15 mins)	22	11.0
901-1080 (15-18 mins)	14	7.0
1081-1800 (18-30 mins)	34	17.0
1801 plus (30 mins plus)	20	10.0

It is important to note that analysis of the key questions, and specifically the answers given to the eight scenarios, established that length of survey completion showed no correlation with correct answers. There was no evidence that taking longer to complete the survey led to a greater number of correct answers. On that basis, segmentation by length of completion has been excluded from the analysis.

10.2. Descriptive data

Among the 407 who started the survey, 51.8% were pharmacists and 24.8% locums – the remainder were ineligible on the basis of job title, or were excluded because they did not want to report AEs or had worked for one of the four organisations chosen for exclusion.

Among those completing the survey, pharmacists constituted 68.0% and locums 32.0%. Of the 312 who answered the type of outlet question, 46.5% were working in independent outlets (small chains of up to 49 outlets) and the rest were working in multiples. When the completed surveys were analysed, the ratio was 49.0% independents to 51.0% multiples.

Quotas were set within the target sample based on CIG Research panel composition, since national statistics across all pharmacists are not available, and are skewed by the size of the outlet. The following quotas taken from the panel of 35,175 pharmacy staff were closely matched by the achieved sample, with the exception of job title, where fewer proprietors and managers and more pharmacists and locums were present.

Table 10-2: Sample quotas set and quotas achieved

	Quotas set proportion (+/-5%)	Quotas achieved (200 sample)
Single outlet independent	15%	15%
Group branch independents 2-49 outlets	35%	35%
Multiples (50 plus outlets)	50%	50%
Pharmacist Proprietor	10%	4%
Pharmacist Manager / Supervisor	30%	17%
Pharmacist	40%	47%
Locum Pharmacist	20%	32%
Urban	50%	58%
Suburban	35%	32%
Rural	15%	11%
London and South East/South West	45%	37%
Midlands and East of England	20%	29%
North East/North West	25%	12%
Scotland Wales, N Ireland	10%	12%

Within the multiples, a large range of outlet brands were included. 42.2% of the 102 working in multiples worked in Boots, and 12.8% in LloydsPharmacy and 18.6% in supermarket pharmacies. The 'Other multiples' included:

- Lincolnshire Co-op
- Superdrug
- Tesco
- Medicare
- Morrisons
- Paydens

Table 10-3: Description of pharmacists: job title, outlet type, multiple

Total number of respondents	N=407 Started	%	N=200 Completed	%
What is your job title?				
Pharmacist Proprietor	12	2.9	8	4.0
Pharmacist Manager / Supervisor	46	11.3	34	17.0
Pharmacist	153	37.6	94	47.0
Locum Pharmacist	101	24.8	64	32.0
Other (discontinued)	95	23.5		
What type of outlet do you work in?				
One shop independent	41	10.1	30	15.0
Group branch shop (2 to 5 outlets)	42	10.3	24	12.0
Group branch shop (6 to 9 outlets)	24	5.9	15	7.5
Group branch shop (10 to 49 outlets)	38	9.3	29	14.5
Group branch shop (50 plus outlets)	125	30.7	94	47.0
Multiple head office	12	2.9	8	4.0
Other (discontinued)	125	30.7		
Which multiple do you work in?				

	N=102	%
Boots	43	42.2
LloydsPharmacy	13	12.8
Superdrug	2	2.0
Rowlands Pharmacy	8	7.8
Well Pharmacy	7	6.9
Day Lewis	4	3.6
Supermarket Pharmacy	19	18.6
Other	6	5.9

While 57.5% of respondents completing the survey worked in community pharmacies based in city or town centres, 31.5% worked in suburban outlets, and the remainder in villages or rural settings. For analysis purposes, suburban pharmacists were grouped with those working in village and rural settings. The sample was spread across the UK in line with the market, with Greater London (16.0%), the South East (12.0%) and South West (8.5%) constituting the largest share of the market and consumer population.

Table 10-4: Description of pharmacists: location

Question	N=200	%
Where is your pharmacy?		
Scotland	11	5.5
Northern Ireland	3	1.5
Wales	11	5.5
North East	4	2.0
North West	19	9.5
Yorkshire and the Humber	21	10.5
West Midlands	23	11.5
East Midlands	20	10.0
South East	24	12.0
South West	17	8.5
East of England	15	7.5
Greater London	32	16.0

Among the 200 pharmacists, 52.5% were men, 42.5% women and the remainder preferred not to answer, or classified themselves as 'other'. There were more women pharmacists working in multiples (57.8%) than in independents (26.5%).

The average age of the pharmacists was 40.5 years, with the women (37.8 years) slightly younger than the men (44.6 years). The average number of years that the 200 pharmacists had been qualified for was 15.6. Men tended to have been qualified for longer (18.6 years) than women (12.9 years), in line with their relative ages. The age profile of those conducting consultations on Gina, having read the aRMMs (approximately half of all pharmacists in the UK) is no different from average ages typically achieved on samples drawn by CIG Research on all pharmacist surveys conducted without these quota controls.

Table 10-5: Description of pharmacists: age

Question	N=200	%
What is your age?		
Under 25	4	2.0
25-29	29	14.5
30-34	37	18.5
35-39	34	17.0
40-44	26	13.0
45-49	12	6.0
50-54	15	7.5
55-59	12	6.0
60-64	18	9.0
65 plus	8	4.0
Prefer not to say	5	2.5
Mean age		40.5
For how many years have you been qualified as a pharmacist?		
Mean number of years	200	15.59

Among pharmacists eligible to participate in this research on demographic grounds, 77.7% had conducted consultations on Gina, and of these, 98.6% had read the training materials or checklists. The penetration of pharmacists conducting consultations in independent community pharmacies and multiple outlets did not differ significantly, and the proportion of those conducting consultations in these two cohorts who had also read the aRMMs did not differ significantly.

Table 10-6: Responses to questions about Gina consultations and materials – completed surveys

Base (those eligible on demographic grounds	Total sample 281	%	Independents N=145	Multiples N=137
In the last six months, have you held any consultations regarding the supply of Gina (estradiol hemihydrate 10 micrograms vaginal tablets) in the pharmacy?				
Yes	216	77.7%	73.6%	82.1%
No (discontinued)	162	22.3%	26.4%	17.9%
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?				
Yes,	213	98.6%	99.1%	98.2%
No (discontinued)	3	1.4%	0.9%	1.8%

10.3 Main results

10.3.1 Reading and utilising of each of the aRMMs

The materials most likely to have been read to help minimise risk when having consultations regarding the supply of Gina were the Pharmacy Guide for the supply of Gina and the Pharmacy checklist. These were followed by the Summary of Product Characteristics (SmPC) and the pack copy, both of which were read by around five in 10 pharmacists.

Table 10-7: Responses to questions about materials used to help minimise risk – completed surveys

Question	N=200	%	Precision or Margin of Error (±%)
Which, if any, of these materials have you read to help minimise risk when having consultations regarding the supply of Gina?			
Pharmacy guide for the supply of Gina	185	92.5	3.7
Pharmacy checklist	182	91.0	4.0
SmPC	107	53.5	6.9
Pack copy	89	44.5	6.9

There were no significant differences between the materials which were read in independents or in multiples.

The utilising of these materials during consultations was reported by pharmacists in a second question. These materials had been used in conjunction with consultations by at least three in four pharmacists and in the case of the Pharmacy Checklist, by 96.2%, and while more pharmacists had read the Pharmacy Guide for the supply of Gina than the Pharmacy checklist, it was the checklist which was most likely to be used in conjunction with consultations (Table 10-8).

The SmPC was considered very useful or essential when making a decision about the supply of Gina by 58% of pharmacists, while the Pharmacy Guide for the supply of Gina was considered important by 82.5%, and the Pharmacy Checklist by 88.5%.

The Pharmacy Checklist was used with every patient during consultations by 87.4% of pharmacists and with only a few patients by 10.2%.

Table 10-8: Responses to questions about materials used in conjunction with consultations – completed surveys

Question	Base (read materials)	N	%	Precision or Margin of Error (±%)
Which, if any, of these materials have you used in conjunction with consultations regarding the supply of Gina in the pharmacy?				
Pharmacy Guide for the supply of Gina	185	163	88.1	4.7
Pharmacy checklist	182	175	96.2	6.4
SmPC	107	81	75.7	8.1
Pack copy	89	67	75.3	9.0
Which patients do you use the Gina Pharmacy Checklist with?				
With every patient	175	153	87.4	4.9
Only with new patients	175	18	10.2	4.4
Only with a complicated/ complex patients	175	4	2.2	2.2
How useful do you find each of the following sources in helping you make decisions about the supply of Gina?				
The Gina Summary of Product Characteristics (SmPC)				
Not useful at all	194	1	0.5	1.4
Not very useful	194	8	4.1	3.8
Quite useful	194	69	34.6	6.7
Very useful	194	83	41.8	6.9
Essential	194	33	17.0	5.2
Mean score (+5 to +1)			**3.61**	
The Pharmacy Guide for the supply of Gina				
Not useful at all	198	0	0.0	
Not very useful	198	0	0.0	
Quite useful	198	33	16.7	5.2
Very useful	198	78	39.4	6.8
Essential	198	87	43.9	6.9
Mean score (+5 to +1)			**4.23**	
The Pharmacy Checklist				
Not useful at all	198	0	0.0	
Not very useful	198	0	0.0	
Quite useful	198	21	10.6	4.3
Very useful	198	65	32.8	6.5
Essential	198	112	56.6	6.9
Mean score (+5 to +1)			**4.42**	

This level of positivity was seen equally among male and female pharmacists for each of the three information sources, and equally among the older pharmacists and the younger pharmacists. (Full results are in Table 2, appendix 1.3). The mean usefulness rating for each of these three information sources among those based in independents also did not differ significantly from the rating among those based in multiples.

10.3.2 Numbers of consultations held

This survey was conducted fourteen months after the launch of Gina, so it was reasonable to consider whether pharmacists had had much experience in the consultation process. Given that the sample consisted of those who had conducted consultations and had read the aRMMS, it was also relevant to examine the effect of more consulting experience on the correct decisions being made regarding supply. Across the total sample, the average number of consultations conducted was 15.27 – equivalent to approximately one every two weeks, although this mean hides a wide range of responses from 1 to 200-plus.

Table 10-9: Number of consultations pharmacists had with patients – completed surveys

Question	N=200	%	Precision or Margin of Error (±%)
How many consultations do you estimate that you have had with patients about Gina in the pharmacy in the last six months?			
Mean number of consultations	21.55	Range 1-200	Std dev. 20.60

Of the 200 respondents who had conducted consultations and read the appropriate materials, 21.5% had conducted only one consultation in six months, and 57.0% had conducted fewer than 10. Only 7.5% had conducted more than 100.

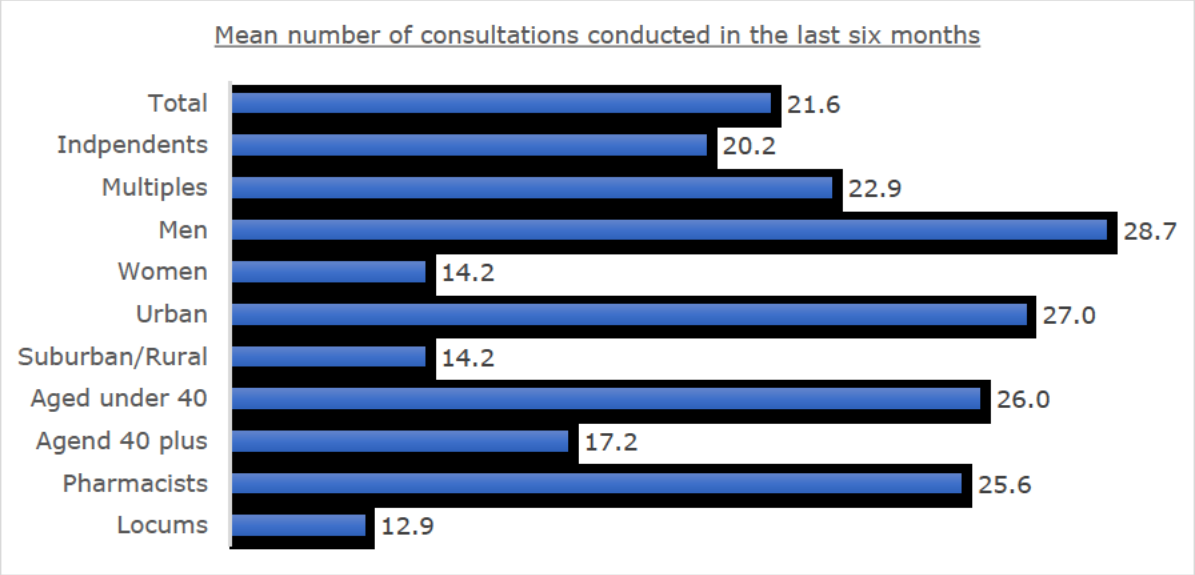
The sample was split into three approximately equal sized groups for analysis of their understanding of the scenarios (Table 10-10), and their levels of confidence in advising and supplying estradiol (Table 10-18).

Table 10-10: Distribution of number of consultations held – completed surveys

Number of consultations held in the last six months	N=200	(%)
1	34	17.0
2	12	6.0
3	12	6.0
4	14	7.0
5	13	6.5
6-10	40	20.0
11-20	24	12.0
21-30	15	7.5
31-60	17	8.5
61-100	4	2.0
101+	15	7.5

The number of consultations conducted varied by segment, with male pharmacists conducting the most (28.7 in six months), followed by those in urban outlets (27.0), those aged under 40 (26.0) and those with the job title Pharmacist (25.6), while locum pharmacists (12.7), those in suburban/rural outlets (14.2) and women pharmacists (14.2) averaged the fewest.

Illustration 1: Mean number of consultations conducted in the last six months



Proportion of consultations resulting the supply of Gina

While 62.7% of all consultations result in the supply of Gina across the sample, this was slightly higher among those aged under 40 (65.8%) than those aged 40 plus (59.9%) and slightly higher among those working in multiples (64.8%) than those working in independents (60.4%). Neither of these differences have significance at the 95% confidence level margin of error.

Table 10-10.1: Proportion of consultations resulting the supply of Gina – completed surveys

	N	Proportion of consultation %	Precision or Margin of Error (±%)
Total	200	62.7	6.7
Independents 1-49 outlets	98	60.4	9.7
Multiples (50 plus outlets)	102	64.8	9.3
Men	105	61.8	9.3
Women	85	63.9	10.2
Pharmacists	136	62.3	8.2
Locums	64	63.4	11.8
Urban	115	65.8	8.7
Suburban/Rural	85	58.4	10.5
Aged under 40	104	65.8	9.1
Aged 40 plus	91	59.9	10.1
Conducted 1-4 consultations	72	61.0	11.3
Conducted 5-10 consultations	53	62.4	13.0
Conducted 11 plus consultations	75	63.7	10.9

10.3.3 Use of consulting facilities and ease of access to aRMMs in pharmacy during consultation

Pharmacists conducting consultations reported that 84.0% of their consultations took place in a private consultation area in the pharmacy, and 14.0% at the pharmacy counter. The proportion using consulting rooms in independents (90.4%) exceeds that in multiples (77.9%) where 19.2% of consultations take place at the counter.

The Pharmacy Guide for the supply of Gina was rated as easily accessible to 97.8% of pharmacists when giving consultations, and the Pharmacy Checklist to 98.4%.

Table 10-11: Responses to questions about consultations in the pharmacy – completed surveys

Question	N=200 (figures are % of consultations)	%	Precision or Margin of Error (±%)	Independents N=98 (%)	Multiples N=102 (%)
Where in the pharmacy are these consultations conducted? (percentage of consultations total = 100%)					
In a private consultation area	84.03	84.0	5.1	90.4	77.9
At the pharmacy counter	14.01	14.0	4.8	8.6	19.2
Elsewhere	1.97	2.0	1.9	1.1	2.8

Were the materials easily accessible to you when giving consultations? Yes.				
Question	Base	N	%	Precision or Margin of Error (±%)
Pharmacy guide for the supply of Gina	185	181	97.8	2.1
Pharmacy checklist	182	179	98.4	1.8
SmPC	107	98	91.6	5.3
Pack copy	89	87	97.8	3.0
Other	200	106	53.0	6.9

10.3.4 Scenarios relating to understanding of aRMMs

10.3.4.1 Decision to supply or not supply (Table 10-12)

For each scenario, two questions were asked:

1. Whether to supply or not supply Gina
2. Which reason was the most suitable reason for supplying or not supplying (from a multiple choice of four).

KPI-aligned results

On average, taking all 1,600 responses across the eight scenarios into account, the average correct response level was 86.4% (+/- 1.68%). This exceeded the KPI of 80% set for the primary objective:

Across the total sample, in seven of the eight scenarios, the option to supply or not supply Gina reached the threshold of 80% set as a KPI, within the margin of error of 5.5%.

In the case of scenario 8, 72.5% (+/- 6.2%) of pharmacists took the correct decision regarding supply of Gina. The 27.5% choosing the 'do not supply' answer, were choosing a conservative option which minimised risk of incorrect supply (see Section 10, Table 10-17 for more detail).

Illustration 2: Correct responses: Supply/do not supply

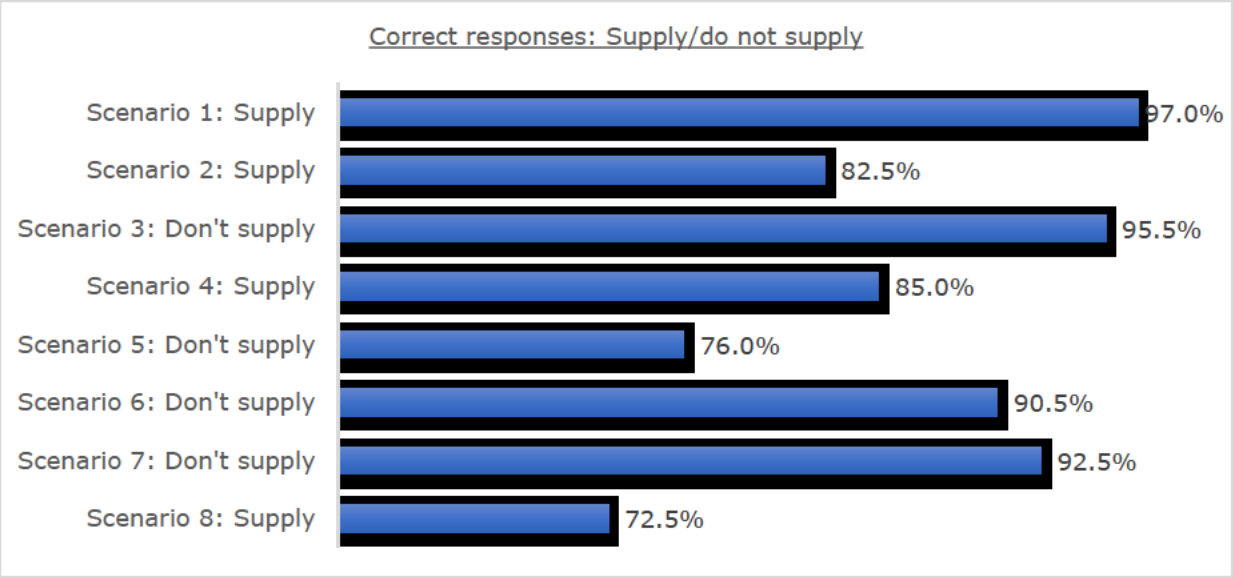


Table 10-12: Responses to scenarios relating to aRMMs – completed surveys

Scenario	Supply/ Don't supply	Correct (%)	Margin of error (+/-%)
1	Supply	97.0	2.4
2	Supply	82.5	5.3
3	Don't supply	95.5	2.9
4	Supply	85.5	4.9
5	Don't supply	76.0	5.9
6	Don't Supply	90.5	4.1
7	Don't supply	92.5	3.7
8	Supply	72.5	6.2
	MEAN	86.4% (N=1600)	1.68

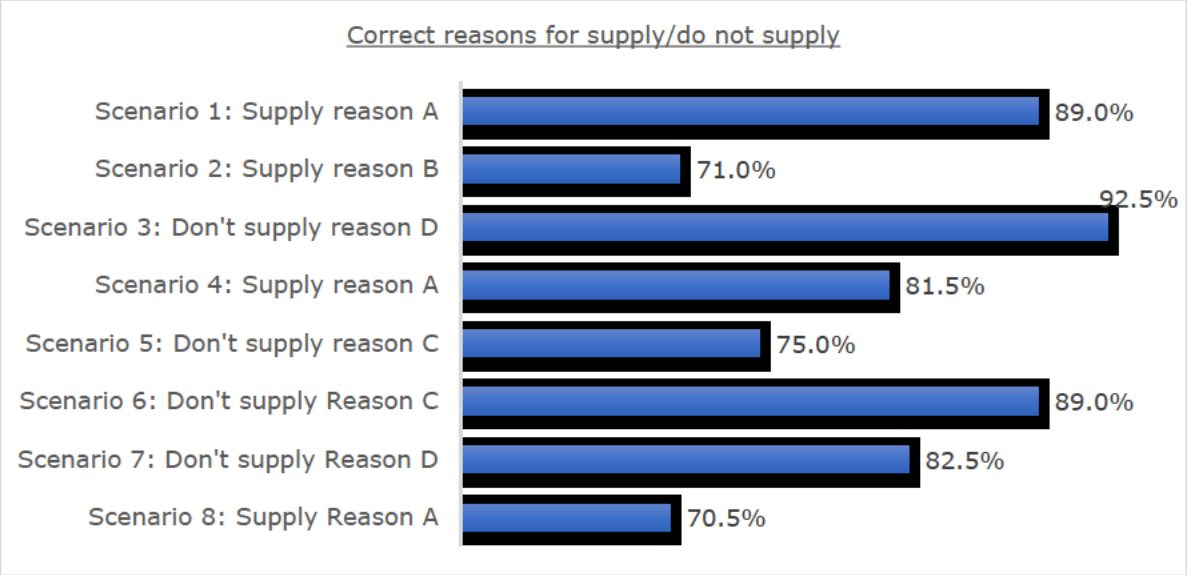
10.3.4.2 Reasons for decision (Table 10-13)

Respondents were presented with four possible reasons for supply/do not supply (two for each) and were required to choose the one they felt best described the reason for their decision. In scenarios 1, 3, 4, 5, 6, and 7, the proportions giving the right reason for supply or not supply of Gina met the KPI of 80%, subject in each case to margins of error. In scenarios 2 and 8, the threshold was not met, although both scenarios 2 and 8 fell only slightly short of the threshold (71.0% +/- 6.3% and 70.5% +/- 6.3% respectively).

In the case of scenario 2, 82.5% of all pharmacists had chosen the correct 'supply' answer, and the majority of these people (86%) chose the right reason (reason B) while only 14% chose the wrong answer. 17.5% chose the incorrect 'do not supply' option mitigating incorrect supply risk.

In scenario 8, the correct response was to supply (chosen by 72.5% +/- 6.2%), and 95.9%of these respondents also gave the right reason. 27.5% of pharmacists chose – incorrectly – the "do not supply " response on this scenario. Importantly, when pharmacists were unsure of the correct response, they chose the "do not supply" option i.e., the conservative choice. This was because it was important for them to ensure that a consumer was not inappropriately exposed to the product. This behaviour may be viewed as being correct.

Illustration 3: Correct reasons: Supply/do not supply



Regarding secondary consideration of the reason to supply or not supply Gina, it fell short of the high KPI objective that 80% of pharmacists would select a correct reason for their decision across all of the eight scenarios provided. This was primarily due to the complexity of the multi-parameter scenarios, and particularly two of the scenarios where the correct answer was selected by 71.0% in one case and 70.5% in the other.

Table 10-13: Questions relating to the understanding of the aRMMs – completed surveys

Scenario	Correct A-D	A N=200 (%)	B N=200 (%)	C N=200 (%)	D N=200 (%)	% Correct	Margin of error (+/-%)
1	A	89.0	11.0	0.0	0.0	89.0%	4.3
2	B	16.5	71.0	2.0	10.5	71.0%	6.3
3	D	2.0	1.0	4.5	92.5	92.5%	3.7
4	A	81.5	6.5	8.0	4.0	81.5%	5.4
5	C	21.5	0.5	75.0	3.0	75.0%	6.0
6	C	3.5	3.5	89.0	4.0	89.0%	4.4
7	D	2.5	5.0	10.0	82.5	82.5%	5.3
8	A	70.5	3.0	19.5	7.0	70.5%	6.3
					Mean	81.4%	1.91

The two scenarios not reaching the KPI threshold are examined in more detail in section 10.3.4.4

10.3.4.3 Reasons for decision by segment

While there were some differences between those working in independents and multiples, with those in multiples more likely to choose correct answers, these were not statistically significant. Women were more likely to give correct answers than men. Again, these differences were non-significant, and interestingly, locums were more likely than pharmacists to give correct answers (Table 10-14).

Analysis of time taken to complete the survey showed that there was no difference in accuracy of responses to the questions between the faster and slower respondents. Likewise, analysis of those having conducted more consultations over the last six months compared to those conducting fewer showed no difference currently in the level of accuracy in answering the scenario questions (Table 11.3, appendix 1.3).

Table 10-14: Questions relating to the understanding of the aRMMs – completed surveys by segment: outlet type, gender, role

Scenario	Correct A-D	Independents N=98 % Correct	Multiples N=102 % Correct	Men N=105 % Correct	Women N=85 % Correct	Pharmacists N=136 % Correct	Locums N=64 % Correct
1	A	89.8	88.2	85.7	95.3	86.8	93.8
2	B	68.4	73.5	66.7	77.6	69.1	75.0
3	D	90.8	94.1	90.5	94.1	92.6	92.2
4	A	77.6	85.3	80.0	83.5	80.1	84.4
5	C	71.4	78.4	74.3	76.5	74.3	97.6
6	C	87.8	90.2	82.9	95.3	89.0	89.1
7	D	79.6	85.3	81.0	84.7	81.6	84.4
8	A	67.3	73.5	70.5	71.8	70.6	70.3
	Mean	79.1	83.6	78.9	84.9	80.5	85.8

Those working in a suburban, village or rural settings were no more likely than those working in urban pharmacies to give correct answers (Table 10-15).

Younger pharmacists were less likely to give correct answers than older pharmacists, although this was a not statistically significant difference (Table 10-15).

Table 10-15: Questions relating to the understanding of the aRMMs – completed surveys by segment: urban/suburban, age

Scenario	Correct A-D	Urban N=106 (%)	Suburban/ rural N=85 (%)	Under 40 years old N=90	Aged 40 plus N=100
1	A	88.7	89.4	83.7	94.5
2	B	71.3	70.6	63.5	79.1
3	D	92.2	92.9	90.4	94.5
4	A	84.3	77.6	76.0	86.8
5	C	74.8	75.3	69.2	87.1
6	C	87.8	90.6	89.4	89.0
7	D	79.1	87.1	80.8	86.8
8	A	71.3	69.4	70.2	69.2
	Mean	81.2	81.6	77.9	85.9

An additional table comparing numbers of consultations conducted (Table 11.3) is included in appendix 1.3.

10.3.4.4 Analysis of the two scenarios which did not meet the KPI

Regarding secondary consideration of the reason to supply Gina or not, it fell short of the high KPI objective that 80% of pharmacists would select a correct reason for their decision in two of the eight scenarios provided. This was primarily due to the complexity of the multi-parameter scenarios where an incorrect reason was selected by 29.0% of respondents in one case and 29.5% in the other. This section examines in more detail the two scenarios where the secondary consideration of choosing reasons for supply/not supply fell short of the KPI of 80%.

Scenario 2 (Table 10-16)

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.

82.5% of the pharmacists took the correct decision and supplied Gina to this hypothetical patient.

However, the correct reason for supplying (B - Supply. Significant symptom improvement may not be experienced until after the second pack) was only chosen by 71.0%. The incorrect reason (A - supply but suggest she asks her GP to investigate other causes.) was selected by 11.5% of respondents.

The correct reason for supplying is that 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.

As seen in Table 10-16, within the segments, there were few differences in the levels of correct reasons, with the exception of age, with those under 40 much less likely (63.5%) to be correct than those aged 40 plus (79.1%).

Pharmacists show increased confidence in advising and correctly supplying Gina as they have more experience of consultations (from 17% feeling completely confident about advising patients and 15% feeling completely confident about correctly supplying Gina for those having conducted 1-5 consultations to 20.9% and 22.1% respectively among those who have conducted eleven or more consultations).

The increased number of consultations did not result in a larger proportion of correct answers to scenario 2. 77.8% of those conducting 1-5 consultations were correct and 72.1% of those who had conducted at least eleven consultations were correct (Table 11.3 appendix 1.3).

In this scenario, 14% of pharmacists who chose the 'supply' option also suggested that Ms E asks her GP to investigate other causes, which was the correct 'supply' response, but for the wrong reason. It isn't possible from this information to surmise why these people took a cautious approach, rather than the correct reason.

Within the segments in this analysis, it is clear that the KPI was met in more segments than it failed – it was met for those working in multiples, women, locums, those in suburban and rural pharmacies, those aged 40 plus and those who had conducted 1-5 consultations and those conducting 11 or more consultations in the last six months.

Table 10-16: Response to scenario 2 – completed surveys by segment: outlet type, gender, role, urban/suburban, age, number of consultations

B Correct - Supply. Significant symptom improvement may not be experienced until after the second pack.	N	Correct answer B %	Precision or Margin of Error (±%)
Total	200	71.0	6.3
Independents	98	68.4	9.2
Multiples	102	73.5	8.6
Men	105	66.7	9.0
Women	85	77.6	8.9
Pharmacists	136	69.1	7.8
Locums	64	75.0	10.6
Urban	115	71.3	8.3
Rural	85	70.6	9.7
Aged under 40	104	63.5	9.3
Aged 40 plus	91	79.1	8.4
Conducted 1-4 consultations	72	77.8	9.6
Conducted 5-10 consultations	53	60.4	13.2
Conducted 11 plus consultations	75	72.1	10.1

Scenario 8 (Table 10-17)

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.

In this scenario, 72.5% of pharmacists made the correct decision to supply Gina and 27.5% took the more conservative decision and opted for no supply.

Among the 72.5% making the correct decision to supply, the vast majority (95.9%) did so for the correct reason (A -Supply: Gina may be used by women who have had a hysterectomy. While the remaining 4.1% selected the correct answer to supply, but with incorrect reason (B - Supply. Endometrial hyperplasia can be treated with oestrogen).

The most prevalent answer after A (the correct answer) was C (C - Do not supply. Local oestrogens are contraindicated in women who have had a hysterectomy.). Given that the correct response was to supply Gina, pharmacists unsure of the right answer were more likely to choose a do not supply option in order to minimise risk of incorrect supply.

The level of correct response did not vary by segment, although those who had conducted only one or two consultations in the last six months were less likely than those who had conducted more to get this answer correct, and more likely to be correct for the wrong reason (Table 11.3 Appendix 1.3)

Table 10-17: Response to scenario 8 – completed surveys by segment: outlet type, gender, role, urban/suburban, age, number of consultations

A Correct: Gina may be used by women who have had a hysterectomy.	N	Correct answer A %	Precision or Margin of Error (±%)
Total	200	70.5	6.3
Independents	98	67.3	9.3
Multiples	102	73.5	8.6
Men	105	70.5	8.7
Women	85	71.8	9.6
Pharmacists	136	70.6	7.7
Locums	64	70.3	11.2
Urban	115	71.3	8.3
Rural	85	69.4	9.8
Aged under 40	104	70.2	8.9
Aged 40 plus	91	69.2	9.5
Conducted 1-4 consultations	72	63.9	11.1
Conducted 5-10 consultations	53	73.6	11.9
Conducted 11 plus consultations	75	74.4	9.9

10.3.5 Confidence and self-rated knowledge

As shown in Table 10-18, 54.0% of all respondents reported feeling completely or very confident about advising patients on the use of Gina. Those aged 40 plus and younger pharmacists, men and women had a similar level of confidence as each other. Locums (43.8%) were somewhat less confident than pharmacists (58.9%), and those working in urban pharmacies (60.0%) were more confident than those working in rural pharmacies (45.9%).

Similarly, 55.0% of all pharmacists felt completely or very confident about correctly supplying Gina, rising to 57.7% among younger pharmacists (compared to 52.8% among those aged 40 plus). Men (59.0%) were more confident about supplying Gina than were women (51.8%) (Table 10, Appendix 1.3). Pharmacists (59.6%) were more confident than locums (45.3%) about supplying Gina, and those in urban locations (59.2%) more so than those working in suburban and rural locations (49.4%) (Table 10.1, Appendix 1.3).

Those who had only conducted up to five consultations in the last six months (54.2%) were less confident about correctly supplying Gina than those who had conducted eleven plus consultations (57.1%) but the difference is small, suggesting that the increased experience of supplying Gina is not in itself a long learning process (Table 10.1, Appendix 1.3).

Table 10-18: Responses to questions relating to confidence – completed surveys by segment: age, gender

Question	Total sample N=200	%	Precisionor Margin of Error (±%)	Under 40 years old N=90	Aged 40 plus N=100	Men N=104	Women N=90
How confident do you feel about advising patients on the use of Gina?							
Completely (5)	41	20.5	5.6	20.2%	22.0%	21.9%	21.2%
Very (4)	67	33.5	6.5	34.6%	30.8%	33.3%	31.8%
Fairly (3)	81	40.5	6.8	42.3%	38.5%	36.2%	44.7%
Not very (2)	11	5.5	3.2	2.9%	8.8%	8.6%	2.4%
Not at all (1)	0	0.0	0	0.0%	0.0%	0.0%	0.0%
Mean score (+5 to +1)	200	3.7	Std.dev. 0.86	3.72	3.66	3.69	3.72
And how confident are you about correctly supplying Gina?							
Completely (5)	36	18.0	5.3	17.3%	19.8%	17.1%	21.2%
Very (4)	74	37.0	6.7	40.4%	33.0%	41.9%	30.6%
Fairly (3)	82	41.0	6.8	40.4%	40.7%	35.2%	45.9%
Not very (2)	8	4.0	2.7	1.9%	6.6%	5.7%	2.4%
Not at all (1)	0	0.0	0	0.0%	0.0%	0.0%	0.0%
Mean score (+5 to +1)	200	3.7	Std. dev. 0.81	3.73	3.66	3.70	3.71

Self-rated knowledge about estradiol

Pharmacists were asked to rate their own knowledge about Gina, and 67.5% of them rated their knowledge as excellent or very good for its mode of action, 63% for its side-effects, 81% for its recommended dosage and frequency, 62.5% for its use with concomitant medication and 65% for its red flags and contraindications. This picture pertains across the segments, with men more positive about their levels of knowledge than women (Table 10-19).

Table 10-19 also shows that a small number of pharmacists considered themselves to have poor levels of knowledge.

Table 10-19: Responses to questions relating to self-rated knowledge – completed surveys by segment: age, gender

Question	Total sample N=200	%	Precision or Margin of Error (±%)	Under 40 years old N=90	Aged 40 plus N=100	Men N=104	Women N=90
How would you rate your own level of knowledge about Gina?: Its mode of action							
Excellent	37	18.5	5.4	16.3%	20.9%	19.0%	18.8%
Good	98	49.0	6.9	52.9%	45.1%	50.5%	47.1%
Fair	58	29.0	6.3	26.0%	31.9%	26.7%	30.6%
Poor	7	3.5	2.5	4.8%	2.2%	3.8%	3.5%
Very poor	0	0.0	0	0.0%	0.0%	0.0%	0.0%
How would you rate your own level of knowledge about Gina?: Its side effects							
Excellent	32	16.0	5.1	16.3%	16.5%	17.1%	16.5%
Good	94	47.0	6.9	46.2%	46.2%	49.5%	43.5%
Fair	69	34.5	6.6	34.6%	35.2%	29.5%	38.8%
Poor	5	2.5	2.2	2.9%	2.2%	3.8%	1.2%
Very poor	0	0.0	0	0.0%	0.0%	0.0%	0.0%
How would you rate your own level of knowledge about Gina?: Recommended dosage, frequency							
Excellent	66	33.0	6.5	34.6%	31.9%	36.2%	31.8%
Good	96	48.0	6.9	45.2%	51.6%	46.7%	50.6%
Fair	36	18.0	5.4	20.2%	14.3%	15.2%	17.6%
Poor	2	1.0	1.4	0.0%	2.2%	1.9%	0.0%
Very poor	0	0.0	0	0.0%	0.0%	0.0%	0.0%
How would you rate your own level of knowledge about Gina?: Its use with concomitant medication							
Excellent	30	15.0	4.9	13.5%	16.5%	18.1%	11.8%
Good	95	47.5	6.9	49.0%	46.2%	45.7%	51.8%
Fair	62	31.0	6.4	31.7%	29.7%	27.6%	31.8%
Poor	13	6.5	3.4	5.8%	7.7%	8.6%	4.7%
Very poor	0	0.0	1	0.0%	0.0%	0.0%	0.0%
How would you rate your own level of knowledge about Gina?: Red flags/contraindications							
Excellent	38	19.0	5.4	17.3%	20.9%	21.9%	16.5%
Good	92	46.0	6.9	46.2%	46.2%	44.8%	48.2%
Fair	61	30.5	6.4	31.7%	28.6%	29.5%	30.6%
Poor	9	4.5	2.9	4.8%	4.4%	3.8%	4.7%
Very poor	0	0.0	0	0.0%	0.0%	0.0%	0.0%

Those who had conducted more consultations tended to be more confident in their knowledge of Gina than those who had only conducted up to five consultations (Table 10-20):

- Those considering their knowledge of the mode of action of Gina to be excellent (16.7%) after no more than five consultations compared to 22.7% of those having completed at least 11 consultations considering this to be so
- Those considering their knowledge of the side effects of Gina to be excellent (15.3%) after no more than five consultations compared to 24.0% of those having completed at least 11 consultations considering this to be so

- Those considering their knowledge of the concomitant medication and Gina to be excellent (12.5%) after no more than five consultations compared to 21.3% of those having completed at least 11 consultations considering this to be so.
- Those considering their knowledge of the red flags and contraindications with Gina to be excellent (15.3%) after no more than five consultations compared to 23.3% of those having completed at least 11 consultations considering this to be so.

Table 10-20: Responses to questions relating to self-rated knowledge – completed surveys by segment: role, urban/suburban, number of consultations

Question	Locums N=39 (%)	Pharmacists N=161 (%)	Urban N=106 (%)	Suburban/ rural N=94 (%)	1-4 consults N=72 (%)	5-10 consults N=53 (%)	11+ consults N=75 (%)
How would you rate your own level of knowledge about Gina?: Its mode of action							
Excellent	21.8	16.9	20.0	16.5	16.7	15.1	22.7
Good	45.3	50.7	51.3	45.9	54.2	37.7	52.0
Fair	31.2	27.9	25.2	34.1	26.4	37.74	25.3
Poor	1.5	4.4	3.5	3.5	2.8	9.4	0.0
Very poor	0.0	0.0	0.0	0.0	0.0	0.0	0.0
How would you rate your own level of knowledge about Gina?: Its side effects							
Excellent	12.5	17.6	20.0	10.6	15.3	5.7	24.0
Good	51.5	44.8	44.4	50.6	45.8	37.7	54.7
Fair	35.9	33.8	33.9	35.3	37.5	49.1	21.3
Poor	0.0	3.7	1.7	3.5	1.4	7.6	0.0
Very poor	0.0	0.0	0.0	0.0	0.0	0.0	0.0
How would you rate your own level of knowledge about Gina?: Recommended dosage, frequency							
Excellent	31.2	33.8	34.8	30.6	38.9	24.5	33.3
Good	43.7	50.0	47.0	49.4	43.1	49.1	52.0
Fair	25.0	14.7	18.3	17.7	18.1	22.6	14.7
Poor	0.0	1.5	0.0	2.3	0.0	3.8	0.0
Very poor	0.0	0.0	0.0	0.0	0.0	0.0	0.0
How would you rate your own level of knowledge about Gina?: Its use with concomitant medication							
Excellent	10.9	16.9	17.4	11.8	12.5	9.4	21.3
Good	53.1	44.9	48.7	45.9	51.4	35.9	52.0
Fair	32.8	30.2	30.4	31.8	31.9	37.7	25.3
Poor	3.1	8.1	3.5	10.6	4.2	17.0	1.3
Very poor	0.0	0.0	0.0	0.0	0.0	0.0	0.0
How would you rate your own level of knowledge about Gina?: Red flags/contraindications							
Excellent	15.6	20.6	20.9	16.5	15.3	15.1	25.3
Good	46.9	45.6	47.0	44.7	48.6	37.7	49.3
Fair	32.8	29.4	28.7	32.9	30.6	37.7	25.3
Poor	4.7	4.4	3.5	5.9	5.6	9.4	0.0
Very poor	0.0	0.0	0.0	0.0	0.0	0.0	0.0

10.4 Adverse events/adverse reactions

This survey did not generate any pharmacovigilance issues and no AEs were reported.

11 Discussion

11.1 Key results

The objectives for this survey were three-fold:

1. To demonstrate that the aRMMs are effective in enabling pharmacists to make appropriate decisions to supply based on contraindications and special warnings; this includes awareness and mitigation of safety concerns
2. To identify whether there are particular contraindications or warnings for which pharmacists consistently make the wrong supply decision
3. To establish ease of access to and ease of use of the aRMMs.

The survey demonstrated that the aRMMs were effective in minimising the risk of wrong supply and enabling pharmacists to make appropriate decisions to supply or not supply, on complex and multi-safety parameter scenarios. Those not clear about which was the correct reason for not supplying were tending to take the correct decision of non-supply, mitigating incorrect supply risk.

The materials for Gina were rated as easily accessible to pharmacists when giving consultations, and for all four of the materials included (the Pharmacy Guide for the supply of Gina, The Pharmacy Checklist, SmPC and Pack Copy).

On average, taking all 1,600 responses across the eight scenarios into account, the correct decision to supply/not supply Gina was 86.4% (+/- 1.68%), and exceeded the KPI of 80%.

Respondents were then presented with four possible reasons for supply/do not supply (two for each) and were required to choose the one they felt best described the reason. In the cases of scenarios 1, 3, 4, 5, 6 and 7, the proportions giving the right reason for supply or not supply of Gina met the KPI of 80%, subject in each case to margins of error.

For scenarios 2 and 8, the threshold was not met, but fell only slightly short of the threshold (71.0% +/- 6.3% and 70.5% +/- 6.3% respectively). Pharmacists' answers were generally not to supply when supply could have taken place, hence minimising risk to the patient.

55% of all respondents reported feeling completely or very confident about advising patients on the use of Gina. Importantly, levels of confidence in advising patients increased with the number of consultations conducted.

Pharmacists participating in this study had conducted at least one consultation on Gina in the last six months, and on average had conducted 21.6 consultations. Given that the research took place only fourteen months after the launch of the product, the level of appropriate decision-making was relatively high.

Those who had conducted more consultations tended to be more confident in their knowledge of Gina than those who had only conducted one or two consultations. This implies that as more time elapses and the average number of consultations increases, the levels of knowledge about Gina will increase and with it there will be an increase in the proportion of correct reasoning for supply/do not supply.

11.2 Limitations

It is a limitation that the participating pharmacists were self-selected since respondents voluntarily responded to the invitation to participate. However, the survey recruitment strategies were intended to recruit a representative sample. The sample was representative of the demographic profile of pharmacists in the UK and so it can be assumed that the complete survey represented the state of understanding and use of aRMMs in all pharmacies where they have been received and read, and in conjunction with consultations.

All data from the survey was self-reported and therefore susceptible to possible reporting bias. There could be discrepancies between what pharmacists reported about their practices and their actual behaviours, given that this survey was based on recall of a six month period of consultations. In this case, it would be difficult to validate whether pharmacists' responses to practice-related questions completely concur with their actual behaviours since this was a self-reported survey.

A secondary limitation inherent in the survey research is the reliance on the respondents' recall of whether or not the aRMM materials were read and utilised. If respondents said they did not read and utilise the aRMMs, they were screened out. It is possible that pharmacists may simply not recall the tools that were received and read. In the event, very few respondents were excluded on this basis.

The objective of this PASS is to measure the effectiveness of the pharmacy training materials. The study looked at two process indicators: a) reaching the target population and b) assessing clinical knowledge. These process indicators were intended to provide insight into the extent to which the dissemination of pharmacy materials had been executed as planned and whether the intended measures impacted the correct decision to supply or not supply Gina.

11.3 Interpretation

With regard to the reported tool utilisation, data indicates that the majority of pharmacists found the tools essential or very useful, and in the case of the Pharmacy Checklist, the majority considered it essential in helping to make decisions about the supply of Gina. Further, nobody considered the the materials not useful.

Although an a priori threshold of 80% correct per risk question was used to define the success of the study, the selection of this threshold for success is subjective and not based on prior knowledge, experience or established scientific criteria in the education or risk communication literature (as acknowledged by EMA: 7 May 2015 PRAC Rapporteur PASS Protocol Assessment Report; Procedure no.: EMEA/H/C/000387/MEA 087.2[4]). In this case, the choice of an 80% threshold for the KPI was in line with 'best in class' practice for PASS. Had a lower threshold of 70% been chosen (in line with many similar studies), it would have resulted in the KPI across all eight scenarios being achieved.

11.4 Generalisability

The CIG Research panel of 35,175 pharmacy staff contains a majority of all registered UK pharmacists (currently 42,990), and can be assumed to be reasonably representative of the universe. However, from the panel, just 0.6% completed the survey. On this basis, it is not likely that the findings generated are completely representative of the universe of UK community pharmacists. In the case of the margin of error on each scenario, figures as high as +/- 10-12% for various segments indicate that the results only approximate to that representation.

12 Other information

Not applicable.

13 Conclusions

The results of this survey show that:

- The aRMMs were effective in minimising the risk of wrong supply and enabling pharmacists to make appropriate decisions to supply or not supply Gina in complex and multi-safety parameter scenarios, achieving the 80% predefined KPI.
- The key safety messages outlined in the aRMMs were effectively communicated to pharmacists, but the expected reason for supply was not consistently chosen in two of the eight scenarios. This specific parameter therefore fell short of the pre-defined KPI. However, there may be legitimate reasons why a different medical rationale was chosen in order to make the correct supply/not supply decision, given the complexity of the scenarios.
- Where pharmacists were unsure about their reasons for choosing to supply Gina, there was a tendency towards the safer option of non-supply and referring patients to a doctor, thus minimising the risk of incorrect supply. Referring a decision to a more experienced colleague, in the face of uncertainty, is common medical practice and ensures patient safety is maintained and should not in itself be considered as “incorrect”.
- As would be expected, the degree of confidence in advising patients and choosing to supply Gina increased with the number of consultations conducted.
- All decisions of “no supply” in women who were not suitable, were correct and met the 80% KPI.
- The aRMMs were easily accessed by pharmacists.

Based upon this current evaluation of knowledge, understanding and behaviours, the aRMMs were determined to be effective in minimising the risk of providing Gina. Corrective action plans and materials are to be provided by each company to improve correct reasoning for supply/no supply of Gina.

14 References

1. Clopper, CJ, Pearson, ES. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika. 1934;26(4):404-413.
2. MHRA *'GXP' Data Integrity Guidance and Definitions* letter (publishing.service.gov.uk)
3. 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)
4. EMA: *7 May 2015 PRAC Rapporteur PASS Protocol Assessment Report; Procedure no.: EMEA/H/C/000387/MEA 087.2*

Annex 1. List of standalone documents

No.	Document Reference No	Date	Title
1.	Appendix 1.1	Jan 2022	Protocol
2.	Appendix 1.2	Sept 2021, Oct 2021	User test and pilot report
3.	Appendix 1.3	Feb 2022	Final Tables and Listings

Appendix 1.1: NON-INTERVENTIONAL STUDY (NIS) 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 21st March 2023 Version 5
EU Post Authorisation Study register number	Study not yet registered. Registration will be performed upon Medicines and Healthcare Products Regulatory Agency (MHRA) approval of this protocol
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

1. Contents

Contents

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LIST OF STAND-ALONE DOCUMENTS

I. Gina Training Materials

1. Pharmacy Guide for the Supply of Gina
2. Pharmacy Checklist

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

3. Responsible Parties

Name	Title	Affiliation	Address
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Novo Nordisk Ltd	3, City Place, Beehive Ring Rd, Gatwick RH6 0PA
[redacted]	[redacted]	Novo Nordisk Ltd	3, City Place, Beehive Ring Rd, Gatwick RH6 0PA

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.

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

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

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

5. Gina Summary of Product Characteristics (SmPC) https://www.medicines.org.uk/emc/product/13930/smpc#ORIGINAL
6. 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)
7. MHRA *'GXP' Data Integrity Guidance and Definitions* letter (publishing.service.gov.uk)
8. 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)

9. 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]

[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?	☐	☐	☒	

Comments:

[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.

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)	☐	☐	☒	
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)	☐	☐	☒	

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
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?	☐	☐	☒	

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
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)				
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	e. Correct	Correct understanding that Gina may be restarted after a break
	f. Incorrect	There is no need to refer back to GP unless there are other reasons such as contraindications
	g. Incorrect	The symptoms are those of vaginal atrophy not thrush as there is no discharge present
	h. Incorrect	Gina may be used after a break in treatment and as often as required
Scenario 2	e. Incorrect	Significant improvement in symptoms may not be experienced until after the second pack
	f. Correct	Correct understanding that significant improvement in symptoms may not be experienced until after the second pack
	g. Incorrect	GP referral is not required after the first pack if symptoms have not worsened
	h. Incorrect	GP referral or a change in treatment is not required after the first pack if symptoms have not worsened
Scenario 3	e. Incorrect	These are red flag symptoms which require referral to GP. Gina will not relieve the symptoms
	f. Incorrect	These are red flag symptoms which require referral to GP. Gina will not relieve the symptoms
	g. Incorrect	These are red flag symptoms which require referral to GP. There is no discharge present, so thrush is unlikely
	h. Correct	Correct understanding of red flag symptoms which require referral to GP
Scenario 4	e. Correct	Correct understanding that women may switch from a prescribed cream to Gina
	f. Incorrect	GP referral is not required as there have been no changes in health status
	g. Incorrect	Gina may be used by women over 50

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

Appendix 1.2: Pilot Topline Reports

The pilot study report is dated 31st July 2023 (appendix 2). The aim of the pilot study is "whether the Assessment of the effectiveness of additional Risk Minimisation Measures (aRMMs) study process runs successfully and that all biases in question wording, scale responses and order effect are mitigated…". The most relevant sections of the report are copied below.

Sampling

This survey was distributed to 250 pharmacist panel members, of whom 60 opened the invitation during the fieldwork period, before the 20 responses had been completed. Those who completed the survey, did it on average in 17 minutes.

- Of the 60, 24 (40%) began the questionnaire, and were happy to participate, and all 24 were happy to report any adverse events and to be identified if required.
- Of the 24, 2 respondents (17%) claimed to have been employed by one of the organisations rendering them ineligible for the study – both had worked for the MHRA in this group.
- None of the respondents were ineligible on the basis of their job title or outlet type.
- 1 respondent had not conducted any consultations regarding the supply of Gina in the last six months. **This represents 4.5% of those otherwise eligible to participate.**
- One eligible respondent dropped out before completing the survey.
- The response time average was 17 minutes (between 8 and 69 minutes) for completing the survey with a wide range of individual response times, including some which may have been extended by time away from the computer.

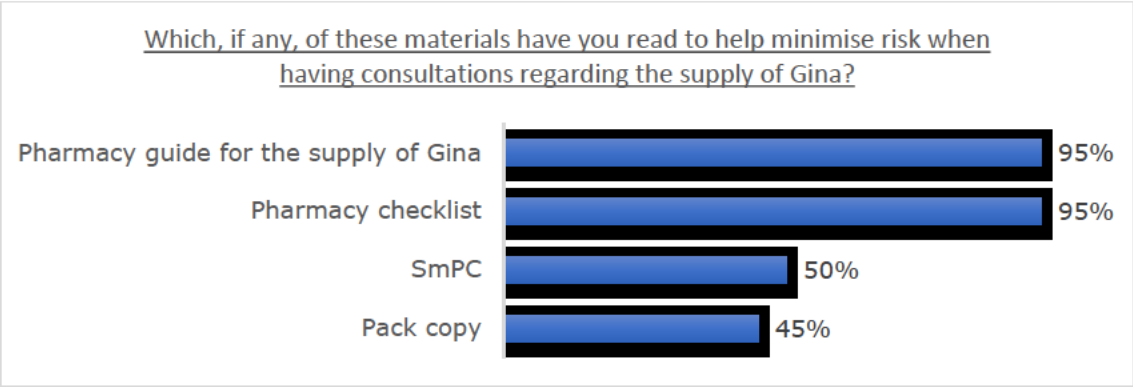
Sample profile

The 20 completed surveys comprised of:

- 40% independents (1-49 outlets) and 60% multiples (50 plus outlets)
- 75% were in city/town centre locations, 10% in suburban areas and 15% in rural locations.
- 45% were from Greater London and the Southeast of England
- 50% were men
- The sample mean age was 39.1 years
- The average number of years qualified as a pharmacist was 13.75

Materials read

Among the sample who completed the survey, all 20 respondents had read the Pharmacy Guide for the supply of Gina and/or the pharmacy checklist to help minimise risk when having consultations. Half had read the SmPC and 45% the pack copy on the Gina packaging.

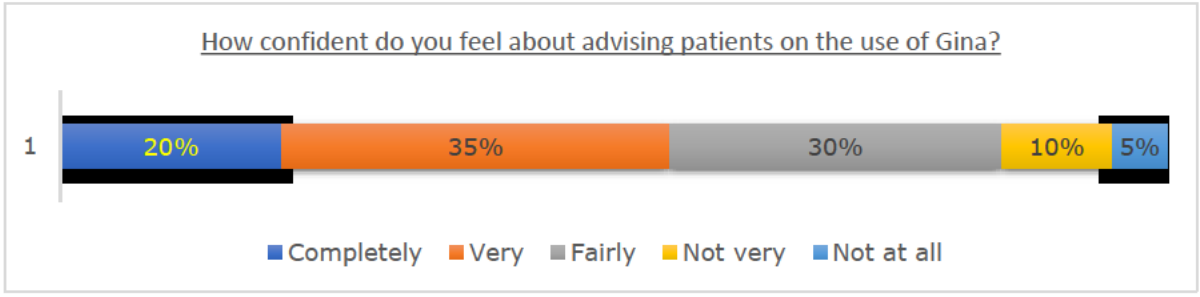


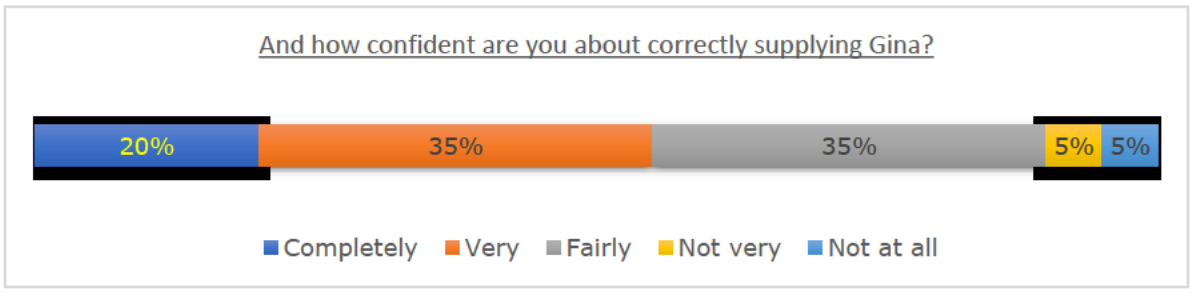
Consultations

In the last 6 months, the average number of total consultations held per respondent has been 17.35. Of these, respondents reported that an average of 11.55 (67%) did not result in the supply of Gina to the patient. They also reported that an average of 14.50 (83%) did result in the supply of Gina. These questions were not structured as a 100% sum, which has resulted in either overclaiming of Gina supply or underclaiming of numbers of consultations. The format of the question will be altered for the full survey to ensure that these figures add to 100% of the consultations figure.

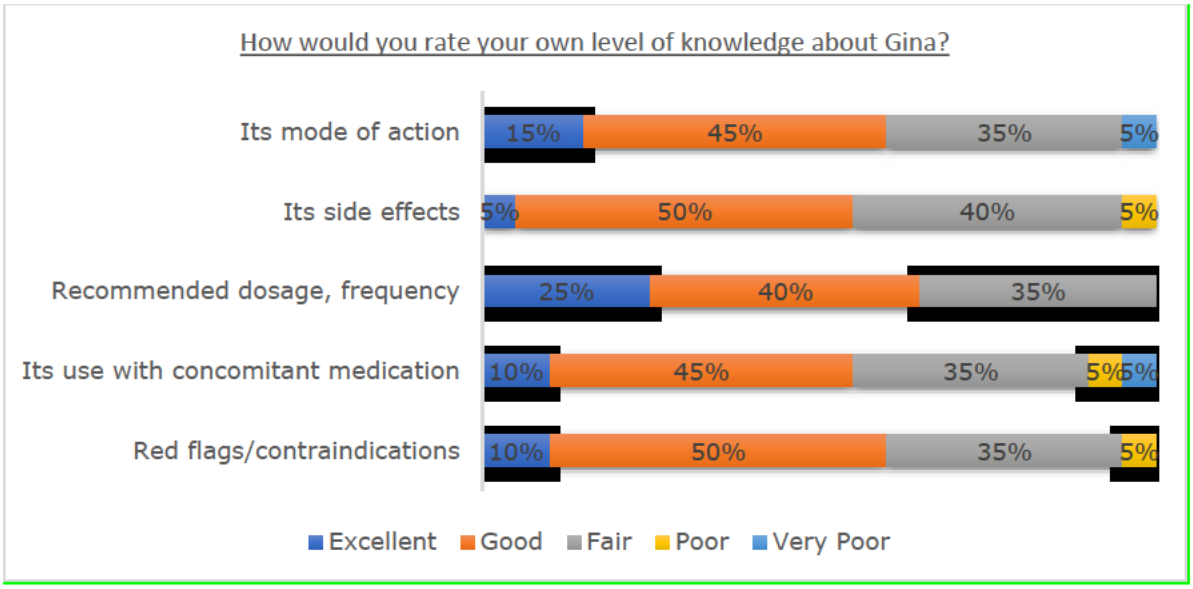
85% of consultations were held in a private consultation area and 15% at the counter.

Confidence and knowledge



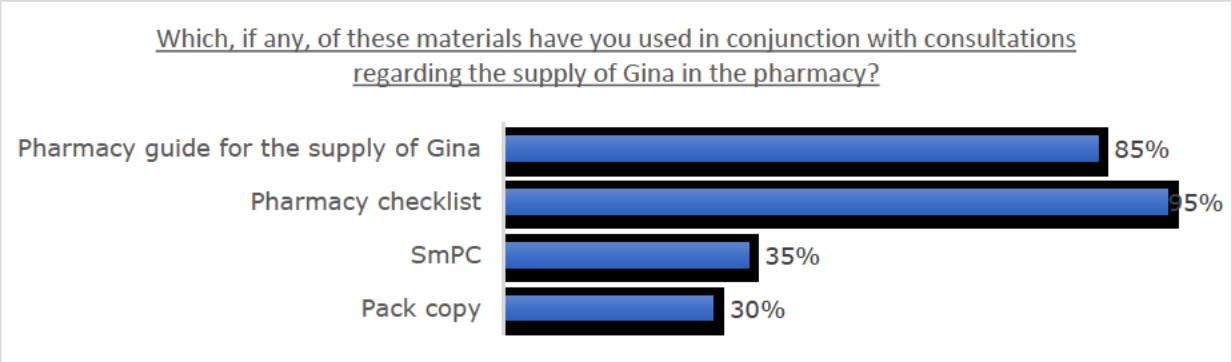


The majority of respondents rate their knowledge as excellent or good on all aspects – most for recommended dosages/frequency (65%) and least for Gina's side effect (55%). Very few rated their knowledge as poor or very poor on any aspect, though Gina's use with concomitant medication generated 10% claiming poor/very poor knowledge.

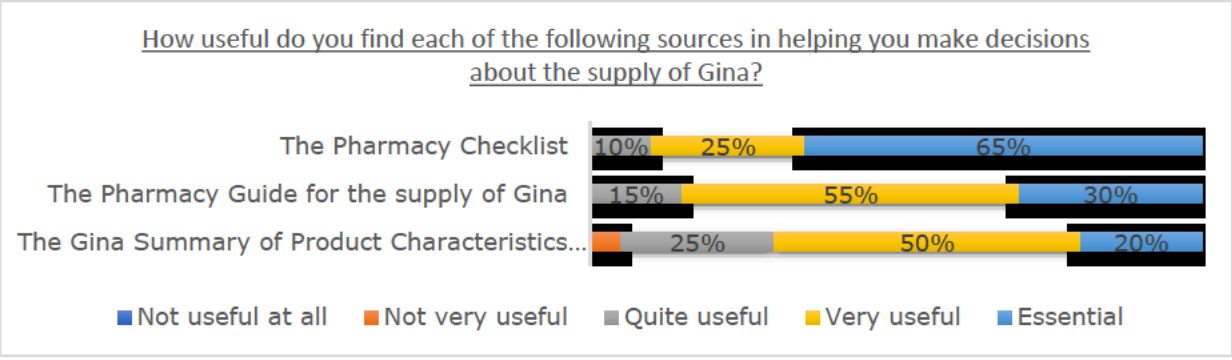


Materials used in conjunction with consultations

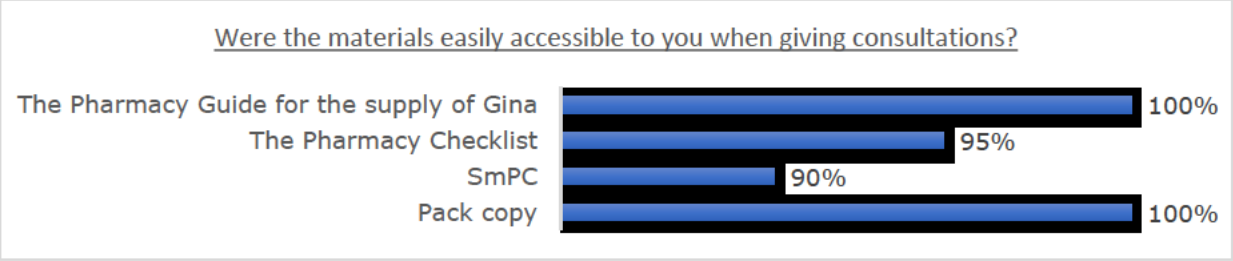
Both the Pharmacy Guide for the supply of Gina (85%) and the pharmacy checklist (95%) were used by almost all pharmacists during consultations, while the SmPC (35%) and pack copy (30% were used by one in three. 84% of those who used it in consultations reported using the pharmacy checklist with every patient, and 16% reported using it with only a few patients.



90% found the pharmacy checklist was essential or very useful, and 85% felt that way about the Pharmacy Guide for the supply of Gina. 70% felt as positive about the SmPC.



Respondents reported that the materials were easily accessible when giving consultations:



Scenarios

Across the eight scenarios there were 160 responses to the first supply/do not supply question from the 20 respondents. The total correct answers were 130 (81%) and incorrect 30 (19%).

The total responses to the reasons for supply/do not supply question were also 160, of which 113 were correct (71%). The correct answers are marked in green below. On this basis, the 80% overall KPI supply/do not supply was met by this sample, but the correct reasons were not given by enough people to meet the KPI. In the case of individual scenarios, those giving particular concern are scenarios 5 and 8, while scenarios 2, 3 and 7 were not answered correctly despite the supply/do not supply answer on these being correct.

Scenario:	1	2	3	4	5	6	7	8
Supply	19	17	3	19	9	1	1	9
Do not supply	1	3	17	1	11	19	19	11

Scenario:	1	2	3	4	5	6	7	8
a	18	5	0	17	7	0	0	11
b	2	13	1	2	3	1	1	1
c	0	0	7	0	10	18	5	6
d	0	2	12	1	0	1	14	2

Incorrect responses:

The 77 incorrect responses were generated by 22 people. Those incorrect on any of the eight scenarios did not differ markedly from the sample as a whole in terms of demographics.

Only 3 people got all 8 scenario answers (supply/do not supply) correct and only one person got all the reasons for supply correct as well.

Key findings of the pilot report

This pilot survey for the *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 was completed in July 2023 based on responses from 20

pharmacists. The pilot set out to assess the quality of data generated from the survey, rather than to establish statistically valid results.

The results indicate that:

a. 83% of those commencing the survey were both eligible and prepared to complete it.
b. Reading and using the rMMs in consultations were very prevalent.
   Almost all respondents reported that the training materials are easily accessible in the pharmacy.
c. While the majority of respondents feel very or completely confident in advising on and supplying estradiol, four in ten felt fairly or less confident.
d. The large majority of respondents rated themselves as having excellent or good levels of knowledge of the product and how it should be used.
e. The eight scenarios were correctly answered on the supply/do not supply Gina question 81% of the time although in 15% of cases this was for the wrong reasons.

In this pilot sample, the 80% KPI set for correct supply response was reached. Based on the insights after analysis of the results, a number of amendments to the questionnaire are recommended prior to running the full survey.

Appendix 1.3: Final Tables and Listings

Table 1.1: Survey Administration Statistics

Table 1.1.1 Data collection

Between January 20th and February 1st, the pattern of responses was as follows:

Date	Started survey	Completed survey	Cumulative completes
21. 11.2023	154	85	85
22. 11.2023	49	23	108
23. 11.2023	25	10	118
24. 11.2023	61	33	151
25. 11.2023	10	8	159
26. 11.2023	10	6	165
27. 11.2023	98	35	200

Response rate

- 1438 (4.1%) viewed the invitation during the fieldwork period
- 407 (28.3% of those viewing) commenced the survey
- 391 (96.6% of those starting) were happy to take part
- 362 (88.9% of those starting) agreed to report any adverse events
- 328 (80.6% of those starting) had not worked for any of the organisations which would preclude participation
- 316 (77.6% of those starting) were eligible based on their job title
- 282 (69.3% of those starting) were eligible based on their outlet type
- 216 (53.1% of those starting) had held at least one consultation regarding the supply of Gina (estradiol hemihydrate 10 micrograms vaginal tablets) in the last 6 months
- 213 (52.3% of those starting) had read training materials or consultation checklists regarding the supply of estradiol hemihydrate 10 micrograms vaginal tablets (Gina) to help minimise risk when having consultations
- 13 dropped out during the survey
- 200 completed the survey (49.1% of those starting)

Table 1.2 Survey Participant Eligibility Results – All Respondents

Total number of respondents starting the survey	N=407	%
By proceeding to the next screen:I consent to CIG collecting and using the information about me that I voluntarily provide for the purposes of market research.· I have read, understand and agree to the terms described above.		
YES, I am happy to proceed with the market research survey on this basis	391	99.49
NO, I am not happy to proceed with the market research survey on this basis and I do not wish to continue	16	1.84
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?:		
I agree	362	95.0
I do not agree	19	5.0
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?		
I agree	347	97.2
I do not agree	10	2.8
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)? NB: You will still be able to participate in the research regardless of your answer to this question.		
Yes	9	90.0
No	1	10.0
Which, if any, of these organisations have you been employed by or contracted to in the last year?		
Novo Nordisk Ltd (discontinued)	10	2.8
Communications International Group (discontinued)	5	1.4
Consensio LLP (discontinued)	4	1.1

MHRA (discontinued)	9	2.5
None of these	328	92.1
What is your job title?		
Pharmacist Proprietor	12	3.5
Pharmacist Manager / Supervisor	46	13.4
Pharmacist	153	44.5
Locum Pharmacist	101	29.4
Other (discontinued)	32	9.3
What type of outlet do you work in?		
One shop independent	41	13.1
Group branch shop (2 to 5 outlets)	42	13.5
Group branch shop (6 to 9 outlets)	24	7.7
Group branch shop (10 to 49 outlets)	38	12.2
Group branch shop (50 plus outlets)	125	40.1
Multiple head office	12	3.9
Other (discontinued)	30	9.6
In the last six months, have you held any consultations regarding the supply of Gina (estradiol hemihydrate 10 micrograms vaginal tablets) in the pharmacy?		
Yes	216	77.7
No (discontinued)	62	22.3
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?		
Yes	213	98.6
No (discontinued)	3	1.4

Table 1.3 Survey Participant Eligibility Results – By outlet type

	Independents	Multiples
Total number of respondents starting the survey	N=145	N=137
What is your job title?		
Pharmacist Proprietor	7.6%	0.7%
Pharmacist Manager / Supervisor	16.6%	14.6%
Pharmacist	39.3%	51.8%
Locum Pharmacist	36.6%	32.9%
What type of outlet do you work in?		
One shop independent	28.3%	NA
Group branch shop (2 to 5 outlets)	29.0%	NA
Group branch shop (6 to 9 outlets)	16.6%	NA
Group branch shop (10 to 49 outlets)	26.2%	NA
Group branch shop (50 plus outlets)	NA	91.2%
Multiple head office	NA	8.8%
In the last six months, have you held any consultations regarding the supply of Gina (estradiol hemihydrate 10 micrograms vaginal tablets) in the pharmacy?		
Yes	73.6%	82.1%
No (discontinued)	26.4%	17.9%
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?		
Yes	99.6%	98.2%
No (discontinued)	0.9%	1.8%

Table 2: Demographic Description of Eligible Pharmacists – Completed Surveys by segment: outlet type

Question	N=200	%	Independents N=98 (%)	Multiples N=102 (%)
What is your job title?				
Pharmacist Proprietor	8	4.0	7.1	1.0
Pharmacist Manager / Supervisor	34	17.0	16.3	17.7
Pharmacist	94	47.0	42.9	51.0
Locum Pharmacist	64	32.0	33.7	30,4
What type of outlet do you work in?				
One shop independent	30	15.0	30.6	NA
Group branch shop (2 to 5 outlets)	24	12.0	24.5	NA
Group branch shop (6 to 9 outlets)	15	7.5	15.3	NA
Group branch shop (10 to 49 outlets)	29	14.5	29.6	NA
Group branch shop (50 plus outlets)	94	47.0	NA	92.2
Multiple head office	8	4.0	NA	7.8
Which multiple do you work in?				
Boots	43	21.5	NA	42.2
LloydsPharmacy	13	6.5	NA	12.8
Superdrug	2	1.0	NA	2.0
Rowlands Pharmacy	8	4.4	NA	7.8
Well Pharmacy	7	3.5	NA	6.9
Day Lewis	4	2.0	NA	3.6
Supermarket Pharmacy	19	9.5	NA	18.6
Other	6	3.0	NA	5.9
In what type of location is your pharmacy based?				
City centre	36	18.0	19.4	16.7
Town centre	79	39.5	27.6	51.0
Suburb	63	31.5	40.8	22.6
Village	19	9.5	10.2	8.8
Rural	3	1.5	2.0	1.0
Where is your pharmacy?				
Scotland	11	5.5	5.1	5.9
Northern Ireland	3	1.5	1.0	2.0
Wales	11	5.5	3.0	7.8
North East	4	2.0	0.0	3.9
North West	19	9.5	13.32	5.9
Yorkshire and the Humber	21	10.5	8.2	12.8
West Midlands	23	11.5	11.2	11.8
East Midlands	20	10.0	9.2	10.8
South East	24	12.0	8.2	15.7
South West	17	8.5	7.1	9.8
East of England	15	7.5	10.2	4.9
Greater London	32	16.0	23.5	8.8
What is your gender?				
Male	105	52.5	66.3	39.2
Female	85	42.5	26.5	57.8

Other	4	2.0	2.0	2.0
Prefer not to say	6	3.0	5.1	1.0

What is your age?				
Under 25	4	2.0	2.0	2.0
25-29	29	14.5	11.2	17.7
30-34	37	18.5	21.4	15.7
35-39	34	17.0	16.3	17.7
40-44	26	13.0	11.2	14.7
45-49	12	6.0	5.1	6.9
50-54	15	7.5	6.1	8.8
55-59	12	6.0	6.1	5.9
60-64	18	9.0	9.2	8.8
65 plus	8	4.0	7.1	1.0
Mean age		40.5	4.1	1.0
For how many years have you been qualified as a pharmacist?				
Mean number of years	200	15.59	16.59	14.62

Table 3: Responses to all Questions Related to the Reading and Utilising of the aRMMs – Completed Surveys by segment: outlet type

Question	N=200	%	Precision or Margin of Error (±%)	Independents N=98 (%)	Multiples N=102 (%)
Which, if any, of these materials have you read to help minimise risk when having consultations regarding the supply of Gina?					
Pharmacy guide for the supply of Gina	185	92.5	3.7	94.9	90.2
Pharmacy checklist	182	91.0	4.0	89.8	92.2
SmPC	107	53.5	6.9	54.1	52.9
Pack copy	89	44.5	6.9	51.0	38.2
How many consultations do you estimate that you have had with patients about Gina in the pharmacy in the last six months?					
Mean number of consultations	21.55	Range 1-200	Std dev. 20.60	20.2	22.9
Have resulted in the supply of Gina		62.7		60.4%	64.8%
Have not resulted in the supply of Gina		37.3		39.6%	35.2%

Table 3.1: Responses to all Questions Related to the Reading and Utilising of the aRMMs – Completed Surveys by segment: gender, age

Question	Men N=105	Women N=85	Under 40 N=104	40 plus N=91
Which, if any, of these materials have you read to help minimise risk when having consultations regarding the supply of Gina?				
Pharmacy guide for the supply of Gina	96.2%	89.4%	90.4%	94.5%
Pharmacy checklist	87.6%	94.1%	92.3%	90.1%
SmPC	51.4%	55.3%	68.3%	35.2%
Pack copy	45.7%	42.4%	54.8%	33.0%

Table 3.2: Distribution of number of consultations held

Number of consultations held in the last six months	N=200	(%)
1	34	17.0
2	12	6.0
3	12	6.0
4	14	7.0
5	13	6.5
6-10	40	20.0
11-20	24	12.0
21-30	15	7.5
31-60	17	8.5
61-100	4	2.0
101+	15	7.5

Table 3.4: Average numbers of consultations by segment

Segment	Base	Mean number of consultations in the last six months	Proportion of consultations resulting in the supply of Gina %
Independents	98	20.2	60.4
Multiples	102	22.9	64.8
Pharmacists	136	25.6	62.3
Locums	64	12.9	63.4
Urban	115	27.0	65.8
Suburban/rural	85	14.2	58.4
Men	105	28.7	61.8
Women	85	14.2	63.9
Aged under 40	104	26.0	65.8
Aged 40 plus	91	17.2	59.9

Table 4: Responses to all Questions Related to the use of the aRMMs in conjunction with consultation – Completed Surveys

Question	Base (read materials)	N	%	Precision or Margin of Error (±%)
Which, if any, of these materials have you used in conjunction with consultations regarding the supply of Gina in the pharmacy?				
Pharmacy guide for the supply of Gina	185	163	88.1	4.7
Pharmacy checklist	182	175	96.2	6.4
SmPC	107	81	75.7	8.1
Pack copy	89	67	75.3	9.0
Which patients do you use the Gina Pharmacy Checklist with?				
With every patient	175	153	87.4	4.9
Only with new patients	175	18	10.2	4.4
Only with a complicated/ complex patients	175	4	2.2	2.2
How useful do you find each of the following sources in helping you make decisions about the supply of Gina?				
The Gina Summary of Product Characteristics (SmPC)				
Not useful at all	194	1	0.5	1.4
Not very useful	194	8	4.0	3.8
Quite useful	194	69	34.5	6.7
Very useful	194	83	41.5	6.9
Essential	194	33	16.5	5.2
Mean score (+5 to +1)			3.61	
The Pharmacy Guide for the supply of Gina				
Not useful at all	198	0	0.0	
Not very useful	198	0	0.0	
Quite useful	198	33	16.5	5.2
Very useful	198	78	39.0	6.8
Essential	198	87	43.5	6.9
Mean score (+5 to +1)			4.23	
The Pharmacy Checklist				
Not useful at all	198	0	0.0	
Not very useful	198	0	0.0	
Quite useful	198	21	10.5	4.3
Very useful	198	65	32.5	6.5
Essential	198	112	56.0	6.9
Mean score (+5 to +1)			4.42	

Table 4.1: Responses to all Questions Related to the use of the aRMMs in conjunction with consultation – Completed Surveys by segment: gender, age

Question	Men N=105	Women N=85	Under 40 N=104	40 plus N=91
Which, if any, of these materials have you used in conjunction with consultations regarding the supply of Gina in the pharmacy?				
Pharmacy guide for the supply of Gina	88.6%	74.1%	77.9%	84.6%
Pharmacy checklist	82.9%	92.9%	89.4%	85.7%
SmPC	41.0%	41.2%	52.9%	26.4%
Pack copy	31.4%	35.3%	44.2%	22.0%
Which patients do you use the Gina Pharmacy Checklist with?				
With every patient	88.5%	84.8%	85.0%	89.7%
Only with new patients	9.2%	12.7%	12.9%	7.7%
Only with a complicated/ complex patients	2.3%	2.5%	2.2%	2.6%
How useful do you find each of the following sources in helping you make decisions about the supply of Gina?				
The Gina Summary of Product Characteristics (SmPC)				
Not useful at all	1.0%	0.0%	0.0%	1.1%
Not very useful	3.8%	4.7%	2.9%	5.5%
Quite useful	34.3%	31.8%	30.8%	37.4%
Very useful	38.1%	45.9%	42.3%	40.7%
Essential	19.1%	15.3%	20.2%	13.2%
Mean score (+5 to +1)	3.6	3.7	3.7	3.5
The Pharmacy Guide for the supply of Gina				
Not useful at all	0.0%	0.0%	0.0%	0.0%
Not very useful	0.0%	0.0%	0.0%	0.0%
Quite useful	14.3%	17.6%	17.3%	15.4%
Very useful	39.1%	37.6%	46.2%	29.7%
Essential	45.7%	43.5%	35.6%	53.9%
Mean score (+5 to +1)	4.3	4.2	4.2	4.3
The Pharmacy Checklist				
Not useful at all	0.0%	0.0%	0.0%	0.0%
Not very useful	0.0%	0.0%	0.0%	0.0%
Quite useful	11.4%	8.2%	8.7%	13.2%
Very useful	36.2%	28.2%	33.7%	30.8%
Essential	51.4%	62.4%	55.8%	56.0%
Mean score (+5 to +1)	4.4	4.5	4.4	4.4

Table 5: Self-rated Confidence and Knowledge – completed surveys, by segment: age, gender

Question	Total sample N=200	%	Precision or Margin of Error (±%)	Under 40 years old N=104	Aged 40 plus N=91	Men N=105	Women N=85
How confident do you feel about advising patients on the use of Gina?							

Completely (5)	41	20.5	5.6	20.2%	22.0%	21.9%	21.2%
Very (4)	67	33.5	6.5	34.6%	30.8%	33.3%	31.8%
Fairly (3)	81	40.5	6.8	42.3%	38.5%	36.2%	44.7%
Not very (2)	11	5.5	3.2	2.9%	8.8%	8.6%	2.4%
Not at all (1)	0	0.0	0	0.0%	0.0%	0.0%	0.0%
Mean score (+5 to +1)	200	3.7	Std.dev. 0.86	3.72	3.66	3.69	3.72
And how confident are you about correctly supplying Gina?							
Completely (5)	36	18.0	5.3	17.3%	19.8%	17.1%	21.2%
Very (4)	74	37.0	6.7	40.4%	33.0%	41.9%	30.6%
Fairly (3)	82	41.0	6.8	40.4%	40.7%	35.2%	45.9%
Not very (2)	8	4.0	2.7	1.9%	6.6%	5.7%	2.4%
Not at all (1)	0	0.0	0	0.0%	0.0%	0.0%	0.0%
Mean score (+5 to +1)	200	3.7	Std. dev. 0.81	3.73	3.66	3.70	3.71
How would you rate your own level of knowledge about Gina?: Its mode of action							
Excellent	37	18.5	5.4	16.3%	20.9%	19.0%	18.8%
Good	98	49.0	6.9	52.9%	45.1%	50.5%	47.1%
Fair	58	29.0	6.3	26.0%	31.9%	26.7%	30.6%
Poor	7	3.5	2.5	4.8%	2.2%	3.8%	3.5%
Very poor	0	0.0	0	0.0%	0.0%	0.0%	0.0%
How would you rate your own level of knowledge about Gina?: Its side effects							
Excellent	32	16.0	5.1	16.3%	16.5%	17.1%	16.5%
Good	94	47.0	6.9	46.2%	46.2%	49.5%	43.5%
Fair	69	34.5	6.6	34.6%	35.2%	29.5%	38.8%
Poor	5	2.5	2.2	2.9%	2.2%	3.8%	1.2%
Very poor	0	0.0	0	0.0%	0.0%	0.0%	0.0%
How would you rate your own level of knowledge about Gina?: Recommended dosage, frequency							
Excellent	66	33.0	6.5	34.6%	31.9%	36.2%	31.8%
Good	96	48.0	6.9	45.2%	51.6%	46.7%	50.6%
Fair	36	18.0	5.4	20.2%	14.3%	15.2%	17.6%
Poor	2	1.0	1.4	0.0%	2.2%	1.9%	0.0%
Very poor	0	0.0	0	0.0%	0.0%	0.0%	0.0%
How would you rate your own level of knowledge about Gina?: Its use with concomitant medication							
Excellent	30	15.0	4.9	13.5%	16.5%	18.1%	11.8%
Good	95	47.5	6.9	49.0%	46.2%	45.7%	51.8%
Fair	62	31.0	6.4	31.7%	29.7%	27.6%	31.8%
Poor	13	6.5	3.4	5.8%	7.7%	8.6%	4.7%
Very poor	0	0.0	1	0.0%	0.0%	0.0%	0.0%
How would you rate your own level of knowledge about Gina?: Red flags/contraindications							
Excellent	38	19.0	5.4	17.3%	20.9%	21.9%	16.5%
Good	92	46.0	6.9	46.2%	46.2%	44.8%	48.2%
Fair	61	30.5	6.4	31.7%	28.6%	29.5%	30.6%
Poor	9	4.5	2.9	4.8%	4.4%	3.8%	4.7%
Very poor	0	0.0	0	0.0%	0.0%	0.0%	0.0%

Table 6: Self-rated Knowledge – completed surveys, by segment: role, urban/suburban, number of consultations

Question	Locums N=64 (%)	Pharmacists N=136 (%)	Urban N=115 (%)	Suburban/ rural N=85 (%)	1-4 consults N=72 (%)	5-10 consults N=53 (%)	11+ consults N=75 (%)
How would you rate your own level of knowledge about Gina?: Its mode of action							
Excellent	21.8	16.9	20.0	16.5	16.7	15.1	22.7
Good	45.3	50.7	51.3	45.9	54.2	37.7	52.0
Fair	31.2	27.9	25.2	34.1	26.4	37.74	25.3
Poor	1.5	4.4	3.5	3.5	2.8	9.4	0.0
Very poor	0.0	0.0	0.0	0.0	0.0	0.0	0.0
How would you rate your own level of knowledge about Gina?: Its side effects							
Excellent	12.5	17.6	20.0	10.6	15.3	5.7	24.0
Good	51.5	44.8	44.4	50.6	45.8	37.7	54.7
Fair	35.9	33.8	33.9	35.3	37.5	49.1	21.3
Poor	0.0	3.7	1.7	3.5	1.4	7.6	0.0
Very poor	0.0	0.0	0.0	0.0	0.0	0.0	0.0
How would you rate your own level of knowledge about Gina?: Recommended dosage, frequency							
Excellent	31.2	33.8	34.8	30.6	38.9	24.5	33.3
Good	43.7	50.0	47.0	49.4	43.1	49.1	52.0
Fair	25.0	14.7	18.3	17.7	18.1	22.6	14.7
Poor	0.0	1.5	0.0	2.3	0.0	3.8	0.0
Very poor	0.0	0.0	0.0	0.0	0.0	0.0	0.0
How would you rate your own level of knowledge about Gina?: Its use with concomitant medication							
Excellent	10.9	16.9	17.4	11.8	12.5	9.4	21.3
Good	53.1	44.9	48.7	45.9	51.4	35.9	52.0
Fair	32.8	30.2	30.4	31.8	31.9	37.7	25.3
Poor	3.1	8.1	3.5	10.6	4.2	17.0	1.3
Very poor	0.0	0.0	0.0	0.0	0.0	0.0	0.0
How would you rate your own level of knowledge about Gina?: Red flags/contraindications							
Excellent	15.6	20.6	20.9	16.5	15.3	15.1	25.3
Good	46.9	45.6	47.0	44.7	48.6	37.7	49.3
Fair	32.8	29.4	28.7	32.9	30.6	37.7	25.3
Poor	4.7	4.4	3.5	5.9	5.6	9.4	0.0
Very poor	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table 7: Responses to all Questions Related to use of Consulting Facilities and Ease of Access to aRMMs in Pharmacy During Consultation – completed surveys, by segment: outlet type

Question	N=200 (figures are % of consultations)	%	Precision or Margin of Error (±%)	Independents N=98 (%)	Multiples N=102 (%)
Where in the pharmacy are these consultations conducted? (percentage of consultations total = 100%)					
In a private consultation area	84.03	84.0	5.1	90.4	77.9
At the pharmacy counter	14.01	14.0	4.8	8.6	19.2
Elsewhere	1.97	2.0	1.9	1.1	2.8

Were the materials easily accessible to you when giving consultations? Yes.				
Question	Base	N	%	Precision or Margin of Error (±%)
Pharmacy guide for the supply of Gina	185	181	97.8	2.1
Pharmacy checklist	182	179	98.4	1.8
SmPC	107	98	91.6	5.3
Pack copy	89	87	97.8	3.0
Other	200	106	53.0	6.9

Table 8: Responses to all Questions Related to use of Consulting Facilities and Ease of Access to aRMMs in Pharmacy During Consultation – completed surveys, by segment: gender, urban/suburban

Question	Men N=105	Women N=85	Urban N=115 (%)	Suburban/ rural N=85 (%)
Where in the pharmacy are these consultations conducted? (total = 100%)				
In a private consultation area	85.9%	81.5%	80.8%	88.4%
At the pharmacy counter	10.9%	18.1%	16.2%	11.0%
Elsewhere	3.2%	0.4%	3.0%	0.6%

Were the materials easily accessible to you when giving consultations? Yes.				
Question	Men N=105	Women N=85	Urban N=115 (%)	Suburban/ rural N=85 (%)
Pharmacy guide for the supply of Gina	96.0%	100.0%	99.1%	96.2%
Pharmacy checklist	100.0%	96.3%	99.1%	97.4%
SmPC	83.3%	100.0%	92.9%	89.2%
Pack copy	97.9%	100.0%	98.3%	96.6%
Other	48.6%	57.7%	57.4%	47.1%

Table 9: Responses to all Questions Related to Confidence – completed surveys, by segment: age, gender

Question	Total sample N=200	%	Precision or Margin of Error (±%)	Under 40 years old N=109	Aged 40 plus N=91	Men N=105	Women N=85
How confident do you feel about advising patients on the use of Gina?							
Completely (5)	41	20.5	5.6	20.2%	22.0%	21.9%	21.2%
Very (4)	67	33.5	6.5	34.6%	30.8%	33.3%	31.8%
Fairly (3)	81	40.5	6.8	42.3%	38.5%	36.2%	44.7%
Not very (2)	11	5.5	3.2	2.9%	8.8%	8.6%	2.4%
Not at all (1)	0	0.0	0	0.0%	0.0%	0.0%	0.0%
Mean score (+5 to +1)	200	3.7	Std.dev. 0.86	3.72	3.66	3.69	3.72
And how confident are you about correctly supplying Gina?							
Completely (5)	36	18.0	5.3	17.3%	19.8%	17.1%	21.2%
Very (4)	74	37.0	6.7	40.4%	33.0%	41.9%	30.6%
Fairly (3)	82	41.0	6.8	40.4%	40.7%	35.2%	45.9%
Not very (2)	8	4.0	2.7	1.9%	6.6%	5.7%	2.4%
Not at all (1)	0	0.0	0	0.0%	0.0%	0.0%	0.0%
Mean score (+5 to +1)	200	3.7	Std. dev. 0.81	3.73	3.66	3.70	3.71

Table 10: Responses to all Questions Related to Confidence – completed surveys, by segment: role, urban/suburban, number of consultations

Question	Locums N=64 (%)	Pharmacists N=136 (%)	Urban N=115 (%)	Suburban/ rural N=85 (%)	1-4 consults N=72 (%)	5-10 consults N=53 (%)	11+ consults N=75 (%)
How confident do you feel about advising patients on the use of Gina?							
Completely (5)	17.2	22.1	25.2	14.1	13.9	9.4	34.7
Very (4)	26.6	36.8	34.8	31.8	34.7	32.1	33.3
Fairly (3)	54.7	33.8	36.5	45.9	44.4	50.9	29.3
Not very (2)	1.6	7.4	3.5	8.2	6.9	7.6	2.7
Not at all (1)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Mean score (+5 to +1)	3.6	3.7	3.8	3.5	3.6	3.4	4.0
And how confident are you about correctly supplying Gina?							
Completely (5)	10.9	21.3	22.6	11.8	13.9	9.4	28.0
Very (4)	34.4	38.2	36.5	37.7	40.3	35.9	34.7
Fairly (3)	51.6	36.0	39.1	43.5	40.3	49.1	36.0
Not very (2)	3.1	4.4	1.7	7.1	5.6	5.7	1.3
Not at all (1)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Mean score (+5 to +1)	3.5	3.8	3.8	3.5	3.6	3.5	3.89

Table 11: Supply/don't supply responses to Scenarios Relating to Understanding of aRMMs – completed surveys

Scenario	Correct Supply/ Don't supply	Supply N=200 (%)	Don't supply N=200 (%)	Correct (%)	Margin of error (+/-%)
1	Supply	194 (97.0%)	6 (3.0%)	97.0	2.4
2	Supply	165 (82.5%)	35 (17.5%)	82.5	5.3
3	Don't supply	9 (4.5%)	191 (95.5%)	95.5	2.9
4	Supply	170 (85.0%)	30 (15.0%)	85.5	4.9
5	Don't supply	48 (24.0%)	152 (76.0%)	76.0	5.9
6	Don't Supply	19 (9.5%)	181 (90.5%)	90.5	4.1
7	Don't supply	15 (7.5%)	185 (92.5%)	92.5	3.7
8	Supply	145 (72.5%)	55 (27.5%)	72.5	6.2
	MEAN			86.4% (N=1600)	1.68

Table 11.1: Reason responses to Scenarios Relating to Understanding of aRMMs – completed surveys

Scenario	Correct A-D	A N=200 (%)	B N=200 (%)	C N=200 (%)	D N=200 (%)	% Correct	Margin of error (+/-%)
1	A	178 (89.0)	22 (11.0)	0 (0.0)	0 (0.0)	89.0%	4.3
2	B	33 (16.5)	142 (71.0)	4 (2.0)	21 (10.5)	71.0%	6.3
3	D	4 (2.0)	2 (1.0)	9 (4.5)	185 (92.5)	92.5%	3.7
4	A	163 (81.5)	13 (6.5)	16 (8.0)	8 (4.0)	81.5%	5.4
5	C	43 *(21.5)	1 (0.5)	150 (75.0)	6 (3.0)	75.0%	6.0
6	C	7 (3.5)	7 (3.5)	178 (89.0)	8 (4.0)	89.0%	4.4
7	D	5 (2.5)	10 (5.0)	20 (10.0)	165 (82.5)	82.5%	5.3
8	A	141 (70.5)	6 (3.0)	39 (19.5)	14 (7.0)	70.5%	6.3
					Mean	81.4%	1.91

Table 11.2: Reason responses to Scenarios Relating to Understanding of aRMMs – completed surveys, by segment: outlet type, gender, role

Scenario	Correct A-D	Independents N=98 % Correct	Multiples N=102 % Correct	Men N=105 % Correct	Women N=85 % Correct	Pharmacists N=136 % Correct	Locums N=64 % Correct
1	A	89.8	88.2	85.7	95.3	86.8	93.8
2	B	68.4	73.5	66.7	77.6	69.1	75.0
3	D	90.8	94.1	90.5	94.1	92.6	92.2
4	A	77.6	85.3	80.0	83.5	80.1	84.4

5	C	71.4	78.4	74.3	76.5	74.3	97.6
6	C	87.8	90.2	82.9	95.3	89.0	89.1
7	D	79.6	85.3	81.0	84.7	81.6	84.4
8	A	67.3	73.5	70.5	71.8	70.6	70.3
	Mean	79.1	83.6	78.9	84.9	80.5	85.8

Table 11.3: Reason responses to Scenarios Relating to Understanding of aRMMs – completed surveys, by segment: urban/suburban, age

Scenario	Correct A-D	Urban N=115 (%)	Suburban/ rural N=85 (%)	Under 40 years old N=104	Aged 40 plus N=91
1	A	88.7	89.4	83.7	94.5
2	B	71.3	70.6	63.5	79.1
3	D	92.2	92.9	90.4	94.5
4	A	84.3	77.6	76.0	86.8
5	C	74.8	75.3	69.2	87.1
6	C	87.8	90.6	89.4	89.0
7	D	79.1	87.1	80.8	86.8
8	A	71.3	69.4	70.2	69.2
	Mean	81.2	81.6	77.9	85.9

Table 11.4: Reason responses to Scenarios Relating to Understanding of aRMMs – completed surveys, by segment: number of consultations

Scenario	Correct A-D	Conducted 1-4 consults N=72 % Correct	Conducted 5-10 consults N=53 % Correct	Conducted 11 plus consults N=75 % Correct
1	A	93.1	84.9	98.7
2	B	77.8	60.4	88.0
3	D	94.4	90.6	93.3
4	A	87.5	75.5	85.3
5	C	72.2	81.1	76.0
6	C	95.8	92.5	84.0
7	D	88.9	77.4	90.7
8	A	63.9	73.6	76.0
	Mean	84.2	79.5	74.7

Table 12.1: Responses to Scenario 2 – completed surveys, by all segments

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.

A. Correct	Supply but suggest she asks her GP to investigate other causes.
B. Incorrect	Supply. Significant symptom improvement may not be experienced until after the second pack.
C. Incorrect	Do not supply. Refer to GP for a prescription.
D. Incorrect	Do not supply. Refer to GP to change treatment.

B Correct	Base	N	%	Precision or Margin of Error (±%)
Total	200	142	71.0	6.3
Independents	98	67	68.4	9.2
Multiples	102	75	73.5	8.6
Men	105	70	66.7	9.0
Women	85	66	77.6	8.9
Pharmacists	136	94	69.1	7.8
Locums	64	48	75.0	10.6
Urban	115	82	71.3	8.3
Rural	85	60	70.6	9.7
Aged under 40	104	66	63.5	9.3
Aged 40 plus	91	72	79.1	8.4
Conducted 1-4 consultations	72	56	77.8	9.6
Conducted 5-10 consultations	53	32	60.4	13.2
Conducted 11 plus consultations	75	62	72.1	10.2

Table 12.2: Responses to Scenario 8 – completed surveys, by all segments

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.

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

A correct	Base	N	%	Precision or Margin of Error (±%)
Total	200	103	51.5	6.6
Independents	97	47	48.5	9.9
Multiples	103	48	54.4	9.6
Men	104	55	52.9	9.6
Women	90	46	51.1	10.3
Pharmacists	161	83	55.1	7.7
Locums	39	20	51.3	15.7
Urban	106	50	47.2	9.5
Rural	94	53	56.4	10.4
Aged under 40	90	53	58.9	10.2
Aged 40 plus	100	50	45.5	9.8