

FDA Prescribers' Perceptions of Boxed Warnings - In-Depth Interviews with Healthcare Professionals on Boxed Warnings in Prescribing Information

IN-DEPTH INTERVIEW DISCUSSION GUIDE

Research Objective: Conduct in-depth interviews with prescribers (general practitioners and specialists) to understand how they make treatment decisions for patients with [chronic Hepatitis C viral infection (HCV)/vaginal symptoms associated with postmenopause] (Section II), assess how boxed warning and prescription drug label information affects subsequent decision-making (Section III), and assess their thoughts on risk information in labeling more generally (Section IV).

NOTES:

Question probes are *italicized*. These are suggestions for the interviewer to follow, and will be used or modified as deemed relevant and necessary in the natural flow of discussion.

Moderator instructions are highlighted in yellow.

Stimuli prompts are highlighted in blue.

Session Overview:

SECTION I: INTRODUCTION (5 min.)

The purpose in this section is for the moderator to explain the purpose of the research, lay down any ground rules or guidelines, and allow participants to ask any questions.

SECTION II: TREATMENT DECISION MAKING AND GENERAL PERSPECTIVES ON [DRUG] FOR [CONDITION] (18 min.) This section covers how prescribers approach treatment of [chronic HCV/vaginal symptoms associated with postmenopause], including their general approach to using [HCV Direct-Acting Antivirals (DAA)/Vagifem], situations in which they do and do not prescribe [DAA/Vagifem], and how they communicate with their patients about [DAA/Vagifem].

SECTION III: INFLUENCE OF BOXED WARNING INFORMATION ON PERCEPTION OF [DRUG'S] BENEFITS AND RISKS (20 min.)

Participants will discuss their familiarity with the boxed warning information for [DAA/Vagifem]. They will view the boxed warning and prescribing information for [DAA/Vagifem] and share their thoughts, assessments of the risks and benefits, and opinions on the way the information was presented.

SECTION IV: GENERAL THOUGHTS ON RISK INFORMATION IN LABELING (15 min.)

This section will include discussion on risk information for prescription

drugs more generally, including how participants become aware of boxed warnings, how they seek out information, and how this information factors into their decision-making with regard to patient care.

CONCLUSION (2 min.)

If time permits, moderator will check with research team members and observers if they have additional questions (with participant on hold). If yes, moderator asks follow-up questions and then wraps up discussion and ensures that all of the participant's comments have been heard.

SECTION I: INTRODUCTION (5 minutes)

[Please refer to participant by FIRST NAME only.]

- My name is _____, and I'm part of an independent research company. This means that I'm here to listen to you and what you have to tell me, and I have no stake in how you respond.
- This is a study sponsored by the FDA, the Food and Drug Administration, to understand how healthcare professionals approach prescribing decisions. The purpose of today's interview is to get your thoughts and reactions about various topics we will be discussing. I do not have a medical background, so your feedback is extremely helpful.
- Your thoughts are very important to us, and your time today is appreciated.
- We will have about 60 minutes for our discussion.

As we begin, I want to review a few ground rules for our discussion.

- Your participation is voluntary and you have the right to withdraw from the study at any time.
- Most importantly, there are no 'right' or 'wrong' answers and none of this conversation is meant to be a test. We want to know your opinions and what you think about the things we will be discussing.
- Just a reminder, we are not selling anything, and I do not work for the people who are sponsoring this research, so don't hold back from giving me your honest opinions.
- As we move through our discussions, please make sure to refrain from providing any Protected Health Information to us. Please also refrain from providing any identifying information about your practice, such as mentioning its name or names of your colleagues.
- Members of the research team are listening in to this interview for notetaking purposes and may include people from the FDA. This interview will also be audio recorded for data analysis and reporting, and your computer screen will be video-captured as well. Only people who are involved in the project will have access to this data. **Is it ok if I start the audio recording now? [START RECORDING]**

- And just to confirm, can you see my screen on your computer? It should say “Prescribing Decision Study.” OK great, we won’t be using the computer just yet—I will let you know when we get to that part.
- Do you have any questions before we begin?

Okay, great. Let’s get started.

SECTION II: TREATMENT DECISION MAKING AND GENERAL PERSPECTIVES ON [DRUG] FOR [CONDITION] (18 min.)

I’d like to start by talking a little bit about your background as a healthcare professional.

1. To start, could you briefly describe your clinical background and practice?
2. What are some typical patient issues you treat?

[Please refer to Appendix 1 and 2 for scenario-specific questions.]

SECTION III: INFLUENCE OF BOXED WARNING INFORMATION ON PERCEPTION OF [DRUG’S] BENEFITS AND RISKS (20 min.)

[Please refer to Appendix 1 and 2 for scenario-specific questions.]

SECTION IV: GENERAL THOUGHTS ON RISK INFORMATION PRESENTED IN LABELING (15 min.)

Thank you very much for your thoughts on the risk information for [HCV Direct Acting Antivirals/Vagifem]. As we wrap up, I’d like to ask you some more general questions about boxed warning information. You can still think about [HCV Direct Acting Antivirals/Vagifem] and also consider other medications you are familiar with.

1. How do you typically become aware of a boxed warning?
2. How often do you review the information directly from the FDA, such as drugs@fda, or DailyMed, which is managed by the NIH, the National Institutes of Health? Would you say “very often,” “sometimes,” or “not often?”

- a. When are you more likely to go to these sources for information?
 - b. Are there any other sources you receive this information from?
3. What is your understanding of the purpose of the boxed warning?
4. Generally speaking, how useful do you find the information contained in the boxed warning? Would you generally rate the information as “very useful,” “somewhat useful,” or “not useful?”
 - a. What makes the information more useful?
 - b. What makes the information less useful?
5. How, if at all, does your decision-making process differ when it comes to deciding whether to prescribe drugs with boxed warnings compared to drugs without boxed warnings?
 - a. *How does the presence of a boxed warning change the way you think about potential benefits and risks of a drug (compared to drugs that do not have a boxed warning)?*
6. What factors do you consider when you make a treatment decision for an individual patient?
 - a. *How does the presence of a boxed warning on a drug factor into your treatment decision (versus no boxed warning)?*
7. How do you counsel patients with regard to medications?
 - a. *Are there any particular steps you take in order to mitigate risks?*
 - b. *How does the presence of a boxed warning affect that way you may counsel a patient (versus no boxed warning)?*
8. Are there other factors that influence your prescription decisions for drugs that have a boxed warning?
 - a. *How does insurance play a role, if any?*
 - b. *Are there any policies of your healthcare system that play a role?*
9. Do you have any advice for the FDA on how to better communicate with the medical community about any drug’s serious risks?
 - a. [Probe on communication channels if not mentioned.]

SECTION V: Closing (2 min.)

[IF TIME PERMITS - PLEASE CHECK WITH RESEARCH TEAM/OBSERVERS FOR FOLLOW UP QUESTIONS.]

Thank you, this has been helpful. I am going to check quickly with my colleagues to see if there are any follow-up questions for you in the time we have remaining. I will be right back on the line.

[Put participant on hold.]

MODERATOR TO ASK FOLLOW-UP QUESTIONS (if applicable)

[Thank participant.]

Thank you very much for participating in this interview. I have enjoyed getting to know you, and appreciate your time and feedback. Is there anything that you would like to share that you didn't have the chance to share yet?

APPENDIX 1: Hepatitis C Scenario Questions

SECTION II: TREATMENT DECISION MAKING AND GENERAL PERSPECTIVES ON DIRECT ACTING ANTIVIRALS FOR HEPATITIS C (18 min.) CONT'D

Now I'd like to shift our discussion to focus on chronic Hepatitis C viral infections, which I will refer to as chronic HCV.

1. Can you describe your experience treating people with chronic HCV?
 - a. How many of your patients with chronic HCV do you see in a week? A month?
 - b. How would you describe your chronic HCV patient population?
2. Can you briefly describe your general approach to selecting pharmaceutical treatments for patients with chronic HCV?
 - a. What are your primary treatment options? *[Do not probe into much detail here.]*
3. I'm going to ask that we focus our discussion now on the direct acting antiviral medicines, indicated for the treatment of chronic HCV. To simplify, let's consider the fixed dose combination products such as Harvoni, Epclusa, Mavyret, Vosevi, and Zepatier. What is your general assessment of these drugs for this condition?
 - a. *[Encourage discussion of boxed warnings and/or risks if spontaneously mentioned.]*
 - b. *[If needed:]* Have you prescribed any of these drugs in the past month? If no, have you ever prescribed these drugs?
4. What factors play a role in your decision to prescribe or not prescribe a fixed dose combination product at all?
5. How do you go about assessing a *particular* product's potential benefits and risks for an individual patient?
6. *[Time Permitting]* Are there cases where this assessment of benefits and risks of a fixed dose combination treatment is substantially more challenging than is typical for the patients you typically treat?

- a. Can you provide an example of your thought process assessing the benefits and risks for a particular patient you saw in the last month?
 - b. How common is it that you experience a case like this? Up to 10%? Up to 25%? Up to 50% or greater?
7. Are there situations in which you generally do not prescribe *any* of these fixed dose combination products? Let's assume that insurance issues are not at play, that is, your patient would likely be able to access this treatment if prescribed.
- a. Can you provide a recent example of a patient for whom you did not prescribe a fixed dose combination product? Again, assuming that insurance issues were not at play.
8. How do you generally talk to patients about the fixed dose combination products?
- a. *What steps do you take to communicate with your patients about the benefits and risks of these drugs?*
 - b. How do you go about pre-screening and then monitoring your patients for potential safety risks and side effects of the selected product?
 - c. *What steps do you take when it comes to follow-up and evaluating of how the selected product is working for a patient?*
9. What is your approach towards seeking information on any particular one of these products?
- a. [Prompt for/probe into FDA-approved labeling.]

SECTION III: INFLUENCE OF BOXED WARNING INFORMATION ON PERCEPTION OF DIRECT ACTING ANTIVIRALS' BENEFITS AND RISKS (20 min.)

Thank you. We now want to delve into more detail about how you consider information on the benefits and risks of one of these products, and, in particular, information that is contained in a boxed warning.

1. Can you tell me what first comes to mind when you think of the term “boxed warning”?

2. [As you know/may know], all of the fixed combination products we've mentioned, like all drugs in the class of direct-acting antivirals indicated for chronic HCV, have a boxed warning. Would you rate your familiarity with this boxed warning as very familiar, somewhat familiar, or not familiar?

[If not familiar, move to text above Q3. If "very familiar" or "somewhat familiar," prompt the following:]

- a. Can you tell me anything/anything more about this boxed warning? *[Probe for any thoughts.]*
- b. Can you recall how you learned about this boxed warning?
- c. Have you actively sought out any information about the risks in the warning? How so?
- d. *[Probe if not already discussed:]* How, if at all, do you take into account the drug's boxed warning when making treatment decisions?
- e. How, if at all, do you take into account the drug's boxed warning when discussing this treatment option with your patients? Why?

Now, I am going to ask that you use your computer. Are you looking at your computer now? OK, great. To make sure that we have the same reference point, I would like to point you to information in the FDA-approved prescribing information, also known as labeling. I am going to show you the prescribing information for [DAA DRUG: Harvoni/Zepatier/Maryvet] on the screen and will be asking follow-up questions. We selected this product at random from the set of fixed dose combinations, but the boxed warning information is the same for all of these products' labeling. First, I would like to direct you to the boxed warning.

3. Are you able to see the boxed warning information on your screen? Do you have any trouble reading the text?

I'd like to ask you to read through the information in the boxed warning. As you read through, I'd like you to "think aloud" and share any thoughts or questions that come to mind as you are going along. *[Allow participant to walk through process.]*

4. After reviewing this information, what, if any, new thoughts or questions come to mind about the relative potential benefits versus risks of [DRUG]?
5. Have you experienced any of these risks in your own clinical practice? Please explain.

6. Do you have any thoughts on *how* the information is presented in the boxed warning itself?
 - a. Is anything unclear or confusing?

[If time permits:]

Are there any other risks that you would like to view more information about in the Warnings and Precautions section?

I'd now like to invite you to review the sections that contain information relevant to this/these risk(s). Please click to expand any other information of interest within the "Warnings and Precautions" section number 5. Please feel free again to "think aloud" and share any thoughts of questions that come to mind as you are looking through this information. [Allow participant to click through and read remaining prescribing information.]

7. Which warnings and precautions did you review and what drew your focus to them?
8. After reviewing this information, does it raise any new thoughts or questions about the risks of [DRUG] or the relative benefits versus risks?
9. Do you have any thoughts on how the information is presented *in the boxed warning itself* versus *elsewhere* in the prescription label?
 - a. Is anything unclear or confusing?

[REFER BACK TO MAIN BODY OF GUIDE FOR SECTION IV]

APPENDIX 2: Scenario Questions

SECTION II: TREATMENT DECISION MAKING AND GENERAL PERSPECTIVES ON VAGIFEM FOR VAGINAL SYMPTOMS IN POSTMENOPAUSE (18 min.) CONT'D

Now I'd like to shift our discussion to focus on vaginal symptoms associated with postmenopause, also known as atrophic vaginitis, vaginal atrophy, vulvovaginal atrophy, or urogenital atrophy.

1. Can you describe your experience treating people with vaginal symptoms associated with postmenopause, such as atrophic vaginitis? **[May use another term if participant appears to be unfamiliar with terminology or prefers another, such as vaginal atrophy, vulvovaginal atrophy, or urogenital atrophy.]**
 - b. How many of your patients with this condition do you see in a week? A month?
 - c. How would you describe your postmenopausal patient population?
2. Can you briefly describe your general approach to selecting pharmaceutical treatments for patients with these symptoms?
 - a. What are your primary treatment options? **[Do not probe into much detail here.]**
3. I'm going to ask that we focus our discussion now on Vagifem for treating patients with atrophic vaginitis in postmenopause. What is your general assessment of this drug for this condition?
 - a. **[Encourage discussion of boxed warnings and/or risks if spontaneously mentioned.]**
 - b. **[If needed:]** Have you prescribed Vagifem before? *Or other similar locally administered estrogen products?*
4. What factors play a role in your decision to prescribe or not prescribe Vagifem?
 - a. **[For this and following questions, if participant goes into detail about choosing among different forms of estrogen, please direct**

conversation towards prescribing estrogen more generally rather than details about dosage, administration, etc.]

5. How do you go about assessing Vagifem’s potential benefits and risks for an individual patient?
6. Are there situations where Vagifem tends to be among your first choice for treatment?
 - a. Can you provide a recent example – a recent patient for whom you prescribed Vagifem?
 - b. *How often do you prescribe Vagifem, would you say?*
7. Are there situations in which you generally do not prescribe Vagifem?
 - a. Can you provide a recent example of a patient for whom you did not prescribe Vagifem?
8. How do you generally talk to patients about Vagifem?
 - a. *What steps do you take to communicate with your patients about the benefits and risks of Vagifem?*
9. What steps do you take when it comes to follow-up and evaluation of how Vagifem is working for a patient?
 - a. *How do you test and monitor your patients for potential safety risks and side effects?*
10. What is your approach towards seeking information on Vagifem?
 - a. [Prompt for/probe into FDA-approved labeling.]

SECTION III: INFLUENCE OF BOXED WARNING INFORMATION ON PERCEPTION OF VAGIFEM’S BENEFITS AND RISKS (20 min.)

Thank you. We now want to delve into more detail about how you consider information on Vagifem’s benefits and risks, and in particular information that is contained in a boxed warning.

1. Can you tell me what first comes to mind when you think of the term “boxed warning”?

2. [As you know/may know], Vagifem has a boxed warning. Would you rate your familiarity with this boxed warning as very familiar, somewhat familiar, or not familiar?

[If not familiar, move to text above Q3. If “very familiar” or “somewhat familiar,” prompt the following:]

- a. Can you tell me anything about this boxed warning? [*Probe for any thoughts.*]
- b. Did you actively seek out any information about the risks in the warning?
- c. [*Probe if not already discussed:*] How, if at all, do you take into account the drug’s boxed warning when making treatment decisions?
- d. How, if at all, do you take into account the drug’s boxed warning when discussing this treatment option with your patients? Why?

Now, I am going to ask that you use your computer. Are you looking at your computer now? OK, great. To make sure that we have the same reference point, I would like to point you to information in the FDA-approved prescribing information, also known as labeling. I am going to show you the prescribing information for Vagifem on the screen and will be asking follow-up questions. First, I would like to direct you to the boxed warning.

3. Are you able to see the boxed warning information on your screen? Do you have any trouble reading the text?

I’d like to ask you to read through the information in the boxed warning. For now, you need only focus on the Estrogen-Alone Therapy section. As you read through, I’d like you to “think aloud” and share any thoughts or questions that come to mind as you are going along. [*Allow participant to walk through process.*]

4. After reviewing this information, what, if any, new thoughts or questions come to mind about the relative potential benefits versus risks of Vagifem?
5. Have you experienced any of these risks in your own clinical practice? Please explain.
6. Do you have any thoughts on *how* the information is presented in the boxed warning itself?
 - a. Is anything unclear or confusing?

[If time permits:]

Based on your review of the boxed warning, is there other information that you'd like to review in the labeling?

I'd now like to invite you to review the sections that are referenced in the boxed warning. Please click to expand any other information of interest. Please feel free again to "think aloud" and share any thoughts or questions that come to mind as you are looking through this information. [Allow participant to click through and read remaining prescribing information.]

7. Which information did you review and what drew your focus to it?
8. After reviewing this information, does it raise any new thoughts or questions about the risks of Vagifem or the relative benefits versus risks?
9. Do you have any thoughts on how the information is presented *in the boxed warning itself* versus *elsewhere* in the prescription label?
 - a. Is anything unclear or confusing?

[REFER BACK TO MAIN BODY OF GUIDE FOR SECTION IV]