Effectiveness of Xiapex® educational material for healthcare professionals in the treatment of Peyronie's disease - a non-interventional post-authorization safety study

PASS information

Title	Effectiveness of Xiapex® educational material for healthcare professionals in the treatment of Peyronie's disease - a non-interventional post-authorization safety study
Protocol version identifier	Sobi.Xiapex-PASS01
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Active substance	M09AB02 Collagenase *Clostridium histolyticum*
Medicinal product	Xiapex
Product reference	Xiapex-2048
Procedure number	EMEA/H/C/002048/II/0044
Marketing authorization holder(s)	Swedish Orphan Biovitrum AB (publ)
Joint PASS	No
Research question and objectives	The primary objective of this study is to evaluate the effectiveness of the educational material in knowledge transfer of important safety information to the treating physician. This objective will be assessed in the five following identified domains: • Indication • Injection procedure and posology • Treatment cycles • Modelling • Risk identification and minimization In addition, the physician's perception of usefulness of the content on identified safety risks will be assessed. Per identified safety risk, the physician will be asked to score the related educational material as effective/not effective. Physicians that have had Xiapex-treated patients experiencing corporal rupture will be asked to provide information on identified causes.

Country(-ies) of study	Austria, Czech Republic, Denmark, Finland, Norway, Sweden, Spain and the United Kingdom
Author	Sari von Reedtz, Clinical Program Leader Swedish Orphan Biovitrum AB SE-112 76 Stockholm, Sweden

Marketing authorization holder(s)

Marketing authorization holder(s)	Swedish Orphan Biovitrum AB (publ) SE-112 76 Stockholm, Sweden
MAH contact person	Marianne Keisu, QPPV

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1 List of abbreviations

MAH	Marketing authorization holder
PDF	Portable Document Format
QC	Quality control
sCDR	Subversion Clinical Data Repository
Sobi	Swedish Orphan Biovitrum AB

2 Responsible parties

The marketing authorization holder (MAH), Swedish Orphan Biovitrum AB (Sobi) is responsible for the design, conduct and data evaluation of this post-authorization study. This is a non-interventional safety study, eliciting information from health care professionals that complete the Xiapex Peyronie's education material. There are hence no principal investigator or study sites.

3 Abstract

Title

Effectiveness of Xiapex® educational material for healthcare professionals in the treatment of Peyronie's disease - a non-interventional post-authorization safety study

Study protocol no. Sobi.Xiapex-PASS01, Version 4, 13-Apr-2016

Sari von Reedtz, Swedish Orphan Biovitrum AB, SE-112 76 Stockholm, Sweden

Rationale and background

As agreed with the European Medicines Agency, only those physicians who are experienced in the treatment of male urological diseases and who have been appropriately trained in the usage of Xiapex® in the treatment of Peyronie's disease shall use Xiapex.

Comprehensive educational material has been developed to ensure that all physicians who are expected to prescribe/use Xiapex in Peyronie's disease are appropriately trained in the correct administration of the product and in the identified and potential risks associated with the treatment. This study is an additional pharmacovigilance activity to assess the effectiveness of the Xiapex educational material through a survey administered to physicians completing the educational material.

Research question and objectives

The primary objective of this study is to evaluate the effectiveness of the educational material in knowledge transfer of important safety information to the treating physician. This objective will be assessed in the five identified domains:

- Indication
- Injection procedure and posology
- Treatment cycles
- Modelling
- Risk identification and minimization

In addition, the physician's perception of usefulness of the content on identified safety risks will be assessed. Per identified safety risk, the physician will be asked to score the related educational material as effective/not effective.

Physicians that have had Xiapex-treated patients experiencing corporal rupture will be asked to provide information on identified causes.

Study design

This is a non-interventional post-authorization safety study evaluating the effectiveness of the the Xiapex educational material for healthcare professionals for treatment of Peyronie's disease. Surveys administered to physicians registering in the MAH's Peyronie's Trained Physicians database will assess knowledge transfer of 5 domains (i.e., indication, injection procedure and posology, treatment cycles, modelling, and the identified risks associated with Xiapex treatment). Furthermore, the survey will assess the physician's perception of usefulness of the content on identified safety risks. Should the responding physician have had Xiapex-treated patients experiencing corporal rupture, then he/she is asked to provide information on identified causes.

Physicians that have not returned a completed survey within 3 months after distribution will be provided another survey ("Evaluation of Xiapex educational material in Peyronie's disease – Reminder") for the purpose of soliciting information on non-responder characteristics, including whether they have used Xiapex for the treatment of Peyronie's disease.

Based on the results of this study (i.e., the survey responses), the educational material may be revised, as deemed appropriate.

Population

Physicians from Austria, Czech Republic, Denmark, Finland, Norway, Sweden, Spain and the United Kingdom registering in the MAH's Peyronie's Trained Physicians database.

Variables

The response rate (i.e., number of distributed surveys versus number of returned surveys) will be assessed. Responders will be characterized by country of residence/practice, specialty and by experience from clinical use of Xiapex, as provided on the survey.

Responses to knowledge transfer questions will be rated according to correctness (i.e., yes or no). The physicians' perception of usefulness of the content on identified safety risks will be assessed by response category (effective/not effective) for each risk item.

Adverse events identified by physician's as not described in the educational material or that could be avoided through a revised educational material, will be summarized. Reported risk factors/abnormalities for occurred corporal rupture(s) will be listed and summarized if applicable.

Non-responders will be characterized by country of residence/practice as registered in the Trained Physicians database, specialty (if provided when registering in the Trained Physicians database) and by experience from clinical use of Xiapex, as provided on the Reminder survey.

Data sources

The survey distribution and return log maintained in the Trained Physicians database will be the source for evaluation of the response rate and for summarizing specialty of non-responding physicians.

A separate study database will be set up for entry and analysis of survey responses. The data in the study database will be anonymous and will not contain any personal information. Text in local language will be translated to English prior to entry into the study database.

Study size

Overall, up to 100 physicians are expected to have received the survey within the distribution period of 1-Jul-2016 to 1-Oct-2017. The overall return rate is expected to be 30-40%. The aim is to obtain at least 5 returned surveys per country.

Data analysis

The primary analysis set will consist of all physicians who have submitted the "Evaluation of Xiapex educational material in Peyronie's disease" survey.

The primary endpoint, the correctness (yes, no) of answers to each of the 13 knowledge transfer questions, will be summarized descriptively.

Missing data will be summarized descriptively.

Milestones

Start of data collection: 1-Jul-2016; End of data collection: 1-Oct-2017; Registration in the EU PAS register: 1-Jul-2016; Final report of study results; 1-Oct-2018.

4 Amendments and updates

Version 1, dated 20-Apr-2015, Version 2, dated 22-Sep-2015, and Version 3, dated 23-Feb-2016, of this Post-Authorization Safety Study protocol have been submitted to the EMA for evaluation. On the basis of PRAC recommendations of study and survey design, the "Implementation Surveys" collected in accordance with protocol Versions 1 and 2 will not be included in this study. Therefore, the overall start of data collection has been revised to 1-Jul-2016.

5 Milestones

Milestone	Planned date
Overall start of data collection	1-Jul-2016
End of data collection	1-Oct-2017
Registration in the EU PAS register	1-Jul-2016
Final report of study results	1-Oct-2018

6 Rationale and background

As agreed with the European Medicines Agency, only those physicians who are experienced in the treatment of male urological diseases and who have been appropriately trained in the usage of Xiapex® in the treatment of Peyronie's disease shall use Xiapex. Trained physicians will be registered in a Peyronie's database held by the MAH in Europe confirming that he/she has fulfilled the physician training program.

Comprehensive education material has been developed to ensure that all physicians who are expected to prescribe/use Xiapex in Peyronie's disease are appropriately trained in the correct administration of the product and in the identified and potential risks associated with the treatment. A training brochure, approved by the EMA, has been translated into applicable local languages and submitted for local Regulatory Approval. The content of the training brochure can be disseminated through several means, including physician's self-paced review of the training brochure or web-based tutorial, local training sessions, peer-to-peer Xiapex administration training events, etc.

This study is an additional pharmacovigilance activity to assess the effectiveness of the Xiapex educational material through a survey administered to physicians completing the educational material. The survey will assess knowledge transfer and usefulness of the educucational material.

Furthermore, physicians that have had Xiapex-treated patients experiencing corporal rupture will be asked to provide information on identified causes.

7 Research question and objectives

The primary objective of this study is to evaluate the effectiveness of the educational material in knowledge transfer of important safety information to the treating physician. This objective will be assessed in the five identified domains:

- Indication
- Injection procedure and posology
- Treatment cycles
- Modelling
- Risk identification and minimization

In addition, the physician's perception of usefulness of the content on identified safety risks will be assessed. Per identified safety risk, the physician will be asked to score the related educational material as effective/not effective.

Physicians that have had Xiapex-treated patients experiencing corporal rupture will be asked to provide information on identified causes.

8 Research methods

8.1 Study design

This is a non-interventional post-authorization safety study evaluating the effectiveness of the the Xiapex educational material for healthcare professionals for treatment of Peyronie's disease. Surveys administered to physicians registering in the MAH's Peyronie's Trained Physicians database will assess knowledge transfer of 5 domains (i.e., indication, injection procedure and posology, treatment cycles, modelling, and the identified risks associated with Xiapex treatment). Furthermore, the survey will assess the physician's perception of usefulness of the content on identified safety risks. Should the responding physician have had Xiapex-treated patients experiencing corporal rupture, then he/she is asked to provide information on identified causes.

The survey will be sent out as fillable PDFs (portable document format) by email, followed by a phone call to ensure reception and comprehension of the task. Upon physician's request, the survey may also be provided as printed handout through ordinary mail or at a face-to-face meeting with a Sobi representative. The survey ("Evaluation of Xiapex educational material in Peyronie's disease") is provided in Appendix 1. The distribution and return of completed surveys will be tracked. See further details on survey management in Section 8.2.3.

The survey includes an urge to submit a completed Adverse Event form for any non-reported adverse reactions in Xiapex treated patients, specifically corporal ruptures. The Sobi Adverse Event Report form will be provided in the email when distributing the survey (for the form, refer to Appendix 4).

The survey will be sent to the physician at least 6 months *after* his/her registration in the Trained Physicians database. This is to secure that the survey captures enduring knowledge and that the physician may have gained personal experience from treating patient(s) with Xiapex.

Physicians that have not returned a completed survey within 3 months after distribution will be provided another survey ("Evaluation of Xiapex educational material in Peyronie's disease – Reminder", refer to Appendix 2) for the purpose of soliciting information on non-responder characteristics, including whether they have used Xiapex for the treatment of Peyronie's disease.

Based on the results of this study (i.e., the survey responses), the educational material may be revised, as deemed appropriate.

8.2 Setting

8.2.1 Study location

This study is conducted in countries in the European Economic Area (countries in the European Union, with the addition of Norway) where local regulatory approval of Xiapex Peyronie's educational material has been obtained.

In order to allow country-by-country analyses, this study is limited to those countries where the expected number of physicians registering in the Trained Physicians database prior to 30-Dec-2016 is at least 10. Furthermore, country selection is based on expected patient access to Xiapex treatment through private insurance or out-of-pocket payment since most European countries will not provide reimbursement for Xiapex treatment of Peyronie's disease.

The study will be conducted in Austria, Czech Republic, Denmark, Finland, Norway, Sweden, Spain and the United Kingdom.

8.2.2 Study participants

Upon registration in the Xiapex Peyronie's Trained Physicians database the physician will consent to Sobi maintaining his/her information for the purpose of ensuring that only those physicians who are appropriately trained in the correct administration of the product and experienced in the diagnosis and treatment of male urological diseases can have access to Xiapex and for the purpose of assessing the effectiveness of the training programme. Refer to Section 9 for details on personal data protection and Appendix 3 for the Consent form.

Physicians from Austria, Czech Republic, Denmark, Finland, Norway, Sweden, Spain and the United Kingdom registering in the Xiapex Peyronie's Trained Physicians database will be asked to complete the survey. Distribution and return of surveys will be tracked.

Physicians that have not returned a completed form within 3 months following distribution will be asked to complete and return another survey for the purpose of soliciting information on non-responding characteristics.

8.2.3 Survey distribution, tracking and collection

Physicians that register in the Trained Physicians database, and thereby consent to Sobi maintaining his/her personal information, will be provided the "Evaluation of Xiapex educational material in Peyronie's disease" (refer to Appendix 1) survey through email. The distribution of the survey will be logged (to whom and when sent) in the Trained Physicians database. The email will be followed by a phone call to ensure reception and comprehension of the task. Upon physician's request, the survey may also be provided as a printed handout through ordinary mail or at a face-to-face meeting with a Sobi representative.

The "Evaluation of Xiapex educational material in Peyronie's disease" survey distributed via email is fillable so that the physician can enter data electronically, save the completed form and return it to Sobi via email. The form can also be printed, completed, scanned and returned to Sobi via email or in person to a Sobi representative.

The survey is anonymous in the aspect that the responding physician's name will not be requested on the form and the responder will therefore be anonymous when survey data is analysed. As most surveys are expected to be returned via email or in person to a Sobi representative it will still be possible to track the responders. The Trained Physicians database will be updated on the basis of returned surveys given that the responding physician can be identified and his/her "survey status" will be changed from "provided" to "returned", as applicable.

The anonymous surveys will be provided to Sobi Data Management for data entry. If the survey is sent to Sobi via email the email will be archived after the email address and name of the the sender has been blacked outto make sure a response can no longer be connected to a specific physician in the study database.

In order to increase the response rate, one reminder will be sent out by email to physicians that have not returned a completed survey within 1 month from initial distribution. As a further attempt to increase the response rate, the email-reminder will be followed by a phone call to ensure reception and comprehension of the task. The phone call serves also as a second reminder.

Physicians that have not returned a completed survey within 3 months after distribution will be provided the "Evaluation of Xiapex educational material in Peyronie's disease – Reminder" email. This email serves as a survey to obtain information on the non-responder characteristics (for content, refer to Appendix 2). The distribution of the "Evaluation of Xiapex educational material in Peyronie's disease – Reminder" email will be logged (to whom and when sent) in the Trained Physicians database. The physician will submit his/her responses to the short survey by replying to the email. The Trained Physicians database will be updated on the basis of returned survey, i.e., "Reminder-survey status" will be changed from "provided" to "returned".

The anonymous survey response will be provided to Sobi Data Management for data entry. The email will be archived after the email address and name of the the sender has been blacked out to make sure a response can no longer be connected to a specific physician in the study database.

There will be no email/phone reminders to non-responders to the "Evaluation of Xiapex educational material in Peyronie's disease – Reminder" survey.

8.3 Variables

The response rate (i.e., proportion of responders) will be assessed from the survey distribution and return log. The number of returned surveys will be verified with the actual number of surveys received.

Responders will be characterized by country of residence/practice, specialty and by experience from clinical use of Xiapex, as provided on the survey (number of treated patients by categories 0; 1-9; 10-20; >20). Responses to Questions No. 3 to 15 will be used to assess the knowledge transfer in the five domains; Indication (Questions 3 and 4), Injection procedure and posology (Questions 5 to 7), Treatment cycles (Questions 8 to 10), Modeling (Questions 11 and 12), and Risk identification and minimization (Questions 13 to 15). Per each question, the provided response will be rated according to correctness (i.e., yes or no).

Responses to Questions 16 to 19 will be used to assess the physician's perception of usefulness of the content on identified safety risks. Each item in Question 16 will be summarized by response category (effective/not effective).

Adverse events identified by physician's as not described in the educational material or that could be avoided through a revised educational material (Questions 17 and 19), will be summarized.

Corporal rupture risk factors/abnormalities, as provided in reponse to Question 18, will be summarized.

It should however be noted, that the survey is not intended to replace the MAH's standard pharmacovigilance activities. It is therefore clearly stated in the survey that individual case reports of adverse reactions must be submitted separately to the MAH through email or fax, as well as to the local authority in accordance with national regulations. To facilitate reporting to the MAH, an Adverse Event Report form is provided together with the survey. Refer to Appendix 4 for the Adverse Event Report form.

Non-responders will be characterized by country of residence/practice as registered in the Trained Physicians database, specialty (if provided when registering in the Trained Physicians database) and by experience from clinical use of Xiapex, as provided on the Reminder survey (number of treated patients by categories 0; 1-9; 10-20; >20). Reason for not returning a completed survey will be summarized by response category (no intention of using Xiapex in clinical practice/Other).

8.4 Data sources

The Trained Physicians database will be used to assess the response rate (i.e., number of distributed surveys versus number of returned surveys) and to summarize specialty of non-responding physicians.

A separate study database will be set up for entry and analysis of survey responses. The study database will only contain information as entered on the surveys. There will be no transfer of information from the Trained Physicians database to the study database. The data in the study database will be anonymous and will not contain any personal information. Text in local language will be translated to English prior to entry into the study database.

Individual Adverse Event Report forms do not consistute a data source for this study. Those will be managed in accordance with the MAH's routine pharmacovigilance Standard Operating Procedures, and therefore entered and assessed through the MAH's global safety database. Refer further to Section 10.

8.5 Study size

Overall, up to 100 physicians are expected to have received the survey within the distribution period of 1-Jul-2016 to 1-Oct-2017. The overall return rate is expected to be 30-40%. The aim is to obtain at least 5 returned surveys per country. This gives 80% power to reject a Null Hypothesis Proportion of 50% when the true proportion is 95% and the Type I error rate is 5%.

With 30 physicians responding to the test of knowledge transfer, the 95% confidence intervals would have a range of at most ±19% from the estimated probabilities of a correct answer, e.g. with an estimated proportion of correct answers of 50%, a 95% confidence interval would range from 31 to 69%.

8.6 Data management

8.6.1 Data collection

Surveys will be distributed in electronic fillable PDF format or as paper copies and returned and managed as described in Section 8.2.3.

The completed forms will be received by Sobi and free text will be translated into English before entry in the study database by Sobi Data Management.

Prior to anonymizing the returned survey, it will be reviewed for adverse event information (i.e., the responses to Question 17). Any entered adverse events will be verified with individual case reports received through the MAH's standard pharmacovigilance activities. If there is no matching individual case report, the routine pharmacovigilance activities will be applied to obtain further information on the adverse event, provided that the physician submitting the survey can be identified.

8.6.2 Data entry

Data entry of returned surveys will be performed by Sobi Data Management.

Study data will be compiled into an Excel study database stored in the Sobi Subversion Clinical Data Repository (sCDR). The sCDR is an access controlled system used at Sobi for handling and archiving of clinical data. The system is validated according to current regulations and keeps track of potential changes to the data and ensures traceability and audit trail.

Free text will be entered exactly as translated into English. The corresponding free text in original language will not be entered into the database.

8.6.3 Database lock

When all data is entered, source data verified (see section 8.8.1) and quality controlled with an accepted error rate (see section 8.8.2) the Excel database is locked.

8.6.4 Analysis database

After database lock, the Excel database is converted to SAS format to allow statistical analysis of the data. The SAS database will be stored in the sCDR.

8.6.5 Data storage

The Excel database, the SAS database and associated programs and outputs will be stored and handled in the Sobi sCDR as described above. The data storage and handling will comply with Sobi Standard Operating Procedures and applicable guidelines for clinical study data. When the Study Report is finalized, the data will be archived in the sCDR for at least as long as Xiapex is available on any market.

Original surveys (i.e., scanned paper forms, submitted scanned forms and completed fillable PDFs) and translated forms will be stored on a restricted access Sharepoint site. Surveys obtained in original paper format will be stored in a locked fire-proof archive. Surveys (in original paper format and in electronic format) will be stored for 5 years following completion of the Final Study Report.

The Trained Physicians database will be maintained and stored for the duration that Sobi is the MAH for Xiapex, or until the MAH is released from the obligation to ensure that all physicians who are expected to use Xiapex are appropriately trained.

8.7 Data analysis

The primary analysis set will consist of all physicians who have submitted the “Evaluation of Xiapex educational material in Peyronie’s disease” survey.

The primary endpoint, the correctness (yes, no) of answers to each of the 13 knowledge transfer questions, will be summarized descriptively. The number and percentage of physicians giving an answer, a correct answer and a 95% confidence interval for the proportion of correct answers will be presented per question. Finite population correction will not be used. If for any question, less than 80% of physicians provide a correct answer, a revision of the specific domain of the educational material will be considered.

The number and percentage of physicians providing a correct answer by item will also be presented for the subgroup of physicians who have treated at least one patient and the subgroup of physicians who have not yet treated any patient. Depending on final sizes of subgroups, the corresponding analysis will also be done by each queried subgroup of number of treated patients (0/1-9/10-20/>20).

The primary endpoint as well as the subgroups analyses will be presented by country and by speciality of physicians.

The total number and percentage of correct answers of the 13 knowledge transfer questions per survey will be presented in a frequency table, i.e, number and percentage having 13 correct answers, number and percentage having 12 correct answers, etc. This will also be presented by country and by speciality of physicians.

The number and percentage of physicians' responses (effective versus not effective) to each item on the identified safety risk form will be presented. This will also be presented by country and by speciality of physicians.

The physicians' responses to the corporal rupture question (question 18) will be listed and summarized descriptively if applicable.

Adverse events which could have been avoided if better described in the educational material, as captured in response to Question 17 of the survey, will be coded and presented using MedDRA.

Number of responders and non-responders will be summarized in total and by country, and also by specialty as provided by physicians registered in the Peyronie's Trained Physicians database. Responders will be characterized by country of residence/practice, specialty and by experience from clinical use of Xiapex, as provided on the survey (number of treated patients by categories 0; 1-9; 10-20; >20).

Two types of missing data might occur in the study: non-responders respectively missing answers to any knowledge transfer question.

- The number of non-responders as well as the responses to the Non-responder survey will be summarized by response category but not formally analyzed or modeled.
- Number and percentages of missings answers to any knowledge transfer question will be summarized descriptively.

All data will be listed.

8.8 Quality control

8.8.1 Source data verification

Data entered into the study database will be verified by proof reading of 100 % of the collected source data versus the study database. Proof reading will not be performed by the person entering the data in the database. All discrepancies will be checked against the source PDF forms (not done by the person who did the proof reading). When an error is confirmed, the database will be updated.

8.8.2 Data quality control

When all data has been collected and verified against source as described above an additional Quality Control (QC) of data will be performed to ensure that data entry and verification have been performed adequately.

- 5% of the entered records will be randomly selected and all variables will be checked against source for accuracy with the allowed error rate of 1%. Errors found will be updated.

If the allowed error rate is exceeded the process will be repeated until the error rate is below or equal to the set limit.

The result of the QC will be documented and archived as a separate document.

8.9 Limitations of the research methods

It is expected that there may be a difference in the physicians' response rate, depending on their knowledge level in the five domains; Indication, Injection procedure and posology, Treatment cycles, Modelling, and Risk identification and minimization. Physicians may perceive the survey as a personal qualification test instead of an assessment of the effectiveness of the knowledge transfer. This will be mitigated by anonymized data entry and assessment of completed surveys and by explaining the survey purpose at phone and/or personal contacts.

It is further expected that there may be a difference in the physicians' response rate depending on how useful they find the education material. Thus, physicians perceiving the education material to be suboptimal and/or have identified adverse events or medication errors that may be avoided by a revision of the education material can be more motivated to complete and submit the survey compared to physicians finding the material adequate. This will however not affect the objective of the study, as the secondary objective is to identify any potential areas of the education material that would benefit from revision in order to avoid adverse events and medication errors.

It is also recognized that physicians may review the educational material and also use Xiapex for the treatment of Peyronie's disease without registring in the Xiapex Peyronie's Trained Physicians database. Such physician will thus not be given the opportunity to participate in this

study. The robustness of the results of this study is however secured by not making the surveys publically available via a website, and thus running the risk of including anonymous responses from non-eligible persons (e.g., from non-participating countries, non-physicians etc.) in the data analyses.

8.10 Other aspects

Not applicable.

9 Protection of human subjects

Upon registration in the Xiapex Peyronie's Trained Physicians database the physician will consent to Sobi maintaining his/her information for the purpose of:

a. ensuring that only those physicians who are appropriately trained in the correct administration of the product and experienced in the diagnosis and treatment of male urological diseases can have access to Xiapex
b. for the purpose of assessing the effectiveness of the training programme

Swedish Orphan Biovitrum AB (publ), 112 76 Stockholm, Sweden, is responsible for the Trained Physicians database, including the survey distribution and return log. The management and maintenance will comply with applicable data protection legislation. The Trained Physicians database will only be accessible to persons administering the database, the conduct of the surveys or ensuring correct administration on Xiapex in the treatment of Peyronie's disease. The database will not be used for other purposes (e.g. marketing activities). Upon authority request, data may be shared with the applicable authority. Information contained in the database will not be transferred outside of the European Economic Area.

Should any completed survey contain any personally identifiable information, then that information will be deducted from the completed form and will not be entered into the study database.

10 Management and reporting of adverse events/adverse reactions

This study is not designed to capture all observed adverse events in a study database for the purpose of safety evaluation of Xiapex treatment. The objective of this study is to evaluate the effectiveness of risk minimization measures and accordingly this study only captures information on any adverse events that, in the opinion of the investigator, could possibly be avoided by an improved educational material.

Any adverse events or medication errors captured in the survey will be considered solicited and will be analyzed as part of the protocol, and will be followed up per routine pharmacovigilance activities. Any captured case report will be entered into the global safety database and included

in the routine pharmacovigilance activities for Xiapex including signal detection, regulatory reporting and inclusion in PSURs as applicable.

Additionally, the physicians are instructed in the survey to separately report any adverse reactions associated with Xiapex to Sobi Drug Safety via a provided Adverse Event Report form either through email or by fax, as well as to the local Regulatory Authority according to national requirements. Physicians are specifically requested to report any events of corporal ruptures.

11 Plans for disseminating and communicating study results

The final study report will be submitted to the EMA as per GVP module VIII.

The results of this study will be posted in the ENCePP database. Any revised training material, as a result from this study, will be distributed to physicians in the Trained Physicians database, as applicable.

12 References – Not applicable

Appendix 1 Evaluation of Xiapex educational material in Peyronie's disease

EVALUATION OF XIAPEX EDUCATIONAL MATERIAL IN PEYRONIE´S DISEASE

The European Medicines Agency (EMA) has requested evaluation of the effectiveness of the educational material for Xiapex in Peyronie's disease. The survey questions are intended to evaluate the adequacy and clarity of the educational material. Your answers will be assessed anonymously.

Please complete ALL questions below, and return

By mail:
Medical Information,
Swedish Orphan Biovitrum AB (publ)
SE-11276 Stockholm, Sweden

By fax:
+46 8 697 32 30

By email:
medical.info@sobi.com

GENERAL INFORMATION

Specialty: **Urology** ☐ **Andrology** ☐ **Other:**_____

1. PLEASE IDENTIFY YOUR COUNTRY

Austria	☐	Norway	☐
Czech Republic	☐	Spain	☐
Denmark	☐	Sweden	☐
Finland	☐	United Kingdom	☐

2. HOW MANY PATIENTS HAVE YOU TREATED SINCE YOUR TRAINING?

☐ **0** ☐ **1-9** ☐ **10-20** ☐ **>20**

EVALUATION OF CLARITY AND ADEQUACY OF EDUCATIONAL MATERIAL

The following questions, in five domains: Indication; Injection procedure and posology; Treatment cycles; Modelling; and Risk identification and minimization, are intended to evaluate the adequacy and clarity of the education material:

Indication

3. XIAPEX IS APPROVED FOR TREATMENT OF

- ☐ **Adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 15 degrees**
- ☐ **Adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees**
- ☐ **Adult men with Peyronie's disease with a palpable plaque and curvature of any degree**
- ☐ **don´t know**

4. XIAPEX IS SUITABLE FOR TREATMENT OF

- ☐ **Dorsal and lateral Peyronie's plaques**
- ☐ **Dorsal, lateral and ventral Peyronie's plaques**
- ☐ **Dorsal, lateral and hourglass Peyronie's plaques**
- ☐ **don´t know**

Injection procedure and posology

5. HOW LONG SHOULD ONE WAIT BETWEEN TWO INJECTIONS

- ☐ **2 injections can be administered during the same day**
- ☐ **3 days in between injections**
- ☐ **1-3 days in between injections**
- ☐ **don´t know**

6. INJECTIONS OF XIAPEX SHOULD BE MADE WITH THE PENIS IN

- ☐ **the erect state, entering the plaque from the side**
- ☐ **the flaccid state, entering the plaque from the side**
- ☐ **the flaccid state, entering the plaque perpendicularly**
- ☐ **don´t know**

7. THE INJECTION AREA SHOULD BE MARKED

- ☐ **in the erect state of the penis**
- ☐ **in the flaccid state of the penis**
- ☐ **in either erect or flaccid state of the penis**
- ☐ **don´t know**

Treatment cycles

8. HOW MANY TREATMENT CYCLES ARE RECOMMENDED AT MAXIMUM

- ☐ four
- ☐ six
- ☐ eight
- ☐ don´t know

9. THE INTERVAL BETWEEN TREATMENT CYCLES IS APPROXIMATELY

- ☐ two weeks
- ☐ six weeks
- ☐ ten weeks
- ☐ don´t know

10. EACH TREATMENT CYCLE CONSISTS OF

- ☐ two Xiapex injections
- ☐ three Xiapex injections
- ☐ four Xiapex injections
- ☐ don´t know

Modelling

11. MODELLING BY THE PHYSICIAN IMPLIES THAT

- ☐ at a follow-up visit 1 to 3 days after the first injection of each treatment cycle, a penile modelling procedure should be performed on the erect penis
- ☐ at a follow-up visit 1 to 3 days after the first injection of each treatment cycle, a penile modelling procedure should be performed on the flaccid penis
- ☐ at a follow-up visit 1 to 3 days after the second injection of each treatment cycle, a penile modelling procedure should be performed on the flaccid penis
- ☐ don´t know

12. MODELLING BY THE PATIENT IMPLIES THAT

- ☐ **Stretching should be performed in the flaccid state 3 times a day**
- ☐ **Stretching should be performed in the flaccid state 3 times a day and straightening should be performed in the erect state (after any type of erection) once a day**
- ☐ **Stretching should be performed in the flaccid state 3 times a day and straightening should be performed in the erect state (only after spontaneous erection) once a day**
- ☐ **don´t know**

Risk identification and minimization

13. PATIENTS SHOULD BE TOLD THAT TO MINIMIZE THE RISK OF CORPORAL RUPTURE THEY CANNOT HAVE SEXUAL INTERCOURSE, PROVIDED PAIN AND SWELLING HAVE CEASED

- ☐ **For a week after the 2nd injection in each cycle**
- ☐ **For two weeks after the 2nd injection in each cycle**
- ☐ **For two weeks after the 1st injection in each cycle**
- ☐ **don´t know**

14. XIAPEX IS A NON-HUMAN PROTEIN MEDICINAL PRODUCT AND MAY THEREFORE TRIGGER AN IMMUNOLOGICAL RESPONSE. WITH XIAPEX TREATMENT

- ☐ **No antibodies against the collagenases in Xiapex have been seen. However, there is a theoretical risk of cross reaction with human matrix metalloproteinases that could give rise to a musculoskeletal syndrome and to develop or exacerbate autoimmune disorders.**
- ☐ **Antibodies against the collagenases in Xiapex develop in more than half of patients but have not been shown to affect clinical response or safety of Xiapex. However, there is a theoretical risk of cross reaction with human matrix metalloproteinases that could give rise to a musculoskeletal syndrome and to develop or exacerbate autoimmune disorders.**
- ☐ **don´t know**

15. ARE ANY PARTICULAR PRECAUTIONS NEEDED IN PATIENTS WITH COAGULATION DISORDERS OR THOSE TAKING ANTICOAGULANTS?

- ☐ **Less than 10 % of patients develop local hematoma as a result of treatment. Therefore, no particular precautions need to be taken with patients with coagulation disorders or those taking anticoagulants.**
- ☐ **More than 60 % of patients develop local hematoma. Therefore, use of Xiapex in patients who have received anticoagulants (with the exception of up to 150 mg acetylsalicylic acid daily) within 7 days prior to receiving an injection of Xiapex is not recommended**
- ☐ **Use of Xiapex in patients who have received any type of anticoagulant within 7 days prior to receiving an injection of Xiapex is not recommended**
- ☐ **don´t know**

16. HOW EFFECTIVE WERE THE MATERIALS IN PRESENTING THE SAFETY RISKS ASSOCIATED WITH THE USE OF XIAPEX AND THE MEASURES INTENDED TO PREVENT THESE RISKS?

IDENTIFIED SAFETY RISK	EFFECTIVE	NOT EFFECTIVE
1. Risk of corporal rupture (penile fracture)		
2. Risk of local reactions		
3. Risk of medication errors		
4. Potential risk of injury to the urethra, including in patients with hourglass deformities and ventral plaques		
5. Potential risk for hypersensitivity/anaphylaxis		

6. Potential risk with injection site bleeding in patients with coagulation disorders including those on concurrent anti-coagulation therapy		
7. Potential risk for reactions related to cross-reactivity with endogenous human matrix metalloproteinases (including musculoskeletal syndrome and development/exacerbation of autoimmune disorders)		
8. Making me realize the importance of reporting Adverse reactions in connection with treatment		

If you answered “not effective” on any of the statements, please provide applicable item number (1 to 8) and comment below.

17. IN RETROSPECT, HAVE YOU HAD PATIENTS EXPERIENCING ADVERSE EVENTS THAT WERE NOT DESCRIBED IN THE TRAINING MATERIAL, OR EVENTS THAT COULD HAVE BEEN AVOIDED IF THEY HAD BEEN MORE ACCURATELY DESCRIBED OR WARNED FOR IN THE TRAINING MATERIAL?

If so, we ask you to summarize the type of event(s) here (without patient data). We also ask you to report them, as well as all other not yet reported adverse reactions you may have experienced, according to question 21 below.

DESCRIPTION OF EVENT(S) THAT IS NOT SUFFICIENTLY DESCRIBED IN THE TRAINING MATERIAL AND THEREFORE COULD HAVE BEEN AVOIDED	Reported: YES/NO (If NO, please refer to question 21)

18. IF YOU HAVE EXPERIENCED PATIENTS WITH CORPORAL RUPTURE IN CONNECTION TO XIAPEX TREATMENT, PLEASE DESCRIBE IF YOU HAVE IDENTIFIED RISK FACTORS CAUSED BY INAPPROPRIATE OR INSUFFICIENT INFORMATION TO THE PATIENT, OR IF YOU FOUND OTHER PATIENT SPECIFIC ABNORMALITIES THAT MAY HAVE INCREASED THE RISK FOR RUPTURE.

19. IN CASE OF OCCURRENCE OF ADVERSE EVENTS OR MEDICATION ERRORS, DO YOU HAVE AN IDEA WHICH PART OF THE EDUCATIONAL MATERIAL SHOULD BE AMENDED TO BE ABLE TO PREVENT THESE EVENTS?

20. IN RETROSPECT, ARE THERE ANY FURTHER MATERIALS OR INSTRUCTIONS THAT YOU THINK WOULD HAVE BEEN HELPFUL TO ENSURE A CONSISTENT COMPREHENSION OF THE SAFE ADMINISTRATION OF XIAPEX IN YOUR CLINIC?

21. IN CASE YOU HAVE OBSERVED ANY ADVERSE REACTIONS, IN RESPONSE TO THE TREATMENT THAT YOU SO FAR HAVE NOT REPORTED, SOBI ASKS YOU TO DO SO ACCORDINGLY BY USE OF THE ENCLOSED ADVERSE EVENT REPORT FORM. SPECIFICALLY WE ASK YOU TO PAY ATTENTION TO AND REPORT ANY OBSERVED CORPORAL RUPTURES

BY MAIL: drugsafety@sobi.com

OR BY FAX: +46 8 697 32 30

AND TO YOUR LOCAL AUTHORITY IN ACCORDANCE WITH NATIONAL REGULATIONS.

THANK YOU FOR PROVIDING YOUR VALUABLE INPUT.

Appendix 2 Evaluation of Xiapex educational material in Peyronie's disease – Reminder

According to our registry of distributed and returned surveys, our current understanding is that you have not returned a completed survey.

As agreed with the European Medical Agency, we kindly ask you to respond to the below question by returning this completed survey through email to medical.info@sobi.com.

□ I have already returned a completed survey [Sobi will hence update the registry]
□ I have chosen NOT to return the survey

Since I registered in Sobi's Trained Physicians database;
□ I have NOT used Xiapex in clinical practice
□ I have used Xiapex in clinical practice; then please provide range of treated patients:
- □ 1-9
- □ 10-20
- □ >20

The reason for not returning a completed survey is:
□ I have no intention of using Xiapex in clinical practice
□ Other:

Appendix 3 Consent form - Xiapex Physicians Training Database

Dear Healthcare Provider,

Thank you for requesting training in the administration of Xiapex for patients with Peyronie´s disease.

As agreed with the European Medicines Agency (EMA), a database of physicians who have completed the training programme is being maintained to ensure that only those physicians who are appropriately trained in the correct administration of the product and experienced in the diagnosis and treatment of male urological diseases can have access to Xiapex.

As also agreed with the EMA, Sobi will assess the effectiveness of the training programme through a survey. You will be asked to complete a questionnaire approximately 6 months after completion of the training programme.

In order to fulfil this agreement with the EMA, Sobi is requesting your confirmation of the following. Please read this letter, including the terms and conditions, sign and return as below.

---

1) By signing below I attest that I have fulfilled the physician training programme requirements by reading the treatment training brochure and/or attending a training event for Xiapex treatment of Peyronie's disease.

2) As you have completed your training Sobi requires your permission to:
   a. keep your details in a database
   b. track the provision and return of the training questionnaire

Terms and Conditions: You agree that your information will be held on a database administered by Sobi and that Sobi may contact you (including by email) in relation to the administration or updating of the database or in relation to any other licence requirement. You also agree that we may use your details to record that you have completed the Xiapex training programme and for the evaluation of the programme. Your information will not be used other purposes (e.g. marketing activities). Sobi respect the confidentiality of personal information. Only Sobi, or organisations working with the company in the administration of the above information will have access to your information. It will not be disclosed to any other third parties unless specifically agreed above. Your responses to the questionnaire will be handled anonymously. Your information will not be transferred outside of the European Economic Area. You will at any time have the right to access your information, you can request that your information on the database is amended, or you can withdraw any of the consents that you have given at any time by writing to us at Swedish Orphan Biovitrum AB (publ), att. Medical Information, 112 76 Stockholm, Sweden.

Name of Physician	Click here to enter text.
Title	Click here to enter text.
Specialty	Click here to enter text.
Institution	Click here to enter text.
Address	Click here to enter text.
City	Click here to enter text.
Post code	Click here to enter text.
Country	Click here to enter text.
Telephone number	Click here to enter text.
Mobile phone number	Click here to enter text.
e-mail	Click here to enter text.

I agree to items 1 and 2 and the associated terms and conditions set out above:

Signed: .....

Date: .....

Print name: .....

Name of practice: .....

Name of institution: .....

Return to Sobi at the following address:

Swedish Orphan Biovitrum AB (publ)
Att. Medical Information
112 76 Stockholm, Sweden

OR scan/email OR fax this form to:

medical.info@sobi.com
fax: +46 8 697 2330

Yours sincerely,

SOBI AB

Appendix 4 Sobi Adverse Event Report Form

sobi
Pioneer in Rare Diseases

ADVERSE EVENT REPORT FORM

01Jun2015

Sobi ref no:

Sobi DS: Enter ref number

Please complete the following sections, including as much info as possible.

1. Patient details

Patient's Initials (F-M-L): ☐ Male ☐ Female Pregnant: ☐ Yes ☐ No Date of Birth (dd/mmm/yyyy):

Weight: ☐ kg ☐ lbs Height: ☐ cm ☐ in Age (at onset of event):

2. Primary Suspect Drug (If more than one add additional page)	**Indication**	**Dose, Units** (at AE start)	**Frequency**	**Route**	**Start Date** dd/mmm/yyyy	**Stop Date** dd/mmm/yyyy

Batch number (LOT): ☐ Not available

Expiry date (dd/mmm/yyyy): ☐ Not available

Was a product defect suspected? ☐ Yes ☐ No

3. Adverse Events (AEs) or Special Situations Special Situations include exposure during pregnancy (male or female) and exposure from breastfeeding, Lack of efficacy, Medication Errors, Overdose, Abuse, Misuse, Occupational exposure, Suspected transmission of an infectious agent		**Start Date** dd/mmm/yyyy	**Stop Date or Duration** dd/mmm/yyyy	**Serious**		**Outcome** (see below and choose numbers)
AE no. 1				☐ Yes	☐ No	
AE no. 2				☐ Yes	☐ No	
AE no. 3				☐ Yes	☐ No	
AE no. 4				☐ Yes	☐ No	

If any SERIOUS adverse event, select seriousness criteria (more than one can be chosen)

- ☐ Patient died
- ☐ Life threatening
- ☐ Required inpatient hospitalization
- ☐ Required prolonged hospitalization
- ☐ Resulted in persistent or significant disability/incapacity
- ☐ Congenital anomaly/birth defect
- ☐ Other medically important condition

Outcome, add applicable numbers for each AE above:

Recovered/Resolved = 1 Recovered with sequel = 4

Recovering/Resolving = 2 Fatal = 5

Not recovered/Not resolved = 3 Unknown = 6

If the Patient died

Specify cause of death:

Date of death: dd/mmm/yyyy

Autopsy performed? ☐ Yes ☐ No *If yes, please attach report*

4. Actions taken with Suspect Drug due to the Adverse Events or Special Situations described

a. Was the Suspect Drug discontinued? ☐ Yes, permanently ☐ Yes, temporarily ☐ No

b. Was the dose changed? ☐ Yes, increased ☐ Yes, decreased ☐ No

If Suspect Drug was discontinued or dose changed:

c. Did any Adverse Event (AE) improve? ☐ Yes, AE number: ☐ No, AE number: (see table above for AE number)

If Suspect Drug was stopped:

d. Was the suspect drug re-introduced? ☐ Yes ☐ No

e. If yes, did any AE reappear? ☐ Yes, AE number: ☐ No

5. Possible causes for the event

If the reporter of the event is a **health care professional (HCP)**: Was a Sobi drug suspected to have caused the event? What other possible factors may have contributed to the event?

6. Narrative. Please provide any further relevant information about the Adverse Events or Special Situations, including results of related investigations and interventions (please include reference value for laboratory tests)

7. Other illnesses (for example, other relevant medical conditions, allergies, past drug reactions)

Condition	Onset Date (dd/mmm/yyyy)	Status
		☐ Past ☐ Present
		☐ Past ☐ Present
		☐ Past ☐ Present
		☐ Past ☐ Present
		☐ Past ☐ Present

8. Concomitant Drug(s) (exclude drugs for treatment of the AEs)	Indication	Daily Dosage, Units	Route	Start Date dd/mmm/yyyy	Stop Date dd/mmm/yyyy

9. Reporter Contact Details

Reporter's Qualification: ☐ Physician ☐ Nurse ☐ Pharmacist ☐ Other HCP (specify): ☐ Non HCP (specify):

Reporter's Name:
E-mail:
Reporter's Hospital:
Address:
Phone: Fax:

10. Prescriber Contact Details – Patient's prescribing physician

☐ Same as Reporter

Prescriber's name:
E-mail:
Prescriber's Hospital:
Address:
Phone: Fax:

Case reported to Regulatory Authority by patient/HCP? ☐ Yes ☐ No ☐ Unknown

If the reporter of the information is a **health care professional**: Does the reporter agree to be contacted for follow-up? ☐ Yes ☐ No

If the reporter of the information is a **patient or consumer**: Does the reporter allow Sobi to contact the responsible health care professional for follow-up? ☐ Yes ☐ No

11. Person completing this form (if not the same as reporter or prescriber)

Name: Title: Organization/Company:
E-mail: Phone: Fax: Internal ref no for this case:

12. Date of awareness – to be completed by Sobi personnel and person working on behalf of Sobi

Date you first received the information provided in this report (dd/mmm/yyyy):

Signature: **Date** (dd/mmm/yyyy):

Please return to: Drug Safety Swedish Orphan Biovitrum, SE-112 76 Stockholm, Sweden
FAX: +46 8 697 32 30 Phone: +46 8 697 20 00 (switchboard) e-mail: drugsafety@sobi.com