NOVARTIS

Novartis Research and Development

Non-Interventional Study Protocol (PASS)

ICL670 (deferasirox)

REDACTED PROTOCOL

Protocol CICL670A2429

Title	Survey to assess physicians' knowledge of Exjade posology and biological monitoring recommendations as described in the Educational Materials
Protocol version identifier	v01(Clean)
Date of last version of protocol	20-Jul-2023
EU PAS register number	Study not registered yet
Active substance	Deferasirox (ATC code: V03AC03)
Medicinal product	Exjade® (deferasirox)
Product reference	EU/1/06/356/011-022
Procedure number	EMEA/H/C/000670

Name and address of marketing authorization holder	Novartis Europarm Limited, Vista Building Elm park, Merrion Road, Ireland, regulatory.nel@novartis.com
Joint PASS	No
Research question and objectives	The objective of this survey is to assess the knowledge of HCPs in relation to the recommended posology and biological monitoring for Exjade, based on the current locally valid Exjade educational materials (including the physician's reference checklist)
Countries of study	Austria, Belgium, France, Germany, Poland, Italy, Hungary, Spain, Sweden, UK
Authors	[redacted], PhD, [redacted], [redacted] [redacted], [redacted], Novartis

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List of abbreviations

CI	Confidence Interval
CRO	Contract Research Organization
DT	Dispersible Tablet
EEA	European Economic Area
EMA/EMEA	European Medicines Agency
EMs	Educational Materials
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FCT	Film-Coated Tablet
GPP	Good Pharmacoepidemiology Practices
HCP	Healthcare provider
ICMJE	International Committee of Medical Journal Editors
NCA	National Competent Authority
NIS	Non-Interventional Study
PASS	Post-Authorization Safety Study
PRAC	Pharmacovigilance and Risk Assessment Committee
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UK	United Kingdom

1 Responsible parties

Table 1-1 Responsible parties

Company	Address	Role/Responsibilities
[redacted]	[redacted] USA	Contract Research Organization (CRO) / Conduct of survey
Novartis Europharm Limited	Vista Building Elm Park, Merrion Road Dublin 4, Ireland	Marketing Authorisation Holder
Novartis Pharma AG	Lichtstrasse 35 4056 Basel Switzerland	Sponsor

2 Abstract

Title

Survey to assess physicians' knowledge of Exjade posology and biological monitoring recommendations as described in the Educational Materials .**Version and date**

v01, 20 July 2023

Name and affiliation of main authors

[redacted], [redacted]

[redacted] Novartis Pharma AG

Rationale and background

Compliance with the posology and biological monitoring requirements for Exjade is one of the important potential risks included in the current EU (European Union) risk management plan (RMP), version 20.1. This potential risk listed in the RMP is currently addressed by routine pharmacovigilance activities. It is also addressed by additional risk minimization activities which include updated labeling and Educational Materials (EMs). To assess the impact of the above-mentioned activities in relation to this potential risk, the European Medicines Agency (EMA) had requested Novartis to conduct two physician surveys (CICL670A2425 conducted in 2015 and NO6987 conducted in 2018-2019). The results of the last completed survey showed only a modest physicians' understanding of dosing and biological monitoring recommendations for Exjade. For example, the correct response rate was 66% for administration and dosing questions and 64% for biological monitoring questions in survey NO6987.

As a result of survey NO6987, the EMs were updated with the creation of a new Physician's reference checklist. This new Physician's reference checklist was created to further support the appropriate and safe use of the Exjade in the EU. The updated EMs were developed by taking into consideration feedback obtained from PRAC (Pharmacovigilance and Risk Assessment Committee) and represent a more comprehensive and improved version of these prescribing aids.

The prior version of the EMs and Physician's reference checklist (which was based on RMP v17.1) was distributed in the EU as per local country requirements. The distribution campaign started on 17-Dec-2020 and was completed in 2021. Subsequently, the EMs and Physician's reference checklist were further updated (at the time when changes were made to RMP v20.1) and were distributed in the EU as per local country requirements. The distribution campaign started on 12-Oct-2022 and is ongoing. Of note, in some EU countries the changes introduced in the updated EMs (based on RMP v20.1) did not warrant a new distribution; therefore, in some countries the updated EMs and Physician's reference checklist were not distributed and the current locally valid EMs are those which were distributed in 2021. In both distribution campaigns, the targeted pyhsicians were those who prescribe Exjade/deferasirox based on their medical specialization such as oncologists or hematologists. Although the receipt of the EMs was tracked, it was not feasible to ensure that physicians read the EMs.

The need to assess the effectiveness of the updated EMs was highlighted by the PRAC during the assessment of the previous survey NO6987 (procedure EMEA/H/C/000670/II/0068

submitted in July-2019). In line with that request, this protocol describes a new physician survey, aiming at evaluating physician's knowledge of Exjade (deferasirox) posology and biological monitoring recommendations as described in the current locally valid EMs (including Physician's reference checklist). Both the EMs and the checklist are aligned with the approved Exjade EU SmPC. Results of this survey will be used to assess the impact of the risk minimization measures on the appropriate use of Exjade (deferasirox).

Research question and objectives

The main objective of this survey is to assess whether sufficient levels of knowledge of posology and biological monitoring recommendations as described in the Exjade EU Summary of Product Characteristics (SmPC) can be attained among prescribers of Exjade/deferasirox, through the provision of Exjade EMs (which includes a Physician's reference checklist) developed by Novartis.

The survey will consist of two sections assessing the following (see Appendix 1 in Section 13.1 for full survey instrument):

- Posology of Exjade (deferasirox)
- Biological monitoring associated with the prescribing of Exjade (deferasirox)

Success criteria of the survey are based on the observed mean correct response rate for each section. A threshold of the observed mean correct response rate of at least 70% or more will be considered as a success for each section of the survey.

Study design

This is a multi-national, cross-sectional, non-interventional survey. It will be conducted among prescribers (physicians) in 10 countries: Austria, Belgium, France, Germany, Hungary, Italy, Poland, Spain, Sweden and the United Kingdom.

Physicians will be recruited from national databases containing contact information for health care professionals in each of the 10 countries planned to be included in the survey. Only physicians who have prescribed Exjade and/or generic versions of deferasirox will be screened. Feasibility for attainment of each sample size in each country (detailed in Section 7.5) was determined in consultation with medical professional survey panel companies (e.g. M3 Global Research, Survey Healthcare Global). Novartis will make every effort to target prescribers who have received EMs.

Following recruitment, prescribers' knowledge of posology and biological monitoring recommendations will be evaluated using an online survey. Each invitation will include information on how to access the survey online, and will include a unique link for each prescriber to ensure that the invitation is used only once.

For ease of understanding of the invitation and of the survey, all of the physician outreach (including any reminder letters) will be conducted in the local country language.

The survey will consist of multiple choice and close-ended questions. No open-ended questions will be included. Multiple choice questions will include distractor or intentionally incorrect response options.

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

The screening questions in the survey include questions to assess inclusion and exclusion criteria for participation.

Setting and study population

A sample of approximately 400 Exjade (deferasirox) prescribers will be recruited for this study from 10 countries: Austria, Belgium, France, Germany, Hungary, Italy, Poland, Spain, Sweden and the UK (United Kingdom). The recruitment will be derived from national databases containing physicians that would be eligible to prescribe Exjade/deferasirox.

Variables

The following variables will be collected:

1. Variables related to physician participation
    - Response rate
    - Refusal rate
2. Variables related to physician practice information:
    - Location (country)
    - Physician primary specialization
    - Years practicing as a physician
    - Practice setting (Comprehensive Care Center, treatment center, hospital hematology department, other)
    - Past experience with Exjade/deferasirox (years of experience, overall number of patients)
    - Time since last prescription of Exjade/deferasirox
3. Variables related to physician knowledge related to:
    - Posology of Exjade (methods of administration, starting dose, lowering dosage, maximum daily dose, serum ferritin value at which treatment should be interrupted)
    - Biological monitoring recommendations for Exjade, i.e. monitoring recommendations before treatment with deferasirox, creatine clearance level for deferasirox contraindication, monitoring recommendations after initiation of deferasirox, recommended courses of action as a function of specific lab values (e.g. renal, liver labs), monitoring recommendations during treatment with deferasirox, dosing in pediatric patients with non-transfusion-dependent thalassemia, monitoring recommendation for serum ferritin, preferred test for iron overload in patients with non-transfusion-dependent thalassemia, monitoring recommendation for auditory/ ophthalmic testing
4. Confirmation of review of Educational Materials

- Respondent verification if they have received Exjade EMs, if they reviewed the EMs and if not received/not reviewed, what is the primary source of information used to learn about deferasirox dosing and biological monitoring recommendations.

Data sources

HCPs (Healthcare providers) will be recruited from the target population of HCPs who may prescribe Exjade/deferasirox and have received Exjade Educational Materials. If after two reminders the target sample size has not been achieved, the sample may be supplemented through additional outreach based on internet research or outreach through applicable professional societies, inclusion of additional countries within the EU/EEA, or extension of the survey period until approximately 400 completed surveys have been obtained. All data for this study will be gathered using the survey provided in Appendix 1.

Study size

Total sample size for this study is set to include approximately N=400 survey respondents.

Data analysis

The primary outcome of the survey is the mean correct response rate (in percentage) for each survey section. This is calculated by taking the average of the proportion of correct responses within each section based on all physicians participating in the survey. The survey questionnaire (Appendix 1) constitutes of multiple-choice questions with a correct response for each question consistent with the current locally valid EMs and Exjade EU SmPC. The proportion responding correctly will be tabulated separately for each item in the survey instrument. Point estimates for the proportion with correct responses will be calculated for each question. In the case of multiple-choice questions, the number and proportion of prescribers reporting each response will also be provided. Success criteria of the survey is based on the observed mean correct response rate meeting a threshold of at least 70% for each of the two sections of the survey:

i. Administration and dosing of Exjade (questions A.1 to A.8),

ii. Biological monitoring during Exjade treatment (questions B.1 to B.14).

Milestones

Tentative dates of study milestones:

Registration in the EU PAS register: Prior to start of data collection

Start date of data collection: 1Q 2024

Last date of data collection: 3Q 2024

Final report of study results: 4Q 2024

3 Amendments and updates

None.

4 Milestones

Table 4-1 Tentative dates of study milestones

Milestone	Planned date
Start of data collection	1Q 2024
End of data collection	3Q 2024
Final report of study results	4Q 2024
Registration in the EU PAS register	Prior to start of data collection

5 Rationale and background

Background

In the European Union (EU), deferasirox was first approved in 2006 under the tradename Exjade®. It is currently approved for the treatment of chronic iron overload due to frequent blood transfusions (≥ 7 ml/kg/month of packed red blood cells) in patients with beta thalassemia major aged 6 years and older.

It is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups:

• In pediatric patients with beta thalassemia major with iron overload due to frequent blood transfusions (≥ 7 ml/kg/month of packed red blood cells) aged 2 to 5 years

• In adult and pediatric patients with beta thalassemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older

• In adult and pediatric patients with other anemias aged 2 years and older

Further, Exjade is also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

Exjade was first registered as a dispersible tablet (DT) formulation in dose strengths of 125 mg, 250 mg, and 500 mg. In 2016, a film-coated tablet (FCT) formulation in dose strengths of 90 mg, 180 mg, and 360 mg was also approved. Currently, Exjade is available in the EU only as a FCT, since the DT formulation was discontinued as of 01-Mar-2021 and was removed from the EU Exjade labeling documents as of 21-Dec-2021. In addition, as of January 2023, no other manufacturer commercialized a DT formulation in any of the countries planned to be included in the proposed survey.

Compliance with the posology and biological monitoring requirements for Exjade is one of the important potential risks included in the current effective EU risk management plan (RMP), version 20.1. This potential risk listed in the RMP is currently addressed by routine pharmacovigilance activities. It is also addressed by additional risk minimization activities which include labeling and Educational Materials (EMs).

To assess the impact of the above-mentioned activities on this potential risk, the European Medicines Agency (EMA) has requested the conduct of two physician surveys (CICL670A2425 conducted in 2015 and NO6987 conducted in 2019). The results of these 2 completed surveys

showed only a modest physicians' understanding of dosing and biological monitoring recommendations for Exjade. For example, the correct response rate was 66% for administration and dosing questions and 64% for biological monitoring questions in survey NO6987.

As a result of the last conducted surveys NO6987, the EMs were updated with the creation of a new Physician's reference checklist for Exjade. This was included to support the appropriate and safe use of the Exjade in the EU. The updated EMs and Physician's reference checklist were developed by taking into consideration feedback obtained from PRAC and represent a more comprehensive and improved version of these prescribing aids.

Purpose and Rationale

The need to assess the effectiveness of the current locally valid EMs was highlighted by PRAC during the assessment of the previous survey (procedure EMEA/H/C/000670/II/0068). In line with that request, this protocol describes a new physician survey, aiming at evaluating physician's knowledge of Exjade (deferasirox) posology and biological monitoring recommendations. Results of this survey will be used to assess the impact of the risk minimization measures on the appropriate use of Exjade (deferasirox).

Dates of start and completion of the communication campaign

The following recent versions of the RMP were associated with an update of the EM:

RMP version 17.1 (procedure EMEA/H/C/000670/II/68). This was released to countries for further distribution to HCPs on 17-Dec-2020. The corresponding dispatch of the local version was completed at national EU level in 2021.

RMP version 20.1 (procedure EMEA/H/C/000670/II/82/G). Updates to EMs were made with this RMP version; primarily to reflect the discontinuation of the dispersible tablets. This was released to countries in 12-Oct-2022. Local dispatch (when applicable) is ongoing.

Targeted physicians for the distribution of updated checklist and EMs

The dissemination plan for RMP EMs has been agreed by each National Competent Authority but in principle the targeted physicians are those who may prescribe Exjade/deferasirox based on their medical specialization such as oncologists or hematologists. In most countries, tracking of receipt is done by monitoring returns/unsuccessful deliveries.

6 Research question and objectives

The central research question and main objective of this study is if, with the provision of current locally valid EMs (including Physician's reference checklist) developed by Novartis released with RMP versions 17.1 and 20.1, sufficient levels of knowledge of posology and biological monitoring recommendations as described in the Exjade EU Summary of Product Characteristics (SmPC) can be attained among prescribers of Exjade/deferasirox.

The survey will consist of two sections assessing the following (see Section 13.1 Appendix 1 – HCP Survey questionnaire for full survey instrument):

- Posology of Exjade (deferasirox)

- Biological monitoring associated with the prescribing of Exjade (deferasirox)

Physician knowledge will be evaluated in each of the two key sections separately: posology of Exjade, and biological monitoring recommendation for Exjade. Success criteria of the survey is based on the observed mean correct response rate for each section. A threshold of the observed mean correct response rate of at least 70% or more will be considered as a success for each section of the survey.

7 Research methods

7.1 Study design

This is a multi-national, cross-sectional, non-interventional survey conducted among Exjade prescribers (physicians) in 10 countries: Austria, Belgium, France, Germany, Hungary, Italy, Poland, Spain and Sweden and the United Kingdom. The survey will assess the knowledge of HCPs prescribing deferasirox in relation to the management of posology and biological monitoring needed in patients treated with Exjade. The survey will endeavor to collect approximately 400 completed surveys.

Physicians will be recruited from national databases containing contact information for health care professionals in each of the 10 countries. Only physicians who have prescribed Exjade and/or generic deferasirox will be screened in. Feasibility for attainment of each sample size in country (detailed in Section 7.5) was determined in consultation with medical professional survey panel companies (e.g. M3 Global Research, Survey Healthcare Global). Novartis will make every effort to target prescribers who have received the current locally valid EMs.

Following recruitment, prescribers' knowledge of posology, and biological monitoring recommendations will be evaluated using an online survey. Each invitation will include information on how to access the survey online, and will include a unique link for each prescriber to ensure that the invitation is used only once.

To ensure comprehension of the invitation and survey, correspondence with the physicians (including any reminder letters) will be held in the local country language.

The survey will consist of multiple choice and close-ended questions. No open-ended questions will be included. Multiple choice questions will include distractor or intentionally incorrect response options.

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

The screening questions in the survey include questions to assess inclusion and exclusion criteria for participation.

7.2 Setting

This survey is offered only online. Experience with similar surveys has shown that physicians prefer to complete the surveys online, rather than by telephone or in person. Online surveys allow greater flexibility of completing the survey at a time convenient to the physician, any time of the day and any day of the week. Data collected from similar surveys indicate that the very small numbers of physicians who choose not to access the internet are similar in characteristics to those who complete the survey online.

The survey design is based on experience from risk management evaluation surveys/studies previously completed by Novartis [redacted] in Europe. Recruitment and analytic strategies included in this protocol are similar to those programs. Physicians in the following countries will be included in the final study sample: Austria, Belgium, France, Germany, Hungary, Italy, Poland, Spain, Sweden and the United Kingdom.

A sample of approximately 400 Exjade/deferasirox prescribers will be recruited for this study. The recruitment will be from national databases containing physicians that would be eligible to prescribe deferasirox. From these, those will be identified who have prescribed Exjade and/or deferasirox and are willing to participate in the survey. Physicians will need to fulfill the inclusion / exclusion criteria for participation in the survey. The proportion of physicians who do not qualify will be reported to inform the representativeness of the sample. From prior experience, it is estimated that approximately 12% of physicians contacted will agree to participate in the survey. This means that about 3350 physician survey invitations will have to be sent to reach the targeted number of approximately 400 prescribers participating in the survey. The sampling frame will be from national database lists of specialists in each of the 10 countries who have agreed to participate in surveys, with their email contact information available. Prescribers will be contacted throughout the period of recruitment and data collection. The survey is anticipated to last a minimum of 2 months in each country. The physicians will be recruited through an invitation to participate in the survey sent by email. The invitation will direct the physician to the survey website to complete the survey. If there is no response after the first invitation, then reminder invitations will be sent weekly via email after the first invitation until full sample is achieved.

Physicians will be paid at fair market value for a survey estimated to take 30 minutes to complete. Fair market value varies by market and ranges from the equivalent of approximately 50 – 75 Euros for the countries included in this study.

The following inclusion and exclusion criteria will be applied to the physician survey:

Inclusion criteria

Physicians will be required to meet all of the following inclusion criteria:

- Must provide consent for participation
- Must spend ≥50% of time in direct patient care
- Have treated patients with transfusional iron overload or non-transfusion-dependent thalassemia with chelation therapy during the last 12 months.
- Have prescribed Exjade and/or generic deferasirox within the last 12 months.

Exclusion criteria

Physicians meeting the following criterion will not be eligible to take the survey:

- Currently employed by a pharmaceutical company, health care company, market research company, advertising agency, or government agency involved in pharmaceutical research or marketing.

7.3 Variables

Physician knowledge will be evaluated in each of the two key sections separately: posology of Exjade, and biological monitoring recommendation for Exjade. Success criteria of the survey will be based on the observed mean correct response rate for each section. A threshold of correct response rate of at least 70% or more will be considered as a success for each section of the survey.

The mean correct response rate (in percentage) for each survey section is calculated taking the average of the proportion of correct responses within each section (total number of correct responses X 100/total number of questions in each section) based on all physicians participating in the survey.

The survey questionnaire is provided in Appendix 1 – HCP Survey questionnaire of this protocol.

The following variables will be collected:

1. Variables related to physician participation
    - Response rate
    - Refusal rate
2. Variables related to physician practice information:
    - Location (country)
    - Physician primary specialization
    - Years practicing as a physician
    - Practice setting (Comprehensive Care Center, treatment center, hospital hematology department, other)
    - Past experience with Exjade/deferasirox (years of experience, overall number of patients)
    - Time since last prescription of Exjade /deferasirox
3. Variables related to physician knowledge related to:
    - Posology of Exjade (methods of administration; starting dose, lowering dosage, maximum daily dose, serum ferritin value at which treatment should be interrupted)
    - Biological monitoring recommendations for Exjade, i.e. monitoring recommendations before treatment with deferasirox, creatine clearance level for deferasirox contraindication, monitoring recommendations after initiation of deferasirox, recommended courses of action as a function of specific lab values (i.e. renal, liver labs), monitoring recommendations during treatment with deferasirox, dosing in pediatric patients with non-transfusion-dependent thalassemia, monitoring recommendation for serum ferritin, preferred test for iron overload in patients with

non-transfusion-dependent thalassemia, monitoring recommendation for auditory/ ophthalmic testing

4. Confirmation of Review of current locally valid Educational Materials
   - Respondent verification if they have received current locally valid EMs for Exjade, if they reviewed the EMs and what is the primary source of information used to learn about deferasirox dosing and biological monitoring recommendations.

7.4 Data sources

All data for this study will be gathered using the survey provided in Section 13.1 Appendix 1 – HCP Survey questionnaire. HCPs will be recruited from the target population of HCPs who may prescribe Exjade/deferasirox Novartis will make every effort to target prescribers who have received the current locally valid EMs. If after two reminders the target sample size has not been achieved, the sample may be supplemented through additional outreach based on internet research or outreach through applicable professional societies. Also, additional EU/EEA countries may be included, and the survey period may be extended until approximately 400 completed surveys have been obtained.

7.5 Study size

The total sample size for this study is set to include approximately N=400 survey respondents. From prior experience, it is estimated that approximately 12% of physicians contacted will agree to participate in the survey. Approximately 3350 physician survey invitations will have to be sent to reach the targeted number of approximately 400 prescribers participating in the survey. The number of participating prescribers in each country is approximately proportional to the volume of Exjade prescriptions/patient exposure in the country. Estimated sample sizes by market are provided in Table 7-1 below. The sample size in the UK will be capped at 50 participants.

Table 7-1 Target Samples Size by Country

Country	Sample size
Italy	115
Spain	88
United Kingdom	50 (maximum)
France	48
Germany	44
Austria	15
Poland	13
Sweden	10
Hungary	9
Belgium	8
Total	**400**

7.6 Data management

All data collected during the survey will be collected via an internet-based survey and will be held confidential. No identifying information will be captured in the survey. Data and data

tables will be managed using the statistical software called Q. Data will be stored on [redacted] dedicated servers.

7.7 Data analysis

The analysis population will comprise all physicians recruited into the survey, meeting eligibility criteria as assessed in the survey screener and completing the survey.

7.7.1 Statistical Analyses

All analyses will be performed by [redacted].

The survey analysis is descriptive in nature. It does not evaluate an *a priori* hypothesis. For continuous variables, counts, means (with standard deviations), medians and ranges will be provided. For categorical variables, frequencies and percentages (with 95% confidence intervals) will be provided.

The proportion of specialists who do not qualify will be reported to inform the representativeness of the sample.

The primary outcome is the mean correct response rate (in percentage) for each survey section is calculated taking the average of the proportion of correct responses within each section based on all physicians participating in the survey. The survey questionnaire (Appendix 1) constitutes of multiple-choice questions with a correct response for each question consistent with the current locally valid EMs and Exjade EU SmPC. The proportion responding correctly will be tabulated separately for each item in the survey instrument.

Point estimates for the proportion with correct responses will be calculated for each question. In the case of multiple-choice questions, the number and proportion of prescribers reporting each response will also be provided.

The following are measures to minimize bias in the sample:

- Physicians will be recruited from national databases in each country containing email contact information for potential respondents.
- The sample of participating physicians will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies implemented are intended to recruit a heterogeneous sample of physicians for participation.
- Respondents who work for or have immediate family members who work for a pharmaceutical or market research company are excluded.
- Respondents will be provided a unique link to gain access to the online survey. After full sample is achieved, links will be deactivated.

The following are measures to minimize bias in the survey:

- All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated in the survey documentation and the computer system will automatically direct the respondent to the next appropriate question based on their previous response. Respondents cannot go back to a question once the

question has been answered and cannot skip ahead. All questions must be answered in sequence to complete the survey.

- Response options presented in a list will be randomized to minimize positional bias, where appropriate.

In order to avoid missing data, respondents will be asked every question in the survey and their survey will not be considered complete until all questions in their survey have been answered.

Information obtained from the survey will be reported as descriptive statistics for the survey administration, population, and questions. The following will be reported as part of this analysis:

- The number of invitations issued
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents who completed the survey
- Description of survey participants:
  - Country
  - Medical specialty
  - Type of medical practice (public/private activity)
  - Years in medical practice
  - Gender
- Self-reported receipt and review of educational materials
- Frequency distribution of responses to each question (the number of respondents who give each answer to each question).
- Primary outcome: mean correct response rate (in percentage) for each survey section, Posology of Exjade (deferasirox), Biological monitoring associated with the prescribing of Exjade (deferasirox)
- Responses will be stratified by country and prescriber medical specialty.
- Additional analyses may be performed as needed.

7.7.2 Success Criteria

Success criteria of the survey are based on the observed mean correct response rate for each section. A threshold of the observed mean correct response rate of at least 70% or more will be considered as a success for each of the two sections of the survey: i. Administration and dosing of Exjade (questions A.1 to A.8), ii. Biological monitoring during Exjade treatment (questions B.1 to B.14).

The mean correct response rate (in percentage) for each survey section is calculated taking the average of the proportion of correct responses within each section based on all physicians participating in the survey.

7.7.3 Analysis of Additional Survey Questions

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

7.7.4 Sample size and precision

It is targeted that approximately 400 physicians will complete the survey. This would be associated with a precision level of 5% assuming a worst-case scenario of 50% proportion of correct responses based on a 2-sided 95% confidence interval (CI) and extending the number of additional EU countries participating in the survey.

In order to reach this target and based on experience on prior Exjade surveys, the aim is to send invitations to approximately 3350 physicians, of whom about 12% are expected to complete the survey. However, neither the number of participant physicians nor the proportion of correct responses can be predicted with certainty.

Therefore, Table 7-2 provides a range of expected precision, based on the binomial CI, for the target sample size of 400. For smaller sample sizes in subgroups, the precision would be reduced.

Table 7-2 Estimated precision of observed rates for different sample sizes (2-sided 95% Confidence Interval)

Sample size	Observed correct response rate	Lower Limit	Upper Limit	Precision/Half-width
400	50%	44.99%	55.01%	5.01%
400	60%	55.01%	64.84%	4.91%
400	70%	65.25%	74.45%	4.60%
400	80%	75.74%	83.81%	4.04%
400	90%	86.63%	92.76%	3.06%
400	95%	92.38%	96.92%	2.27%

The lower and upper limits are calculated using Binomial 95% Confidence Intervals (2-sided)

7.7.5 Subgroups analyses

Although the focus of the analyses and report will be on the overall population of physicians who completed the survey, additional subgroups analyses for some variables may be performed if considered of interest and if the number of respondents in the considered subgroups is considered sufficient, e.g. correct response rate in participants who confirmed they received / reviewed the EMs and those who did not confirm receipt / review of the EMs.

7.8 Quality control

Programming will be reviewed by quality control and pretests will be conducted among a small number of physicians in each country prior to implementing the survey, to ensure questionnaire comprehension and clarity.

During fielding, weekly data checks are conducted to identify respondents who:

- Complete the survey too quickly to have adequately considered their responses
- Provide unrealistic or contradictory information about themselves, practice, etc.

- Provide highly repetitious responses (sometimes referred to as straight-lining).

Respondents are evaluated on a case-by-case basis and will be flagged as bad data and be removed as needed.

7.8.1 Data quality management

Applicable SOPs will be followed to ensure data quality and integrity, including validation and user acceptance testing of the survey database, validation of derived variables and analysis programs, documentation of data cleaning, and description of available data. [redacted] will assure database quality processes are followed in accordance with the data validation plan.

7.8.2 Data recording and document retention

This is not applicable as physicians will not be providing any information about specific patients

7.9 Limitations of the research methods

The main limitation specific to the proposed survey A2429 pertains to the different versions of the EMs that are locally valid. This will be addressed by appropriate subgroup analyses.

Other limitations inherent in the survey design include that the sample of physicians who are invited to participate will be self-selecting from a national database of doctors who voluntarily respond to the invitation and agree to participate in market research. However, the survey recruitment strategies are intended to recruit a heterogeneous sample of prescribers for participation within the screening criteria outlined.

7.10 Other aspects

None.

8 Protection of human subjects

Participating physicians will not provide any information about specific patients. All data collected during the survey will be collected via an internet-based survey and will be held confidential. No identifying information will be captured in the survey.

Informed consent procedures

Survey participation is voluntary. The survey will begin with a question indicating the physician's agreement to participate in the survey. If the individual does not agree, the survey will be ended. Ethics approval will be sought as required by individual countries.

Regulatory and ethical compliance

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of subjects participating in non-interventional studies are protected (consistent with the principles that have their origin in the Declaration of Helsinki) and that the study data are credible and responsibly reported.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2016), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke et al 2007), and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct' (European Medicines Agency 2010).

9 Management and reporting of adverse events/adverse reactions

Not applicable for this physician survey

10 Plans of disseminating and communicating study results

Upon survey completion and finalization of the survey report, the results of this non-interventional survey may be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

The final manuscript will be submitted to EMA and the competent authorities of the Member States in which the product is authorized within two weeks after first acceptance for publication.

11 References

European Medicines Agency (2010) The ENCePP Code of Conduct – for Scientific Independence and Transparency in the Conduct of Pharmacoepidemiological and Pharmacovigilance.

International Society for Pharmacoepidemiology (2016) Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf; 25:2-10.

Vandenbroucke JP, von Elm E, Altman DG, et al (2007) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Ann Intern Med; 147(8):W163-94.

12 Annexes

12.1 Annex 1 – List of stand-alone documents

Table 12-1 List of stand-alone documents

Number	Document reference number	Date	Title
1	Not Applicable	DD MM 2023	Survey Invitation Letter
2	Not Applicable	21 Jul 2022	Educational materials and Check list approved with RMPv20.1
3	Not applicable	26 Nov 2020	Educational materials and Check list approved with RMPv17.1

12.2 Annex 2 – ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacovigilance (EnCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorization safety study (PASS) to a regulatory authority (see the Guidance on the format and the content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Survey to assess physicians' knowledge of Exjade posology and biological monitoring recommendations as described in the Educational Materials

EU PAS Register® number: Not Registered yet
Study reference number (if applicable): CICL670A2429

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				4
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
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 question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	5
2.1.2 The objective(s) of the study?	☒	☐	☐	6
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	7.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	7.1, 7.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	7.3
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 case of primary data collection)	☐	☐	☒	

[1]Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2]Date from which the analytical dataset is completely available

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	7.2, 7.4
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	4, 7.1
4.2.2 Age and sex	☐	☒	☐	
4.2.3 Country of origin	☒	☐	☐	7.1
4.2.4 Disease/indication	☒	☐	☐	5,7.1
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)	☒	☐	☐	7.1, 7.2, 7.4

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)	☐	☐	☒	
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?	☒	☐	☐	6, 7.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	7.3
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)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care 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)	☒	☐	☐	7.7, 7.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	7.7, 7.9

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)	☒	☐	☐	7.7

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)	☒	☐	☐	7.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	7.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	7.3
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)	☒	☐	☐	7.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	7.3, 7.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	7.3
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?	☒	☐	☐	7.7.1
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	7.7.4
10.3 Are descriptive analyses included?	☒	☐	☐	7.7.1
10.4 Are stratified analyses included?	☒	☐	☐	7.7.1, 7.7.5
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?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

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)	☒	☐	☐	7.6, 7.8.2
11.2 Are methods of quality assurance described?	☒	☐	☐	7.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

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?	☒	☐	☐	7.9
12.1.2 Information bias?	☒	☐	☐	7.9
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)	☒	☐	☐	7.5

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	8
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	8

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?	☒	☐	☐	3

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)?	☒	☐	☐	10
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	10

Comments:

Name of the main author of the protocol: _____

Date:19/01/2023

Signature: _____

12.3 Annex 3 – Additional information

None

13 Appendices

13.1 Appendix 1 – HCP Survey questionnaire

SCREENER

Intro1.

Thank you for agreeing to participate in this market research online survey. We are recruiting on behalf of [redacted] a research agency acting on behalf of a pharmaceutical company. [redacted] is totally independent as a company and would like you to be completely honest with your views. Everything you say will be treated in total confidence.

The purpose of this study is to better understand Physicians' of administration, dosing and monitoring requirements for a particular drug.

Begin text for MAIN fielding ONLY intro**********

Intro2.

The questionnaire will be an online survey and should take approximately 30 minutes to complete. Your responses will automatically save as you proceed, therefore you may close and rejoin the survey at any point. Please note however that you will not be able to return to questions once they have been answered. Upon completion of the survey, you will receive remuneration in appreciation of your time and cooperation. This will have been confirmed in a separate notification.

We will comply with all national laws protecting your personal data and with relevant guidelines including Insights Association, Intellus Worldwide (formerly PMRG and PBIRG), ESOMAR, EphMRA, BHBIA, ADM/BVM and all other relevant national codes of practice. The aim of this market research is to gain your views and is not intended to be promotional and no one will try to sell you anything. All information provided will remain confidential and will only be reported as group data with no identifying information.

I confirm that I am happy to take part in this market research interview voluntarily and know that I may terminate the survey or withhold information if I so wish.

I understand that all data from this survey will only be used for market research purposes.

I will treat all information presented to me during this study as confidential. Any information presented during the course of this research is done solely to explore reactions to such information and should therefore be assumed to be hypothetical. The research presented should not be used to influence decisions outside this market research.

Any information I provide will be treated as confidential and I will remain anonymous.

I confirm that if I am employed by a public entity, I have the necessary permission to participate in this market research interview.

Please click here to view [redacted] statement regarding data protection, privacy, invisible processing and ways to contact [redacted]

INSERT PRIVACY STATEMENT

Please click here to view [redacted] Consumer Privacy Statement [INSERT CCPA LINK FROM:// [redacted]

Please click here to view <Recruitment Agency> privacy policy regarding protecting your personal data.

Do you agree to participate in this research survey under these conditions?

1 Yes 2 No terminate

New screen

Intro3.

YOUR RIGHTS UNDER DATA PRIVACY LAWS

Under data protection legislation when your personal information is processed, you have certain rights. These rights include but are not limited to: you being able to request a copy of the information which organisations hold on you; a right (in certain circumstances) to object to processing; to withdraw your consent. Please see the recruitment agency's and [redacted] privacy policy for full details on how to exercise these rights.

[redacted] will only hold your personal data for the purpose of your participation in the market research study. Your personal data will be deleted or destroyed at the end of the project. If you made a subject access request to us after the end of the project, we would be unable to identify any information attributed to you. You would need to request the information from the recruitment agency.

Are you happy to participate with this interview on this basis?

1 Yes 2 No terminate

End text for MAIN fielding ONLY intro**********

S0a.

This is an online market research study and how you answer will, of course, be treated in confidence. However, should you raise during the study any safety information related to the sponsoring company's product(s) including adverse events, we will need to report this even if you have already reported it directly to the company or the regulatory authorities using the normal reporting processes.

In such a situation, do you give permission to waive the confidentiality given to you under the Market Research Society Codes of Conduct specifically in relation to that adverse event? The other responses you provide throughout the study will continue to remain confidential. If you wish, you may remain anonymous in the report.

1	Yes, I waive confidentiality regarding adverse event reporting
2	No, I wish to remain anonymous
3	I no longer want to participate in this study TERMINATE

Recontact (not Adverse Reporting)

S0b.

We may want to further explore your responses to some of the questions answered. Would you be prepared to be re-contacted by the recruiting agency to take part in any follow up research on this topic?

1 Yes 2 No

S0c.

By proceeding to the next screen, I confirm that I have read, understood, and accept the statements presented in the previous screens and I am happy to proceed with the market research survey on this basis.

1	YES, I am happy to proceed with the market research survey on this basis
2	NO, I am not happy to proceed with the market research survey on this basis and I do not wish to continue TERMINATE

S0d.

Are you employed by a pharmaceutical company, health care company (e.g. drug store or drug distributer), market research company, advertising agency or government agency involved in pharmaceutical research or marketing?

1	Yes	terminate
2	No	

S1.

What is your primary specialty?

randomize

1	Hematology/oncology	
2	Adult Hematology	
3	Pediatric Hematology	
4	Thalassemiology	
5	Surgical Oncology	terminate
6	Endocrinology	terminate
7	Pulmonology	terminate
95	Other (specify):	

S2.

How many years have you been in medical practice?

1	Less than 5 years
2	5 – 10 years
3	More than 10 years

S3.

What percent of your professional time is spent in direct patient care?

1	Below 50% of time in direct patient care	terminate
2	50-75%	
3	More than 75%	

S4.

What is the predominant type of medical practice where you prescribe iron chelation therapy?

1	Public practice
2	Private practice
3	Part public/private practice
95	Other (specify)

S5.

How many patients are you actively following with the conditions below that have chronic iron overload and are treated with chelation therapy?

1	Patients with transfusional iron overload	_____
2	Patients with non-transfusion-dependent thalassemia	_____
3	Other patients with chronic iron overload	_____
	TOTAL	S6_Total

if S6_total=0, autofill S7 with 0 and skip to S8

S6.

Of the **S6_TOTAL** patients with chronic iron overload you actively follow, how many are currently being treated with iron chelation therapy?

1	Patients are treated with iron chelation therapy	_____
2	Patients are treated with Exjade Film-Coated Tablets (FCT)	_____
3	Patients are treated with generic deferasirox Film-Coated Tablets (FCT)	_____
4	TOTAL	S7_Total

S7.

When was the last time you prescribed Exjade or generic deferasirox?

1	Within last 12 months	
2	More than 12 months ago	terminate
3	Never	terminate

S8.

For approximately how many patients have you prescribed Exjade or generic deferasirox in the past 12 months?

1	None	terminate
2	1-5	
3	6 -10	
4	11 or more	

SECTION A: ADMINISTRATION AND DOSING OF EXJADE (DEFERASIROX)

A_Intro

Welcome and thank you for agreeing to participate in our survey on chronic iron overload.

Novartis, the maker of Exjade, is surveying physicians about posology and biological monitoring recommendations for Exjade as described in the EU SmPC and the Educational Materials, including the *Brochure for Physician* and *Physician's Reference Checklist* developed to support appropriate dosing and biological monitoring when prescribing Exjade.

Please, if possible answer the survey questions with the support of the Exjade Brochure for Physician and Physician's Reference Checklist that you have received.

score responses on questions in sections A1, A2, & B as "correct" or "Wrong" based on responses indicated in the Questionnaire as correct with a "C". Response score is not to be shown to respondent.

A.1

Please indicate whether the following methods of administrating Exjade film-coated tablets (FCTs) are true or false.

Select one answer per row

	RAndomize	True	False
1	The Exjade film-coated tablets (FCTs) can be swallowed whole with water.	❍ C	❍
2	For patients who are unable to swallow whole tablets, the Exjade film-coated tablets (FCTs) can be crushed and administered by sprinkling the full dose onto soft food, e.g. yogurt or apple sauce.	❍ C	❍
3	If Exjade film-coated tablets (FCTs) are crushed and sprinkled onto soft food, the dose does not need to be consumed immediately and can be stored for future use.	❍	❍ C
4	The Exjade film-coated tablets (FCT) may be taken on an empty stomach or with a light meal.	❍ C	❍

A.2

Based on the information in the Brochure for Physician and/or Physician's Reference Checklist:

In patients with transfusional iron overload, what is the recommended starting dose of deferasirox film-coated tablets (FCTs) after the transfusion of approximately 20 units (about 100 ml/kg) of packed red blood cells (PRBC) or serum ferritin levels are above 1000 µg/L?

Please select the correct answer

1	3.5 mg/kg/day	
2	7 mg/kg/day	
3	14 mg/kg/day	c
4	20 mg/kg/day	

A.3

Based on the information in the Brochure for Physician and/or Physician's Reference Checklist:

In patients with transfusional iron overload, when should an alternative (lower) initial daily dose of deferasirox film-coated tablets (FCTs) of 7 mg/kg body weight be considered?

Please select the correct answer

1	For patients who are receiving less than 7 ml/kg/month of packed red blood cells (approximately <2 units/month for an adult)	c
2	For patients who are receiving more than 14 ml/kg/month of packed red blood cells (approximately >4 units/month for an adult)	
3	For patients being transitioned from deferoxamine given at a dose of 40mg/kg on 5 days per week	

A.4

Based on the information in the Brochure for Physician and/or Physician's Reference Checklist:

In patients with transfusional iron overload, what is the **maximum** recommended daily dose of deferasirox film-coated tablets (FCTs) that can be given?

Please select the correct answer

1	14 mg/kg/day	
2	20 mg/kg/day	
3	28 mg/kg/day	C
4	40 mg/kg/day	

A.5

Based on the information in the Brochure for Physician and/or Physician's Reference Checklist:

In patients with transfusional iron overload, at which serum ferritin value should you consider interruption of deferasirox film-coated tablets (FCTs) treatment?

Please select the correct answer

1	serum ferritin consistently <300 µg/l	
2	serum ferritin consistently <500 µg/l	C
3	serum ferritin consistently <1000 µg/l	
4	treatment should not be interrupted based on serum ferritin values	

A.6

Based on the information in the Brochure for Physician and/or Physician's Reference Checklist:

In patients with non-transfusion-dependent thalassemia (NTDT), what is the recommended starting dose of deferasirox film-coated tablets (FCT), if LIC is ≥5 mg Fe/g dw or serum ferritin consistently above 800 µg/l?

Please select the correct answer

1	3.5 mg/kg/day	
2	7 mg/kg/day	C
3	14 mg/kg/day	
4	20 mg/kg/day	

A.7

Based on the information in the Brochure for Physician and/or Physician's Reference Checklist:

In patients with non-transfusion-dependent thalassemia (NTDT), what is the maximum recommended daily dose of deferasirox film-coated tablets (FCTs) that can be given?

Please select the correct answer

1	14 mg/kg/day	C
2	20 mg/kg/day	
3	28 mg/kg/day	
4	40 mg/kg/day	

A.8

Based on the information in the Brochure for Physician and/or Physician's Reference Checklist:

In patients with non-transfusion-dependent thalassemia (NTDT), when should you consider stopping deferasirox film-coated tablets (FCTs) treatment?

Please select the correct answer

1	LIC <3 mg Fe/g dw or serum ferritin consistently <300 µg/l	C
2	LIC <2 mg Fe/g dw or serum ferritin consistently <200 µg/l	
3	Serum ferritin <500 µg/l	
4	Serum ferritin <1000 µg/l	

SECTION B: BIOLOGICAL MONITORING

B_Intro

Please, if possible, answer the survey questions with the support of the Exjade Brochure for Physician and Physician's Reference Checklist that you have received.

B.1

Based on the information in the Exjade Brochure for Physician and/or Physician's Reference Checklist:

Which are the monitoring recommendations for laboratory tests (i.e. which tests should be assessed) **before** initiating therapy with deferasirox?

Please select the correct answer

1	Serum ferritin (SF)	
2	Serum creatinine	
3	Creatinine clearance (CrCl)	
4	Liver function tests (serum transaminases, bilirubin, alkaline phosphatase)	
5	Proteinuria	
6	All of the above	C

B.2

Based on the information in the Exjade Brochure for Physician and/or Physician's Reference Checklist:

For which of the following laboratory tests is the monitoring recommendation that the test should be repeated twice (i.e. 2x) at baseline (i.e. before initiating therapy with deferasirox)?

Please select the correct answer

1	Serum ferritin	
2	Serum creatinine	C
3	Liver function tests (serum transaminases, bilirubin, alkaline phosphatase)	

B.3

Based on the information in the Exjade Brochure for Physician and/or Physician's Reference Checklist:

Patients with pre-existing renal conditions and patients who are receiving medicinal products that depress renal function may be at increased risk of complications from deferasirox treatment.

Please select the correct answer

1	True	C
2	False	

B.4

Based on the information in the Exjade Brochure for Physician and/or Physician's Reference Checklist:

At what estimated creatinine clearance (CrCl) level is deferasirox contraindicated?

Please select the correct answer

1	<90 ml/min	
2	<60 ml/min	C
3	<40 ml/min	
4	<30 ml/min	

B.5

Based on the information in the Exjade Brochure for Physician and/or Physician's Reference Checklist:

For serum creatinine, what are the monitoring recommendations for patients **after initiation** of deferasirox therapy?

Please select the correct answer

1	Weekly in the first month after initiation of deferasirox or after dose modification and monthly thereafter	C	
2	Monthly after initiation of deferasirox or after dose modification and monthly thereafter		
3	Weekly in the first two months after initiation or modification of therapy and every 2 weeks thereafter		

B.6

Based on the information in the Exjade Brochure for Physician and/or Physician's Reference Checklist:

What is the **first action recommended** if in the renal monitoring in adult patients treated with deferasirox FCT, the serum creatinine is >33% above baseline and creatinine clearance (CrCl) is below lower limit of normal (LLN) (< 90 ml/min) at two consecutive visits and cannot be attributed to other causes?

Please select the correct answer

1	Reduce the daily dose of deferasirox FCT by 7mg/kg/day	C
2	Permanently discontinue treatment with deferasirox FCT	
3	Continue treatment with deferasirox FCT unchanged but increase the frequency of serum creatinine monitoring	

B.7

Based on the information in the Exjade Brochure for Physician and/or Physician's Reference Checklist:

During treatment with deferasirox, it is recommended to monitor (as needed) for any changes in renal tubular function (such as glycosuria in non-diabetics and low levels of serum potassium, phosphate, magnesium or urate, phosphaturia, aminoaciduria).

Please select the correct answer

1	True	C
2	False	

B.8

Based on the information in the Exjade Brochure for Physician and/or Physician's Reference Checklist:

The treatment with deferasirox is not recommended in patients with pre-existing severe hepatic disease (Child-Pugh Class C).

Please select the correct answer

1	True	C
2	False	

B.9

Based on the information in the Exjade Brochure for Physician and/or Physician's Reference Checklist:

Which are the monitoring recommendations for liver function tests (serum transaminases, bilirubin, alkaline phosphatase) **in the first month** after initiating therapy with deferasirox?

Please select the correct answer

1	Once per week	
2	Every 2 weeks	C
3	At the end of 4 weeks	

B.10

Based on the information in the Exjade Brochure for Physician and/or Physician's Reference Checklist:

If there is a persistent and progressive increase in serum transaminase levels that cannot be attributed to other causes, which of the following is true?

Please select the correct answer

1	Deferasirox does not need to be interrupted and can be continued but at a lower dose	
2	Deferasirox should be discontinued and never reintroduced even if liver function returns to normal	
3	Deferasirox should be temporarily interrupted and treatment can be cautiously re-initiated at a lower dose once liver function has returned to normal	C

B.11

Based on the information in the Exjade Brochure for Physician and/or Physician's Reference Checklist:

In pediatric patients with non-transfusion dependent thalassemia (NTDT), deferasirox FCT dose should not exceed 7 mg/kg/day and LIC should be monitored every 3 months when serum ferritin is $\leq$ 800 µg/l, in order to avoid overchelation.

Please select the correct answer

1	True	C
2	False	

B.12

Based on the information in the Exjade Brochure for Physician and/or Physician's Reference Checklist:

What is the monitoring recommendation for serum ferritin during deferasirox treatment?

Please select the correct answer

1	Every 2 weeks	
2	Every month	C
3	Once in 3-6 months	

B.13

Based on the information in the Exjade Brochure for Physician and/or Physician's Reference Checklist:

In patients with non-transfusion-dependent thalassemia (NTDT), Liver Iron Concentration (LIC) is the preferred method of iron overload determination.

Please select the correct answer

1	True	C
2	False	

B.14

Based on the information in the Exjade Brochure for Physician and/or Physician's Reference Checklist:

What is the monitoring recommendation for auditory testing and ophthalmic testing (including fundoscopy)?

Please select the correct answer

1	Before treatment initiation and then yearly	C
2	Before treatment initiation and then every 6 months	
3	No monitoring required	

Section C: Confirmation of Review of Educational Materials (Brochure for Physician and Physician's Reference Checklist) at any time since January 2021 until now

C.1

Please answer honestly. Your remuneration will not be affected by your response.

Select all that apply

		Yes	No	Not sure
	Have you received at any time since January 2021 until now Educational Materials, including the Brochure for Physician and Physician's Reference Checklist for Exjade which were developed to support appropriate dosing and biological monitoring when prescribing Exjade?	❍	❍	❍

	Yes all of it	Yes some of it	No
Have you read or reviewed the EMs including the Brochure for Physician and Physician's Reference Checklist	❍	❍	❍

	EU SmPC	EMs	HA website	Professional society or congress	EMA website	Clinical practice guideline	Litterature /publications	Novartis representative	Other
What is the primary source you use to learn about the dosing and biological monitoring recommendations for Exjade? EU SmPC, EMs, HA website , professional society or congress, the EMA website, clinical practice guidelines, literature/publications, Novartis representative, other (not listed above)	❍	❍	❍	❍	❍	❍	❍	❍	❍