Actelion Pharmaceuticals Ltd.*
(a Janssen Pharmaceuticals Company of Johnson and Johnson)

Non-interventional Postauthorization Safety Study - Protocol

AC-065A403: Post-authorisation safety study (PASS) to evaluate risk minimisation measures for medication errors with Uptravi during the titration phase in patients with pulmonary arterial hypertension (PAH) in clinical practice

EDUCATE

Protocol AC-065A403, AMENDMENT 5

JNJ-67896049 /ACT-293987 (selexipag)

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AUTHORS' SIGNATURES

TITLE:	Post-authorisation safety study (PASS) to evaluate risk minimisation measures for medication errors with Uptravi during the titration phase in patients with pulmonary arterial hypertension (PAH) in clinical practice Protocol number AC-065A403 EDMS-RIM-263804, 9.0
DOCUMENT:	PASS protocol
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SPONSOR RESPONSIBLE PERSONNEL:

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 5 Version 6	22 March 2024
Amendment 4 Version 5	08 April 2022
Amendment 3 Version 4	16 September 2021
Amendment 2 Version 3	26 March 2021
Amendment 1 Version 2	13 February 2017
Original Protocol Version 1	13 February 2016

Amendment 5 Version 6 (22 March 2024)

Overall Rationale for the Amendment: This global protocol amendment applies to global protocol AC-065A403 Version 5, dated 08 April 2022. The main reason for this amendment is to update the study milestones to reflect changes in the completion date of patient recruitment.

Section Number and Name	Description of Change	Brief Rationale
5. Abstract (Milestones); 6. Milestones; Annex 2, ENCEPP Checklist For Study Protocols (Section 1: Milestones)	Study milestones are updated.	To actualize past dates and to reflect changes in the completion date of patient recruitment.
Author's Signatures; 1. PASS Information (Author); 5. Abstract (Sponsor's Responsible Party); Participating Physician Agreement	The name of the Sponsor Responsible Party is updated.	To reflect a transition of responsibilities within the organization.
2. Marketing Authorisation Holder(s) (contact details)	The contact details of the MAH are updated	To reflect a transition of responsibilities within the organization.
Cover page; 1. PASS Information	EU PAS Register Number is replaced by EMA-HMA Catalogues Number	To reflect the replacement of the EU PAS Register by the HMA-EMA Catalogues.

LIST OF ABBREVIATIONS, ACRONYMS AND DEFINITIONS

ADR	Adverse drug reaction
AE	Adverse event
ARMM	Additional risk minimisation measures
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
CTR	Clinical Trials Register
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FC	Functional class
FOIA	Freedom of Information Act
GVP	Good Pharmacovigilance Practices
HCP	Health care professional; will include physicians who have treated patients with PAH with Uptravi, pharmacists, and nurses who have monitored patients with PAH taking Uptravi
ICF	Informed consent form
IEC	Independent Ethics Committee
IP receptor	Prostacyclin receptor, PGI2 receptor
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
MAH	Marketing Authorisation Holder
PAH	Pulmonary arterial hypertension
PAS	Post-authorisation study
PASS	Post-authorisation safety study
PBRER	Periodic Benefit-Risk Evaluation Report
PQC	Product quality complaint
PRAC	Pharmacovigilance Risk Assessment Committee
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
WHO	World Health Organisation

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1. PASS INFORMATION

Title:	AC-065A403: Post-authorisation safety study (PASS) to evaluate risk minimisation measures for medication errors with Uptravi during the titration phase in patients with pulmonary arterial hypertension (PAH) in clinical practice
Protocol version:	6.0
Date of last version of the protocol:	08 April 2022
EMA-HMA Catalogues Number:	EUPAS25699
Active substance (INN common name):	Selexipag
Pharmaco-therapeutic group (ATC Code):	Antithrombotic agents, platelet aggregation inhibitors excluding heparin ATC Code: B01AC27
Medicinal product:	UPTRAVI®
Product reference:	H0003774
Procedure number:	EMEA/H/C/003774
Name of Marketing Authorisation Holder	Janssen-Cilag International NV
Joint PASS	No
Research question and objectives	The goal of this study is to evaluate the effectiveness of medication error risk minimisation measures during the Uptravi titration phase.
Countries of study	Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Netherlands, Norway, Poland, Slovakia, Spain, Sweden, and United Kingdom
Author	PPD Senior Director, Epidemiology, Janssen Pharmaceuticals

2. MARKETING AUTHORISATION HOLDER(S)

Name of Marketing Authorisation Holder:	Janssen-Cilag International NV
Address:	Turnhoutseweg 30 B-2340 Beerse, Belgium
Contact Details:	Person authorised for communication, on behalf of the applicant: PPD Associate Director, EMEA Regulatory Liaison PPD PPD

Qualified Person Pharmacovigilance:	EU Qualified Person Responsible for Pharmacovigilance
Name:	Laurence Oster-Gozet

3. RESPONSIBLE PARTIES

The list of healthcare professionals (HCPs, ie, physicians, pharmacists and nurses) for each country in which the study is to be performed has not yet been finalized.

4. AMENDMENTS AND UPDATES

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents. Summaries of previous amendments are provided below.

Amendment	Date	Main reason(s)
Amendment 1	13 Feb 2017	• To update information about population details for Germany. • To update information about study size, data sources and data management.
Amendment 2	26 Mar 2021	• To modify the study design and sample size to improve the patient recruitment in response to the Pharmacovigilance Risk Assessment Committee (PRAC) assessment report (September 2020) as well as to revise health care professional (HCP) and patient survey questionnaires. • Also, as of 28 September 2018, the date of adoption notification of the European Commission Decision on the transfer of the marketing authorisation, Janssen-Cilag International NV, Belgium, is the new Marketing Authorisation Holder (MAH) for UPTRAVI®. Hence, administrative updates associated with the change in the MAH have also been implemented.
Amendment 3	16 Sep 2021	To align sample size-related content to modified study design, implement updates about 'Patient Data Collection' and 'Management and Reporting of Adverse Events / Adverse Reactions' as well as to include revised patient survey questionnaire in response to PRAC assessment report (June 2021).
Amendment 4	08 April 2022	To implement minor updates to facilitate implementation of the survey questionnaires and editorial changes for consistency.

5. ABSTRACT

Protocol Title: AC-065A403: Post-authorisation safety study (PASS) to evaluate risk minimisation measures for medication errors with Uptravi during the titration phase in patients with pulmonary arterial hypertension (PAH) in clinical practice (6.0, 22 March 2024)

Sponsor's Responsible Party: PPD Senior Director, Epidemiology, Janssen Pharmaceuticals (Main Author)

NOTE: The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided separately.

Background and Rationale

UPTRAVI® (selexipag) is an orally available selective prostacyclin receptor, PGI2 receptor (IP receptor) agonist with marketing authorisation in the European Union (EU) and worldwide. In the EU, Uptravi is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adults with World Health Organisation (WHO) functional class (FC) II–III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist and/or a phosphodiesterase Type 5 inhibitor, or as monotherapy in patients who are not candidates for these therapies.

Treatment with Uptravi includes an initial titration phase, during which the patient receives a low starting dose that is gradually increased over several weeks to an individualised maintenance dose, which is continued long-term. The Uptravi risk management plan includes additional risk minimisation measures (ARMMs) for prevention of medication errors occurring during initiation, titration and transition to individually tolerated dose administered as single strength of the tablet. These measures include the "prescriber kit" for health care professionals (HCPs) and the "titration guide provided in titration pack" for patients [ANNEX 3]. The comprehension and use of these ARMMs are important to minimise the risk of medication errors that can result in reduced effectiveness and/or adverse events (AEs). Therefore, evaluating comprehension and use of the measures and quantifying medication errors can help guide revisions to the materials and awareness of areas for additional education.

Research Question and Objectives

The objectives of this study are to assess HCPs' and patients' awareness (process), knowledge (impact), and comprehension (impact) of the risk minimisation materials and to record the occurrence of patient-reported "wrong dose" medication errors (outcome) at completion of titration or discontinuation of Uptravi during titration.

Process refers to indicators to determine the dissemination of the ARMM (eg, awareness of, receipt of, and reference to "prescriber kit" and "titration pack[1]") and any instructions received from the HCP regarding the titration process [EMA 2013].

Impact involves questions to measure knowledge, comprehension, actions, and behaviour associated with the use of Uptravi in these materials (eg, knowledge of dosing, understanding titration process, what to do if patient misses dose or if an undesirable effect is experienced) [EMA 2013].

Outcome refers to indicators that assess the occurrence of patient-reported medication error (ie, wrong dose during titration) and will only be assessed in patients who completed the titration or discontinued Uptravi during titration [EMA 2013].

[1] Titration pack includes patient titration guide and package leaflet.

Study Design

The study is an observational, cross-sectional survey of awareness, knowledge and self-reported behaviour in the following groups:

- Health care professionals (HCPs: physicians, pharmacists and nurses)
- Patients at completion of titration or discontinuation of Uptravi during titration (ie, ≤ 4 weeks after reaching individual maintenance dose or ≤ 4 weeks after discontinuation during titration).

Population

The study population will involve patients and HCPs from Europe, including centralised healthcare systems (ie, national PAH reference centres) and decentralised systems.

The HCP study population will include physicians and pharmacists who have treated patients with PAH with Uptravi and nurses who have monitored patients with PAH taking Uptravi.

HCPs will be asked to participate in the survey and HCPs and/or patient organisations will be requested to support recruitment of patients with PAH who have completed Uptravi titration or discontinued Uptravi during titration (ie, ≤ 4 weeks after reaching individual maintenance dose or ≤ 4 weeks after discontinuation during titration).

Patient survey will be distributed by the HCPs / patient organisations directly via email. Informed consent form will be included at the beginning of the survey, depending on local regulations. If the patient needs assistance, a caregiver will be allowed to complete the questionnaire on behalf of the patient, but the caregiver should be recording the patient's responses. HCPs who are willing to help recruit patients for this study will document following information into a screening log: the number of patients approached for the study, patient identification, date when patient was contacted, participation answer (Yes/ No), and EDUCATE unique identification number if patient participated in the study. Recruiting patient organisations will document raw number of patients approached and recruited in the study.

Variables

The questionnaires will elicit responses in three effectiveness indicators [EMA 2013] that evaluate ARMM: *process, impact, and outcome* (ie, patient-reported medication error).

HCPs

- Process factors to be measured:
  - Receipt of "prescribers kit" containing: cover letter to the HCP, HCP titration guide, summary of product characteristics (SmPC), package leaflet, and patient titration guide
  - Whether the "prescribers kit" has been reviewed and whether it is referenced routinely
  - Perceived helpfulness of the "prescribers kit"
- Impact factors to be measured:
  - Evaluation of the knowledge of selexipag dosing and understanding and tracking of each step of the titration process
  - Evaluation of actions and behaviours

Patients (completing the survey upon completion/discontinuation of titration of Uptravi)

- Process factors to be measured:
  - Receipt of "titration pack" containing package leaflet and patient titration guide

  - Whether the package leaflet and patient titration guide have been read and, if not, reason for not reading
  - Whether the "titration pack" is referenced routinely
  - Perceived helpfulness of the "titration pack"
  - Whether the patient diary as a component of the titration guide was used to self-record tablets taken during the titration process
- Impact factors to be measured:
  - Evaluation of the knowledge of dosing and understanding and tracking of each step of the titration process
  - Evaluation of actions and behaviours during titration phase
- Outcome (medication error) factors to be measured:
  - Wrong dose during titration (ie, took wrong colour tablet [strength], took wrong number of tablets, missed dose(s) including how many and for how long, wrong timing) and reason for wrong dose, whether there was an undesirable effect associated with wrong dose taken, and whether patients reported this to their HCP.
    - If any medication errors are reported by the patient, regardless of association with an undesirable effect or not, this will trigger reporting to marketing authorisation holder (MAH)'s medical safety department and will be included in the AE database used for the medical evaluation in the Uptravi Periodic Benefit-Risk Evaluation Reports (PBRERs).

To explore factors potentially associated with HCP knowledge and behaviour, HCPs will also be asked to provide demographic information and to characterise their practice in terms of medical specialty, estimated number of patients with PAH seen in the past 12 months, years treating patients with PAH, having a nurse programme / patient support programme, and prior involvement in studies with selexipag.

To explore factors potentially associated with patient knowledge and behaviour, information will be collected in the patient survey, including age, sex, and education, PAH aetiology, patient self-reported limitations in functional activity, date of PAH diagnosis and PAH-specific co-medications.

Data Sources

The source of information for the PASS will be data collected from HCPs and patients (or caregiver on behalf of the patient) through web-based online questionnaires. The questionnaires will contain largely closed questions (eg, multiple choice, yes/no, number), together with four -free-text response fields in the HCP questionnaire and two in the patient questionnaire.

Since the questionnaire administration occurs only at the end of Uptravi titration or Uptravi discontinuation (ie, ≤ 4 weeks after reaching individual maintenance dose or ≤ 4 weeks after discontinuation during titration), there will be no longitudinal data collection.

Study Size

The study will target 60 HCPs in total from selected countries. With the percentage of correct responses (ie, reflecting knowledge of the ARMM) to a yes/no question is 85%, for a study size of 60, the two-sided 95% confidence interval (CI) will be 76% to 94%. No hypothesis testing is planned; all analyses will be of a descriptive nature.

The study will target 200 patients, recruited via HCPs and /or via patient organisations, who will be surveyed at completion/discontinuation of the Uptravi titration phase (ie, ≤ 4 weeks after reaching individual maintenance dose or ≤ 4 weeks after discontinuation during titration). Based on Table 2, a sample size of 200 patients, assuming an expected patient response distribution of 80% for yes/no questions and a

two-sided 95% confidence interval (95% CI), results in a 95% CI of 74.5% to 85.5%. The lower boundary of that CI is greater than 70%, which represents the minimum response distribution for each yes/no question used to evaluate and demonstrate knowledge and/or compliance with risk minimisation procedures, including titration procedures.

Data Analysis

Data analyses will be descriptive in nature and will focus on summarising the questionnaire responses from HCPs and patients, information on characteristics of the respondents, and PAH characteristics.

Summary tables consisting of frequencies with percentages and 95% CIs for the proportion of correct responses will be created for all questionnaires. If sample size allow, results will be analysed and presented by country. Before starting data analysis, a statistical analysis plan describing methods of analysis and providing table shells will be developed.

Milestones

Milestone	Planned date
Final protocol submission to Pharmacovigilance Risk Assessment Committee (PRAC)	16 September 2021
Registration in the EU PAS register	15 October 2018
Start of data collection	02 December 2022
Collection of targeted number (60) of HCP surveys completed	16 June 2023
Second interim report submission	Once 100 patients' questionnaires are completed
End of data collection	At time of PRAC agreement that commitment is fulfilled
Submission of final report of study results	12 months after PRAC agreement

Past dates have been actualized.

6. MILESTONES

The planned dates for key milestones in this study are outlined below.

Milestone:	Planned Date:
Final protocol submission to PRAC	16 September 2021
Registration in the EU PAS register	15 October 2018
Start of data collection	02 December 2022
Collection of targeted number (60) of HCP surveys completed	16 June 2023
Second interim report submission	Once 100 patients' questionnaires are completed
End of data collection	At time of PRAC agreement that commitment is fulfilled
Submission of final report of study results	12 months after PRAC agreement

Past dates have been actualized.

7. BACKGROUND AND RATIONALE

7.1. Background

Pulmonary arterial hypertension (PAH) is a rare, severe and progressive disease ultimately leading to right heart failure and death [McLaughlin 2004, Galiè 2016].

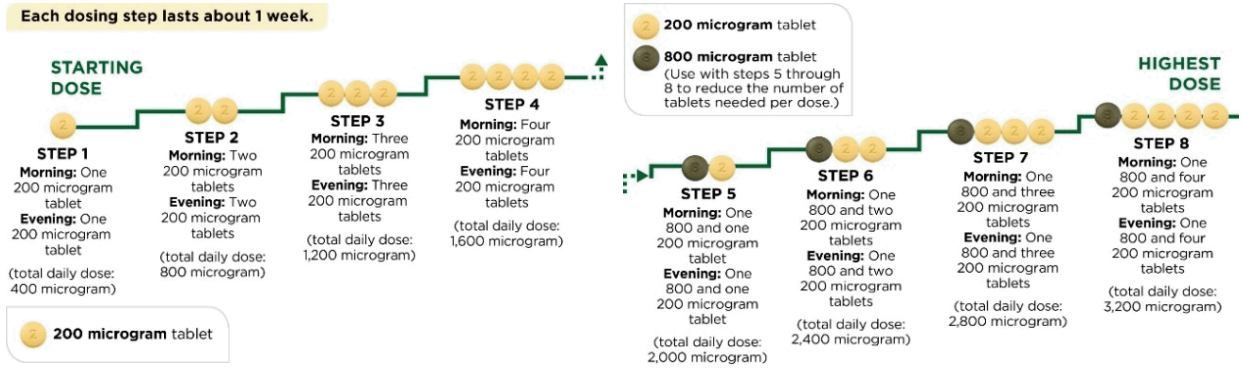
Uptravi® (selexipag) is an orally available selective IP receptor agonist approved in the European Union (EU). Uptravi is indicated for the long-term treatment of PAH in adult patients with World Health Organisation (WHO) functional class (FC) II–III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist and/or a phosphodiesterase Type 5 inhibitor, or as monotherapy in patients who are not candidates for these therapies [Uptravi SmPC].

7.2. Overall Rationale for the Study

Treatment with Uptravi includes an initial titration phase, whereby the patient receives a low starting dose that is gradually increased according to patient's tolerability over several weeks to an individualised maintenance dose, which is continued long-term.

Treatment should be started at a dose of 200 µg twice daily, in the morning and in the evening. If the patient tolerates the dose, the physician may increase the dose every week by 200 µg twice daily, up to a maximum of 1,600 µg twice daily. The 200 µg strength tablet is used as dose increment to step the dose up or down slowly during titration. Once a maintenance dose is established, the individual dose strengths can be used to allow patients to take only one tablet in the morning and one in the evening, instead of multiple tablets each time. Uptravi is available in different strengths (200, 400, 600, 800, 1,000, 1,200, 1,400, and 1,600 µg). The fact that Uptravi is available in different strengths and that the dose is changed usually weekly during the titration phase, medication errors (ie, wrong dose during titration) may occur and in some cases, these may be associated with adverse events (AEs). Figure 1 shows titration process.

Figure 1: Titration Process Diagram



The Uptravi risk management plan includes additional risk minimisation measures (ARMM) for prevention of medication errors occurring during initiation, titration and transition to individually tolerated dose administered as single strength of the tablet. These measures include the "prescriber

kit" for health care professionals (HCPs) and the "titration pack" for patients [ANNEX 3]. In addition, Uptravi will be supplied through country-specific controlled access systems, defined in agreement with national competent health authorities.

The "prescriber kit" provided to the HCP contains the following educational materials:

- A cover letter to the HCP
- HCP titration guide containing information about treatment initiation and titration with Uptravi
- Summary of product characteristics (SmPC)
- Package leaflet
- Patient titration guide

The "titration pack" provided to the patient contains the following educational materials:

- Package leaflet
- Patient titration guide

This post-authorisation safety study (PASS) is designed to assess HCPs' and patients' awareness, knowledge, comprehension, and use of the medication error-related ARMM and to describe the occurrence of patient-reported medication errors during the Uptravi titration phase.

The comprehension and use of these ARMM is important to minimise the risk of medication errors that can result in reduced effectiveness and/or AEs. Therefore, evaluating comprehension and use of the materials and quantifying medication errors can help guide revisions to the materials and awareness of areas for additional education.

The study will be conducted in accordance with the International Society for Pharmacoepidemiology (ISPE) *Guidelines for Good Pharmacoepidemiology Practices (GPP)* [ISPE 2015] and in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* [ENCePP 2015].

8. RESEARCH QUESTION AND OBJECTIVES

The survey design of the study employs online questionnaires eliciting responses in three categories: process, impact, and outcome (patient-reported medication error [patient only]), defined below [EMA 2013]. The questionnaires are answered by HCPs and patients.

Process refers to indicators to determine the dissemination of the ARMM (eg, awareness of, receipt of, and reference to "prescriber kit" and "titration pack") and any instructions received from the HCP regarding the titration process.

Impact involves questions to measure knowledge, comprehension, actions, and behaviour associated with the use of Uptravi in these materials (eg, knowledge of dosing, understanding titration process, what to do if patient misses dose or if an undesirable effect is experienced).

Outcome refers to indicators that assess patient-reported medication error (ie, wrong dose during titration) and will only be assessed in patients.

The objectives of this study are to describe HCPs' and patients' awareness (*process*), knowledge (*impact*), and comprehension (*impact*) of the ARMM and to record the occurrence of patient-reported "wrong dose" medication errors (*outcome*) at completion of titration or discontinuation of Uptravi during titration.

Definitions of these concepts are in Sections 9.3.1.1 (HCP survey) and 9.3.1.2 (patient survey at completion/discontinuation of titration).

9. RESEARCH METHODS

9.1. Overview of Study Design

The study is an observational, cross-sectional survey of awareness, knowledge, and self-reported behaviour among a sample of HCPs and patients (at completion of titration or discontinuation of Uptravi during titration, ie, ≤ 4 weeks after Uptravi titration end or Uptravi discontinuation) and they will be administered a web-based questionnaire. As this is a descriptive study; there will be no formal hypothesis testing.

9.2. Setting and Population

This cross-sectional survey will be conducted in Europe.

9.2.1. Health Care Professionals (HCPs)

Health care professionals (HCPs, ie, physicians, pharmacists, and nurses) who have treated/monitored at least one PAH patient taking Uptravi in the last 12 months are eligible to be included in the HCP survey.

The list of potentially eligible HCPs including their email addresses will be provided by Janssen. HCPs in this study will include prescribing physicians (primarily pulmonologists and/or cardiologists) and pharmacists treating patients for PAH as well as nurses who are monitoring Uptravi-treated patients with PAH. Physicians and pharmacists will be recruited from the list of all prescribers, via the country-specific controlled access systems, who have either prescribed Uptravi or who have received the prescriber kit. Information, such as physician's specialty (eg, cardiologist, pulmonologist), Uptravi experience and geographic location will be used for the sampling process, to achieve a balanced distribution of HCPs. Nurses who are monitoring Uptravi-treated patients with PAH will be invited to participate in the survey by the prescribing physicians. Both HCPs who manage a greater number of Uptravi-treated patients and those who only manage very few Uptravi-treated patients will be included in the HCP survey to provide results from HCPs with any level of experience with Uptravi. The study population of HCPs will

be recruited from selected countries. Recruitment of HCPs will cease once the target number of HCP participants is reached.

9.2.1.1. HCP Eligibility

To be eligible for the study, HCPs must meet all of the following criteria:

- Be included on the list of prescribing HCPs (physicians, pharmacists and nurses) via the country-specific Uptravi controlled access system or be a nurse in the practice with (and recruited by) these physicians.
- Treated or monitored at least one patient with Uptravi in the previous 12 months so they will be able to answer questions regarding their use of the ARMM and instructions to patients.

9.2.2. Patients

Patient survey will be distributed by the HCPs and / or requested patient organisations where both HCPs and patient organisations will approach the patients directly via email. Informed consent will be included at the beginning of the survey. Recruiting HCPs and patient organisations will be sent a survey link and response rates will be monitored to ensure sufficient questionnaire completion rates.

HCPs willing to help with patient recruitment will maintain a screening log that includes the number of patients approached for the study, patient identification, date when patient was contacted, participation answer (Yes/ No), and EDUCATE unique identification number if patient participated in the study. Information on demographics (eg, age, sex, highest level of education achieved), PAH aetiology, patient self-reported limitations in functional activity, date of PAH diagnosis, and PAH-specific co-medications (other than Uptravi) that are prescribed will be collected from the patients participating in the survey.

9.2.2.1. Patient Eligibility

To be eligible for the study, patients must meet all the following criteria:

- ≥ 18 years old at enrolment
- Self-reported: Diagnosis of PAH by physician
- Provision of consent as part of the survey
- Agree to provide treating HCP's contact information (refer to Section 9.6.2)
- Be taking the survey ≤ 4 weeks after reaching individual maintenance dose of Uptravi or ≤ 4 weeks Uptravi discontinuation during titration.

9.3. Variables

9.3.1. Outcome Definitions and Measures

Outcome is defined per ARMM effectiveness indicators [EMA 2013]; process, impact and outcome (ie, patient-reported medication error) [see Section 8]. The questionnaires will elicit responses in these three ARMM effectiveness indicator categories.

The questionnaires will contain mostly closed questions (eg, multiple choice, yes/no, number), eliciting responses measuring awareness, knowledge, and comprehension of the medication error information in the Uptravi prescriber kit educational material and titration packs and patient-reported medication errors during titration (patient survey). There will be two free-text response fields in the Patient Questionnaire to ask about any undesirable effects they might have experienced if they reported a medication error (Question 14c) and to ask them to describe the types of undesirable effects they had, if any, if they took the wrong dose (ie, wrong number or colour of pills; Question 18 and 19). There will be four free-text response field options in the HCP Questionnaire: Question 25a asks about circumstances under which the HCP would not give a patient the Uptravi Patient Titration Package; Question 27 asks about the mode of communication HCPs use with their patients; Question 29a asks why the HCP does not advise their patients to use the diary; and Question 30a asks under what circumstances the prescribing physician would deviate from following the recommended titration schedule.

9.3.1.1. Definitions and Measures in HCP Survey

Process factors to be measured in the HCP survey are as follows:

- Receipt of "prescriber kit" containing cover letter to the HCP, HCP titration guide, summary of product characteristics (SmPC), package leaflet, and patient titration guide [ANNEX 3]
- Whether the "prescriber kit" has been reviewed and whether they are referenced routinely
- Perceived helpfulness of the "prescriber kit"

Impact factors to be measured in the HCP survey are as follows:

- Evaluation of the knowledge of dosing and understanding and tracking of each step of the titration process
  - Strength of tablets available during titration
  - Time of day for dosing
  - Instructions for patients regarding how to take medication, how to monitor medication use, and how to titrate medication
  - What information to review with patients upon initiation of Uptravi
  - What to advise patient to do if they forget a dose
  - What to advise a patient to do if patient stops treatment with Uptravi
  - Maximum dose of Uptravi that can be prescribed
  - Frequently observed adverse reactions
- Evaluation of actions and behaviours
  - Whether they review the titration guide with the patient at treatment initiation
  - Whether they provide the titration guide to the patient and if not, why
  - Frequency and mode of communication with patient during titration phase

- What HCPs advise a patient to do if an adverse reaction is experienced
- Whether they advise patients to use the diary to track Uptravi dosing and if not, why
- Whether they follow the recommended Uptravi titration schedule for all, some, or none of their patients
- Under which circumstances they deviate from the recommended titration schedule

9.3.1.2. Definitions and Measures in Patient Survey upon Completion of Uptravi Titration/Uptravi Discontinuation (Patient Questionnaire)

Process factors to be measured in patients completing the survey at completion of Uptravi titration /Uptravi discontinuation are as follows:

- Receipt of "titration pack" containing package leaflet and patient titration guide [ANNEX 3]
- Whether the "titration pack" has been reviewed and, if not, reason for not reviewing
- Whether the "titration pack" is referenced routinely
- Perceived helpfulness of the "documents included in titration pack"
- Whether the patient diary as a component of the titration guide was used to self-record tablets taken during the titration process

Impact factors to be measured in patients completing the survey at completion of Uptravi titration /Uptravi discontinuation are as follows:

- Evaluation of the knowledge of dosing and understanding and tracking of each step of the titration process
  - Timing of dosing
  - Instructions regarding how to titrate Uptravi
  - Recommendation to take Uptravi with a meal
- Evaluation of actions and behaviours during titration phase
  - What to do if a single dose or multiple doses are omitted
  - What to do if more than prescribed dose is taken
  - What to do if an undesirable effect is experienced
  - Whether the patient increased the dose of Uptravi until they experienced intolerable adverse effects

Outcome: medication error factors to be measured in patients completing the survey at completion/discontinuation of Uptravi titration reflect the EMA guidance document on good practices for recording, coding, reporting, and assessment of medication errors [EMA 2015] and are as follows:

- Wrong dose during titration (ie, took wrong colour tablet [strength], took wrong number of tablets, missed dose[s] including how many and for how long, wrong timing) and reason for

wrong dose whether there was an undesirable effect associated with the wrong dose, and whether they reported this to their HCP.

- If any medication errors are reported by the patient, regardless if associated with an undesirable effect or not, this will trigger reporting to marketing authorisation holder (MAH)'s medical safety department and will be included in the AE database used for the medical evaluation in the Uptravi Periodic Benefit-Risk Evaluation Reports (PBRERs). Section 11 describes management and reporting of AEs in detail.

9.3.2. Exposure Definition and Measures

This is not a cross-sectional study. There are no measures of exposure.

9.3.3. Covariate Definition and Measures

9.3.3.1. Covariate Definitions and Measures in HCP Survey

The country of the HCP's practice will be recorded, and HCPs will be asked to characterise their practice in terms of the following traits to explore factors potentially associated with HCP knowledge and behaviour (use of educational materials). These data will also be captured on eligible HCPs who refuse to participate, when available from the country-specific Uptravi controlled access systems:

- Medical profession (eg, physician, pharmacist, nurse)
- Medical specialty
- Sex
- Whether there is a dedicated pharmacist and/or nurse educator at centre
- Estimated number of patients with PAH cared for currently
- Years treating patients with PAH
- Number of patients prescribed/monitored with Uptravi over the past 12 months
- Prior involvement in Uptravi (selexipag) studies or other studies/trials involving patients with PAH

9.3.3.2. Covariate Definitions and Measures in Patient Survey

Patient-level data will be collected via self-report as part of the questionnaire. The country of patient residence will be recorded in the survey and, where possible, based on privacy laws from eligible patients not invited and patients refusing participation:

- PAH aetiology
- Patient self-reported limitations in functional activity
- Date of PAH diagnosis
- PAH-specific co-medications
- Demographics (eg, age, sex, highest level of education achieved)

9.4. Data Sources

9.4.1. Data Sources for HCPs

The source of information from HCPs will be self-reported through specially designed online questionnaires with closed-ended response choices for all except four questions which will have a free-text response field option. These data will be entered directly by the HCP to an electronic web-based survey system.

9.4.2. Data Sources for Patients

The primary source of information from patients will be self-reported through specially designed questionnaires with closed-ended response choices for all except two free-text response fields in the questionnaire. These data will be entered by the patient (or caregiver on behalf of the patient) via web-based entry to an electronic web-based survey system. Each patient who signs the informed consent form (ICF) will be assigned a unique identification number that will be used by the patient when completing the survey.

9.4.3. Questionnaire Development

Questionnaire development experts have designed the questionnaires for HCPs and patients and will test them using standard survey methodological principles and best practices for instrument development [Groves 2009, Hollis 2014]. These principles and best practices include the generation and testing of introductory materials that explain the purpose of the study in a general but not leading manner. Likewise, best practice includes development and testing of question stems and response options that avoid leading the participant to the correct response. The questions are tailored to the study objectives and the information provided in the HCP "prescriber kit" and in the patient "titration pack". The data collected in the respective questionnaires will provide information needed to assess potential differences across subgroups (eg, medical specialty and HCP experience regarding PAH patient management).

The questionnaires will be translated into the local language. These translations will be reviewed by a local expert in each study country to ensure that the questionnaire items (question stems and response choices) are culturally appropriate and easily and correctly understood by HCPs and patients.

9.5. Study Size

The study will target approximately 60 HCPs (comprised of physicians, pharmacists and nurses) [see Section 9.2.1]). It is expected that in some sites physicians and nurses will agree to participate, while in others only one HCP may agree; thus, the study size could go up to 80 HCPs.

With the percentage of correct responses (ie, reflecting knowledge of the ARMM) to a yes/no question is 85%, then for a study size of 60, the two-sided 95% confidence interval (CI) will be 76.0% to 94.0%. No hypothesis testing is planned; all analyses will be of a descriptive nature.

Table 1 shows the 95% confidence limits assuming various numbers of HCPs and percentages of correct response.

Table 1: Confidence Limits for Various Study Sizes and Proportions of Correct Responses Among HCPs

HCP study size	Proportion of correct responses (%)	Lower 95% confidence limit (%)	Upper 95% confidence limit (%)
60	50	37.3	62.7
60	70	58.4	81.6
60	75	64.0	86.0
60	80	69.9	90.1
60	85	76.0	94.0
60	90	82.4	97.6
80	50	39.0	61.0
80	70	60.0	80.0
80	75	65.5	84.5
80	80	71.2	88.8
80	85	77.2	92.8
80	90	83.4	96.6

HCP = health care professional.

The study will also target 200 patients to be surveyed at completion of titration or discontinuation of Uptravi during titration (ie, ≤ 4 weeks after reaching individual maintenance dose or ≤ 4 weeks after discontinuation during titration).

Based on Table 2, a sample size of 200 patients, assuming an expected patient response distribution of 80% for yes/no questions and a two-sided 95% confidence interval (95%CI), results in a 95%CI of 74.5% to 85.5%.

The lower boundary of that CI is greater than 70%, which represents the minimum response distribution for each yes/no question used to evaluate and demonstrate knowledge and/or compliance with risk minimisation procedures, including titration procedures.

Table 2: Confidence Limits for Patient Study Size with Various Proportions of Correct Responses

Patient study size	Proportion of correct response (%)	Lower 95% confidence limit (%)	Upper 95% confidence limit (%)
150	50	42.0	58.0
150	70	62.7	77.3
150	75	68.1	81.9
150	80	73.6	86.4
150	85	79.3	90.7
150	90	85.2	94.8
200	50	43.1	56.9
200	70	63.6	76.4
200	75	69.0	81.0
200	80	74.5	85.5
200	85	80.1	89.9
200	90	85.8	94.2

9.6. Data Management

The questionnaire can be completed at the participants' (HCPs and patients) convenience. Although participants will be encouraged to complete the questionnaire in a timely manner, once they start the questionnaire, they will be able to stop at any point and resume answering questions from where they stopped at a later time (within 1 week from starting the questionnaire). Participants will not be able to go back and change answers to previous questions, whether or not they have logged out and logged back in. This restriction minimises the likelihood of the respondent searching for answers via the web or other sources or being influenced by answers to subsequent questions. Incomplete questionnaires which are at least 50% complete will be included in the analysis.

9.6.1. HCP Data Collection

An email invitation will be sent to the selected group of HCPs (physicians and pharmacists), inviting them to participate and to invite nurses who work within their practice and providing a link to a web-based questionnaire. In case of no response to the initial invitation, invitations will be sent to each selected physician at least two more times.

After agreement to participate, the HCP will be asked to complete the questionnaire describing their experience with Uptravi, evaluating their awareness and knowledge of medication error-related information in the prescriber kit, as well as use of the Uptravi educational materials.

An electronic web-based survey system will be used in this study. All HCPs will be asked to log in to the study website by entering a unique identification number and password assigned to each HCP participant and provided in the email invitation.

Based on potential country-specific requirements, the recruitment process and some questions in the HCP questionnaire may be different between countries to reflect country-specific attributes (eg, type of centre/practice).

Also, HCPs will be contacted if further information would be required for the documentation of medication error-associated adverse events in MAH safety database.

9.6.2. Patient Data Collection

The patient questionnaire will be completed by patients (or a caregiver on behalf of the patient) online. They will be provided with a unique identification number by their recruiter (HCP / patient organisation) to access the web-based questionnaire. If the patient needs assistance in reading the questions or providing responses online, a caregiver will be allowed to complete the questionnaire on behalf of the patient, recording the patient's responses.

To increase reliability and validity of self-reported information on demographics, patients will be asked upon enrolment and informed consent to provide contact information for their prescribing HCP. The prescribing HCPs will be contacted and asked to review the patient self-reported medical information (ie, PAH diagnosis, date of diagnosis, PAH aetiology, WHO FC, and PAH-specific concomitant medications).

Patients' self-reported information will be available for review by their treating HCP via a secured, cloud-based electronic web-based survey system. Only patients who agree to provide their HCP's contact information and whose HCP provided respective information, will be eligible for inclusion in the study.

These design features of the study (ie, inclusion criteria for treating HCP contact information and review of key parameters by prescribing HCPs) ensure the reliability of key clinical parameters for all study participants.

9.6.3. Data Handling and Management

A data management plan will be developed to guide the handling of data, including the transfer of electronic files. The data management plan will include, if necessary, country--specific modifications due to local regulations or requirements. HCPs and patients will enter data directly into an electronic web-based survey system. Skip logic checks will be embedded in the electronic web-based survey system.

9.7. Data Analysis

Data analyses will be descriptive in nature and will focus on summarising the questionnaire responses from HCPs and patients, information on characteristics of the participants, and self-reported medication errors.

A detailed statistical analysis plan (SAP) describing methods of analysis and presentation, including table shells, will be developed prior to the analysis of the data.

Summary tables consisting of frequencies with percentages and 95% CIs for the proportion of each response will be created for all questionnaire responses:

- For the HCP survey, the process factors and impact factors measured, listed in Section 9.3.1.1, will be summarised.
- For the Patient Questionnaire, the process factors, impact factors, and outcome factors measured, listed in Section 9.3.1.2, will be summarised
- If sample size allow, results will be analysed and presented by country. Analyses by subgroups will include:
- Summaries by HCP specialty, Uptravi experience, and geographic location for the HCP survey
- Summaries by PAH aetiology or patient self-reported limitations in functional activity for patient questionnaires
- Summaries whether or not a caregiver completed the questionnaire on behalf of the patient
- Summaries by time between completion / termination of Uptravi dose titration and completion of questionnaire (≤2 weeks, >2 weeks)
- If sample size allows:
  - Summaries for data by country from participating countries
  - Summaries for data by site type (whether the site recruited both HCPs and patients or only HCPs or patients).

Missing data will not be imputed. The total number of responses (denominator) will be included for each question. The analysis of outcome indicators will be provided as proportions using the number of respondents as the denominator. If patients are not eligible to answer a question because of skip patterns (ie, they are not directed to a follow-on question), then they will not be included in the denominator for those responses.

The SAP will also evaluate predictors of high/low knowledge levels (eg, dichotomous categorisation of above/below mean number of correct answers to questionnaire).

All analyses will be performed using SAS® software, version 9.2 (or higher) (SAS Institute, Inc., Cary, North Carolina). Programmes, logs, and output will be reviewed for accuracy according to relevant standard operating procedures (SOP).

9.8. Quality Control

This project will be conducted in accordance with the guidance listed in Section 10 and the internal SOPs of participating institutions. The SOPs will be used to guide the day-to-day conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

All key study documents, such as the SAP, data collection forms, and study reports, will undergo quality control review, senior scientific review, and editorial review.

9.9. Limitations of the Research Methods

PAH is a rare disease and the number of HCPs who treat/monitor these patients is limited; thus, the study will target 60 HCPs and 200 patients to complete the questionnaires. Therefore, the analysis will focus on aggregated data across all countries. Although the report may display country-specific findings, there may be limitations with drawing country-specific conclusions, particularly for the HCP survey, given the relatively small number of HCPs treating and monitoring patients with PAH within each country.

As with all voluntary studies of this nature, some limitations are inherent. Although the study is designed to ensure the selection of Uptravi HCPs with any level of experience to participate in this study, there exists no exhaustive list of all Uptravi prescribers or patients treated with Uptravi from which to draw a sample; hence, it is impossible to select a random sample of all HCPs. Therefore, the study participants will not necessarily be representative of all HCPs and users of Uptravi, but an effort will be made to collect limited data on nonparticipants to be able to compare with the data on participants. Also, as is true with most surveys, it is possible that respondents who complete the questionnaire will differ from nonrespondents in ways that would influence their responses to the questionnaire (eg, awareness, knowledge, use of the educational materials). The direction and magnitude of such potential respondent bias is not known.

Occasionally, study participants may erroneously provide responses that depend on his/her ability to recall past event. This type of bias can occur where participants are required to evaluate exposure variables retrospectively using a self-reporting method, such as self-administered questionnaires. The longer the time period between the exposure and the questionnaire response, the increase in likelihood for this kind of bias to be present.

9.10. Other Aspects

None.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Institutional Review Board / Independent Ethics Committee Approval

Approval from the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) must be obtained before going through a consent procedure with the HCP and patient and before collecting data via electronic web-based survey system. IRB/IEC information/approval should be documented in a letter to the study coordinator, clearly identifying the documents reviewed and the date of approval.

10.2. Participant Informed Consent

Participating HCPs will provide an electronic or paper informed consent, depending on local regulations, included at the beginning of the questionnaire, before participating in the survey EU-CTR 536/2014. Surveys will be primarily web-based.

The questionnaires will not collect any identifying information about the patient or HCP, and they will be tracked using a study-assigned unique identification number.

10.3. Participant Confidentiality

The research team will not have access to any participant-identifying information. No personal identifying information will be taken from the clinical site. Only de-identified data will be collected by the research staff and MAH. If the patient reports a medication error and/or associated AE, de-identified information will be provided to MAH's medical safety department [see Section 11 for more detail]. Any reports that are generated will not contain any participant identifiers.

For the patient survey, HCPs willing to support the patient recruitment will maintain a screening log that includes details on the number of patients approached about the study, the number of patients who refused to participate as well as the number of hours spent on this activity for the purpose of reimbursement. Log data on eligible patients will be maintained. All data on a patient will be linked through the unique survey identification number thus no personal identifying information will be shared with Janssen. Patient advocacy groups will be asked to provide a raw number of patient contacts instead of a log.

10.4. Compensation

HCP sites participating in the patient survey will be paid a nominal fee, per country-specific regulations, to compensate them for the time spent recruiting patients and providing limited data from patient medical records. The amount and payment methods will be reviewed and approved by the IRB/IEC to ensure that payments are commensurate with the time needed to complete the study tasks and are not coercive.

As with the site compensation, the amount and payment methods will be reviewed and approved by the IRB/IEC to ensure that payments are commensurate with the time needed to complete the forms, not coercive, and made according to local regulations in each country. Patient organisations, if allowed by local regulations, leading on patient recruitment may be paid an agreed nominal fee for administrative efforts such as distribution of the survey to their members. Patients completing the questionnaires may be paid a nominal amount, in those countries where it is acceptable to do so, to compensate them for their time to complete the questionnaire.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Patient self-reported medication errors with Uptravi (selexipag) (indicated in the Patient Questionnaire), regardless if associated or not with an AE, will be reported from web-based questionnaire to the MAH's medical safety department. As a part of the informed consent question, the patients will be asked to provide consent and contact information for their treating HCP to be contacted by the MAH, if follow-up information would be required for the documentation of medication error-associated AEs in the MAH safety database.

In addition, all free-text boxes present in the HCP/patients web-based questionnaires, will be periodically monitored by the MAH and any AEs, special situations and product quality complaints will be reported to MAH safety department and will be followed up as per Janssen procedures, as applicable.

For AE definitions, see ANNEX 4. Any AE information received from EDUCATE, ie, from the web-based questionnaires will be documented by MAH and reported in the PBRER.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The protocol, study status updates, and report(s) will be included in regulatory communications in line with the risk minimisation plan, PBRERs, and other regulatory milestones and requirements. The study description and key protocol elements will be published on the ENCePP register.

In case of communications in other settings (such as conferences or publications), abstracts, presentations, and manuscripts will be prepared in accordance with the guidelines of the EMA Guideline on GVP [EMA 2012, EMA 2013, EMA 2014], the ISPE [ISPE 2015], and the International Committee of Medical Journal Editors [ICMJE 2021].

13. REFERENCES

[EU-CTR 536/2014] Regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC [accessed on 24 August 2016]. Available at: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

[EMA 2012] European Medicines Agency (EMA). Guideline on good pharmacovigilance practices (GVP). Annex I - Definitions. European Medicines Agency; 12 December 2012 [accessed on 1 June 2016]. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129131.pdf.

[EMA 2013] European Medicines Agency (EMA). Guideline on good pharmacovigilance practices (GVP). Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 1). European Medicines Agency; 6 June 2013 [accessed on 1 February 2016]. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500144010.pdf.

[EMA 2014] European Medicines Agency (EMA). Guideline on good pharmacovigilance practices (GVP). Module VI – Management and reporting of adverse reactions to medicinal products. European Medicines Agency; 8 September 2014 [accessed on 6 April 2015]. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500172402.pdf.

[EMA 2015] European Medicines Agency (EMA). Good practice guide on recording, coding, reporting and assessment of medication errors. European Medicines Agency; 23 October 2015 [accessed on 26 May 2016]. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/11/WC500196979.pdf.

[ENCePP 2015] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on methodological standards in pharmacoepidemiology (revision 3). EMA/95098/2010 Rev.4. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; July 2015 [accessed on 6 July 2016]. Available at: http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml.

[Galiè 2016] Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016 Jan 1;37(1):67-119.

[Groves 2009] Groves RM, Fowler FJ, Jr., Couper MP, Lepkowski JM, Singer E, Tourangeau R. Survey methodology, 2nd edition. Hoboken, NJ: John Wiley & Sons, Inc.; 2009.

[Hollis 2014] Hollis KA, Gilsenan AW. Design and implementation of surveys to assess patient and healthcare provider understanding of risks and safe use condition. In: Andrews E, Moore N, editors. Mann's pharmacovigilance. Chichester: John Wiley & Sons, Inc.; 2014.

[ICMJE 2021] International Committee of Medical Journal Editors (ICMJE). Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. International Committee of Medical Journal Editors; December 2021 [accessed on 01 April 2022]. Available from: http://www.icmje.org.

[ISPE 2015] International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP). Revision 3. International Society for Pharmacoepidemiology; 2015 [accessed 28 January 2016]. Available at: http://www.pharmacoepi.org/resources/guidelines_08027.cfm.

[McLaughlin 2004] McLaughlin V, Presberg K, Doyle R, et al. Diagnosis and management of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. CHEST 2004; 126 (1): 1S-92S.

[Uptravi SmPC] European Medicine Agency (EMA). Uptravi. Summary of Product Characteristics [accessed on 28 June 2016]. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003774/WC500207173.pdf.

14. ANNEXES

ANNEX 1: STAND-ALONE DOCUMENTS AND ADDITIONAL INFORMATION

- Health Care Professional (HCP) and Patient Survey Questionnaires

These supporting documents will be made available on demand.

ANNEX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and 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 noninterventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of noninterventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Post-authorisation safety study (PASS) to evaluate risk minimisation measures for medication errors with Uptravi during the titration phase in patients with pulmonary arterial hypertension (PAH) in clinical practice

Study reference number:
To be assigned

Section 1: Milestones		Yes	No	N/A	Section Number
1.1	Does the protocol specify timelines for				
	1.1.1 Start of data collection[a]	☒	☐	☐	6
	1.1.2 End of data collection[b]	☒	☐	☐	6
	1.1.3 Study progress report(s)	☐	☒	☐	
	1.1.4 Interim progress report(s)	☒	☐	☐	
	1.1.5 Registration in the EU PAS register	☒	☐	☐	6
	1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

1.1.3 Study progress reports are not planned.

1.1.4 An interim progress report is planned once 100 patients' questionnaires are completed.

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)	☒	☐	☐	7.2
	2.1.2 The objective(s) of the study?	☒	☐	☐	8
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.1, 9.2.2
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.1

Comments:

2.1.4 This is a descriptive study and will not test any formal hypotheses.

Section 3: Study design		Yes	No	N/A	Section Number
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.7
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

[a] 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.

[b] Date from which the analytical dataset is completely available.

Section 3: Study design		Yes	No	N/A	Section Number
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)	☒	☐	☐	11

Comments:

3.4 This is not an exposure-outcome study, so no measures of association will be determined.

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	9.2.1, 9.2.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	9.2
	4.2.2 Age and sex?	☒	☐	☐	9.2
	4.2.3 Country of origin?	☒	☐	☐	9.2
	4.2.4 Disease/indication?	☒	☐	☐	9.2
	4.2.5 Duration of follow-up?	☐	☐	☒	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

4.2.5 This is a cross-sectional study; there will be no follow-up.

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 classified according to time windows? (e.g. current user, former user, nonuse)	☐	☐	☒	
5.4	Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 5. This is not an exposure-outcome study. There is no relevant exposure.

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?	☒	☐	☐	9.3.1

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

6.3 The outcomes are patient and HCP reported outcomes via questionnaire and there will be no validation of the responses. However, the questionnaires will undergo cognitive testing prior to their utilisation to ensure they are clear and culturally appropriate.

6.4 There are no endpoints relevant for Health Technology Assessments.

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.2.1, 9.2.2
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☐	☒	☐	

Comments:

7.1, 7.1.1 This is not an exposure-outcome study so there will be no assessment of confounding.

7.3 The study covariates are largely patient and HCP reported and there will be no validation of the responses.

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

Comments:

8.1 This is not an exposure-outcome study so there will be no assessment of effect modifiers. Covariates that will be used to describe the populations and potentially used to stratify the descriptive results are in Section 9.3.3.

Section 9: Data sources		Yes	No	N/A	Section Number
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
	9.1.3 Covariates?	☒	☐	☐	9.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.1
	9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3
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)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
	9.3.3 Covariates?	☐	☐	☒	
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.6.2

Comments:

9.1.1, 9.2.1, 9.3.1 There is no exposure in this study.

9.3.2, 9.3.3 These are patient-reported data, there will be no coding of the data.

Section 10: Analysis plan		Yes	No	N/A	Section Number
10.1	Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2	Are descriptive analyses included?	☒	☐	☐	9.7
10.3	Are stratified analyses included?	☒	☐	☐	9.7
10.4	Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5	Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.6	Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

10.4 This is not an exposure-outcome study so there will be no assessment of confounding.

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)	☐	☒	☐	
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

11.1 Information on data storage and security will be described when the research organisation responsible for data collection and data management is determined. This will be included in the Statistical Analysis Plan.

11.3 Independent review of study results is not planned.

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

Comments:

12.1.3 This is not an exposure-outcome study so confounding will not be assessed.

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.3

Comments:

13.2 This protocol will undergo ethics review after EMA approval.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

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

Comments:

ANNEX 3: ADDITIONAL RISK MINIMISATION MEASURES

Annex 3.1: HCP Titration Letter

UPTRAVI (selexipag) treatment initiation and titration

Dear Healthcare Professional,

In this package you will find information on the use of UPTRAVI as a long-term oral treatment for pulmonary arterial hypertension (PAH) in adult patients with World Health Organization (WHO) functional class (FC) II–III.

UPTRAVI may be used as combination therapy in patients insufficiently controlled on treatment with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type-5 inhibitor (PDE-5i), or as monotherapy in patients who are not candidates for these therapies.

Starting patients on UPTRAVI involves dose titration, according to tolerability, to reach the individually appropriate dose for each patient.

To aid you while going through the titration process with your patient, and to reduce the risk of medication error due to the need to take multiple tablets of up to 2 different dose strengths for up-titration, Janssen Pharmaceuticals Ltd has included the following resources in this prescriber kit:

An A4 laminated card (HCP titration guide) containing:

- A titration schedule and dosing explanation
- A guide to communicating with patients through initiation, titration and maintenance

Product information comprising:

- UPTRAVI Summary of Product Characteristics (SmPC)

A patient titration guide and patient leaflet:

- This guide and the patient leaflet are intended for demonstration and discussion with patients about the safe and effective use of UPTRAVI
- The titration guide should be given to the patient after the demonstration

Please note that the patients will receive an identical titration guide and patient leaflet in their titration pack.

Thank you for your support. Please do not hesitate to contact us directly by calling XXXXXXXX if we can be of any further assistance or if you need to order additional patient titration guides.

Yours sincerely,
Country-Specific Contact
(i.e. General/Medical manager)

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CP-122186 | December 2020

Annex 3.2: HCP Titration Guide

Getting Patients Started

Treatment with UPTRAVI should only be initiated and monitored by a physician experienced in the treatment of pulmonary arterial hypertension (PAH).

Patient titration pack includes:

- UPTRAVI 200 microgram film-coated tablets for titration
- A patient titration guide that includes an explanation of the titration process and a diary to record the number of tablets taken daily
  - Upon initiation, be sure to review the titration guide with patients to ensure they fully understand the process and are prepared if they experience side effects

Note: to reduce tablet burden, if a dose higher than 800 micrograms is needed, patients may be given a second UPTRAVI 200 microgram titration pack and a pack of UPTRAVI 800 microgram tablets

Patient Communication

- Contact your patients weekly during the titration period to discuss their progress and to ensure that any pharmacological effects are treated effectively
- Side effects associated with the pharmacological action of UPTRAVI, such as headache, diarrhoea, jaw pain, nausea and vomiting, mylagia, pain in extremity, flushing and arthralgia, have been observed frequently, in particular during the individualised dose titration
- Expected pharmacological side effects are usually transient or manageable with symptomatic treatment
- In clinical practice, gastrointestinal (GI) events have been observed to respond to antidiarrhoeal, antiemetic and antinauseant medications and/or drugs for functional GI disorders. Pain-associated events have been frequently treated with analgesics (such as paracetamol)

Maintenance

- Once a maintenance dose is achieved, an equivalent single-tablet strength for the individualised maintenance dose can be prescribed (200–1,600 microgram tablets available)
- This allows the patient to take one tablet in the morning and one in the evening
- Every patient is different and not everyone will end up on the same maintenance dose. No dose should exceed 1,600 micrograms BID

The single maintenance dose tablets will differ in color and have numbers stamped onto the surface showing the dose (in hundreds of micrograms)

Tablets are not actual size

janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

UPTRAVI®
film-coated tablets
selexipag

Annex 3.3: Patient Titration Guide

TITRATION GUIDE - TITRATION PACK

Page 1

Uptravi film-coated tablets
selexipag

Titration Guide

Starting Treatment with Uptravi

Please read the accompanying patient information leaflet before starting treatment. Tell your doctor if you experience side effects, as your doctor may recommend that you change your Uptravi dose. Tell your doctor if you are taking other medications as your doctor may recommend that you take Uptravi only once daily.

Page 2

Contents

Page 3

Page 4

How should you take Uptravi?
Uptravi is a medicine taken every morning and evening for the treatment of pulmonary arterial hypertension, also called PAH.

The starting dose for Uptravi is 200 micrograms **once in the morning and once in the evening.**
The first intake of Uptravi should be in the evening**.**
You should take each dose with a glass of water, preferably during a meal.

Page 5

There are 2 phases of treatment with Uptravi:

Titration
In the first several weeks, you will work with your doctor to find the dose of Uptravi that is right for you. Your doctor may have you step up from the starting dose to higher doses of Uptravi. Your doctor may step you down to a lower dose. This process is called titration. It lets your body gradually adjust to the medicine.

Maintenance
Once your doctor has found the dose that is right for you, this will be the dose you take on a regular basis. This is called the maintenance dose.

Page 6

How should you step up your dose?

You will start at the 200 microgram dose in the morning and in the evening and after discussing with your doctor or nurse step up to the next dose.
The first intake of the increased dose should be in the evening. Each step usually lasts about 1 week. It could take several weeks to find the dose that is right for you.

The goal is to reach the dose that is most appropriate to treat you.
This dose will be your maintenance dose.

Page 7

Every patient with PAH is different. **Not everyone will end up on the same maintenance dose.**
Some patients may have 200 micrograms in the morning and in the evening as their maintenance dose, while some will reach the highest dose of 1,600 micrograms in the morning and in the evening.
Others may reach a maintenance dose somewhere inbetween. What is important is that you reach the dose that is most appropriate to treat you.

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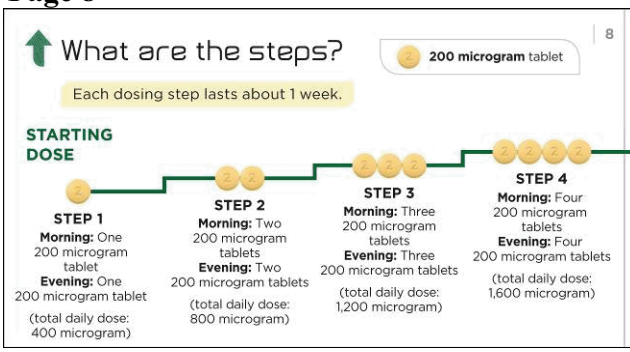

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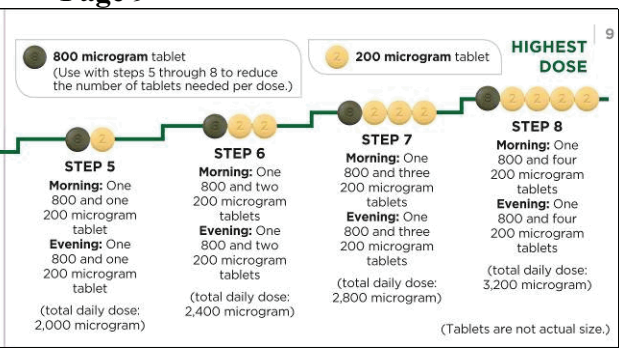


Page 10

↓When should you step down?

As with all medicines, you may experience side effects with Uptravi as you step up to higher doses.
Talk to your doctor or nurse if you have side effects. There are treatments available that can help relieve them.

The most common side effects (may affect more than 1 in 10 people) you may experience while taking Uptravi are:
• Headache • Diarrhoea • Nausea • Vomiting • Jaw pain • Muscle pain • Leg pain • Joint pain • Facial redness

For a full list of side effects see package leaflet for further information.

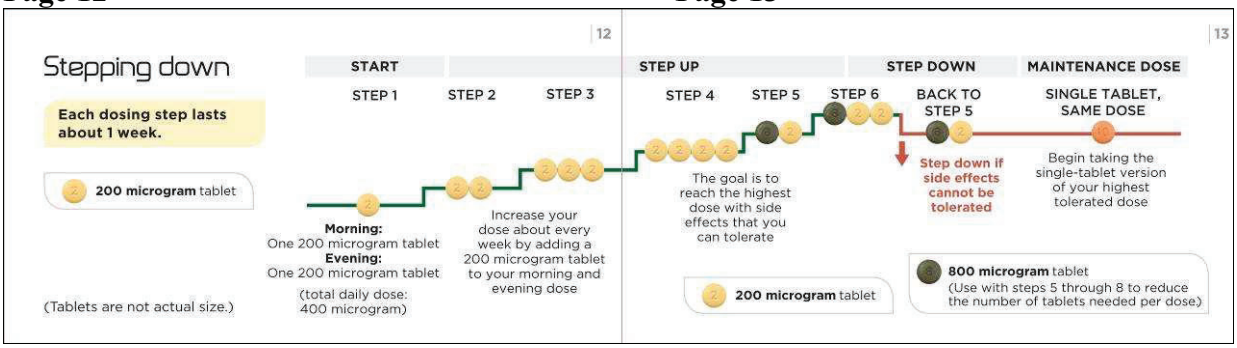
Page 11

If you cannot tolerate the side effects even after your doctor or nurse has tried to treat them, he or she may recommend you step down to a lower dose.

If your doctor or nurse tells you to step down to a lower dose, you should take one less 200 microgram tablet in the morning and one less in the evening.

You should only step down after speaking with your PAH doctor or nurse. This stepping-down process will help you find the dose that is right for you, also called your maintenance dose.

Page 12 **Page 13**



Page 14 **Page 15**

When you move to your maintenance dose

The highest dose that you can tolerate during titration will become your **maintenance dose**. Your maintenance dose is the dose you should continue to take on a regular basis. Your doctor or nurse can prescribe an equivalent **single-tablet strength** for your maintenance dose.
This lets you take just one tablet in the morning and one in the evening, instead of multiple tablets for each dose.

For example, if your highest tolerated dose during titration was 1,200 micrograms once in the morning and once in the evening:

Over time, your doctor or nurse may adjust your maintenance dose as needed.

Page 16 **Page 17**

If you forget to take Uptravi

If you miss a dose, take the dose as soon as you remember, then continue to take your tablets at the usual times. If it is within 6 hours of when you would normally take your next dose, you should skip the missed dose and continue to take your medicine at the usual time.
Do not take a double dose to make up for a forgotten tablet.

If you stop taking Uptravi

Do not stop taking Uptravi unless your doctor or nurse tells you to. If, for any reason, you stop taking Uptravi for more than 3 consecutive days (if you missed 6 doses in a row), **contact your PAH doctor or nurse immediately as your dose may need to be adjusted to avoid side effects.**

Your doctor or nurse may have you resume treatment at a lower dose, gradually increasing to your previous maintenance dose.

Page 18

Titration diary

Please read the instructions in the package leaflet carefully.

The following diary pages help you keep track of the number of tablets you need to take in the morning and evening during titration.

Use them to write down the number of tablets you take in the morning and the evening.

Each step usually lasts about 1 week, unless your doctor or nurse instructs you otherwise. If your titration steps last longer than 1 week there are additional diary pages to track this.

Use pages 20 to 27 to track the first weeks of treatment, when you are using 200 microgram tablets only (steps 1–4).

If you have been prescribed both 200 and 800 microgram tablets, use pages 30 to 37 (steps 5–8).

Page 19

Remember to talk to your PAH doctor or nurse regularly.

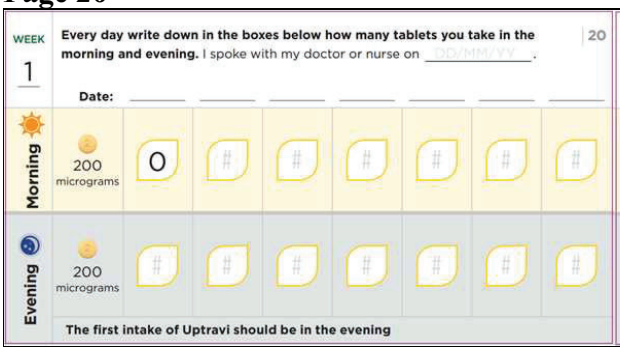
Write down your doctor or nurse's instructions:

Doctor's office telephone and email:

Pharmacist's telephone:

Notes:

Page 20



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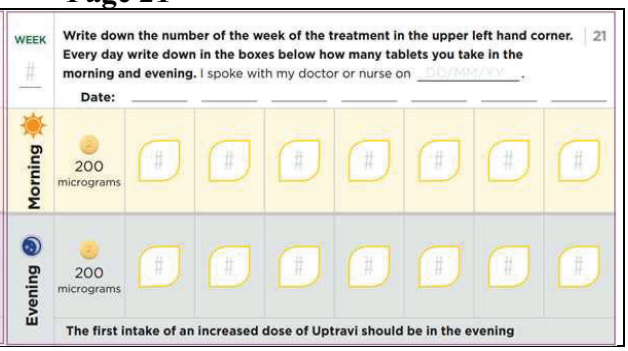

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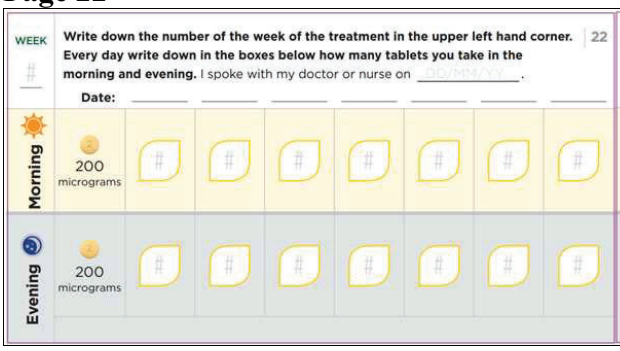

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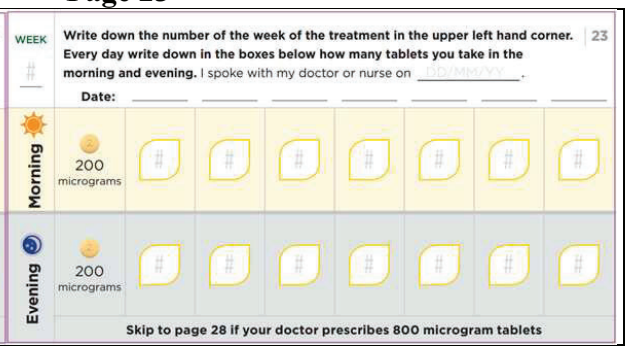

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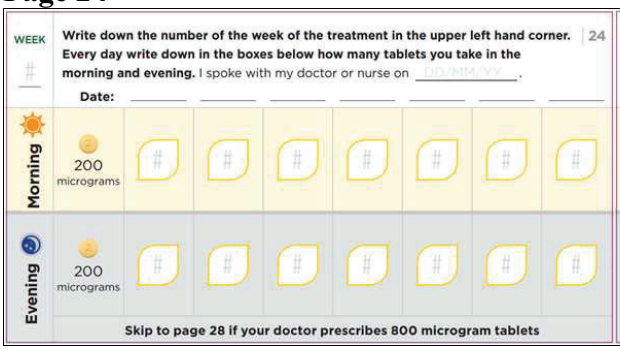

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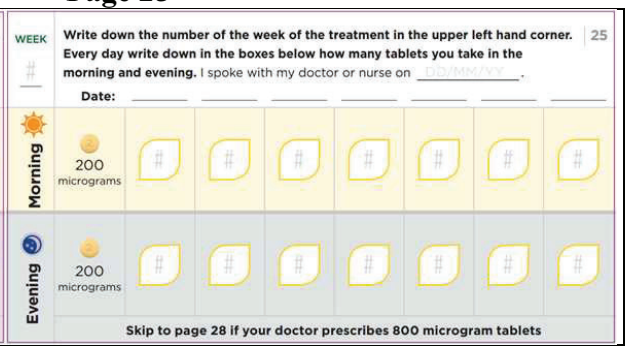

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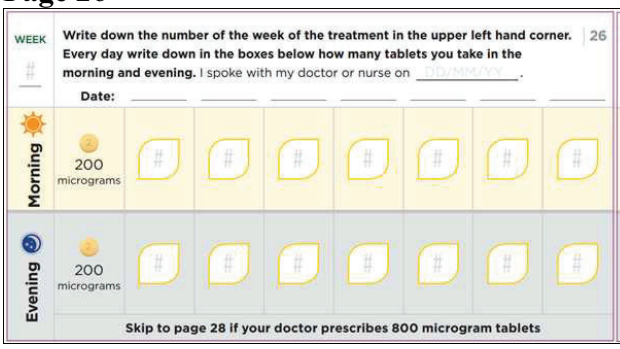

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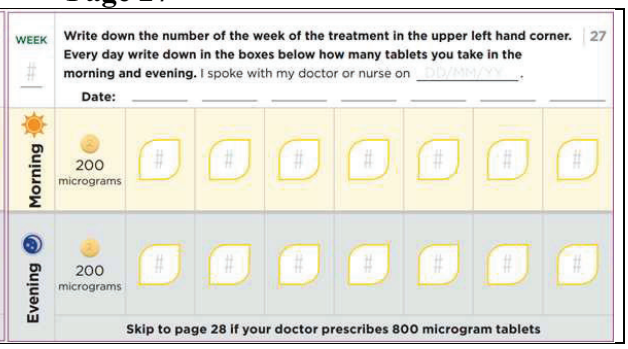

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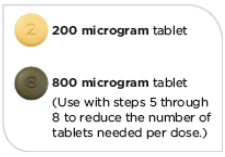
Use the following diary pages if your doctor or nurse prescribes 800 microgram tablets in addition to your 200 microgram tablets.

On the diary pages, check off that you have taken **one** 800 microgram tablet every day in the morning and in the evening with your prescribed number of 200 microgram tablets.



Page 29

Remember to talk to your PAH doctor or nurse regularly.

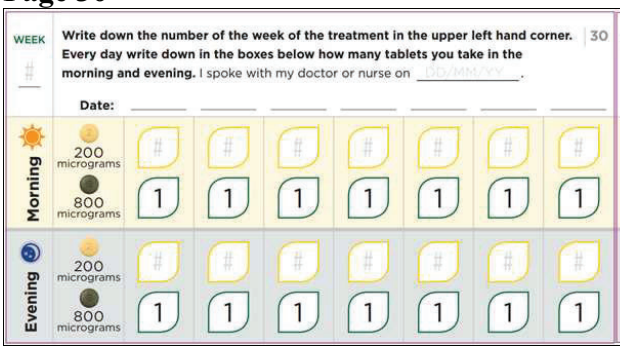
Write down your doctor or nurse's instructions:

Doctor's office telephone and email:

Pharmacist's telephone:

Notes:

Page 30



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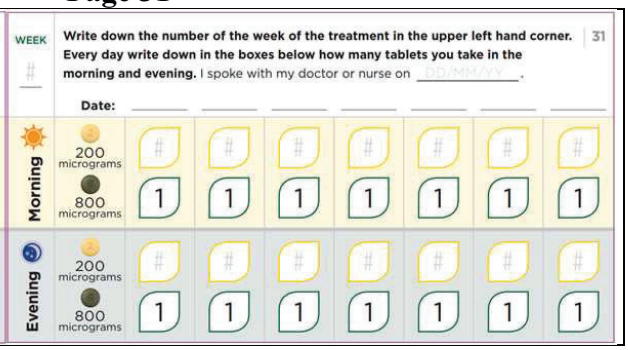

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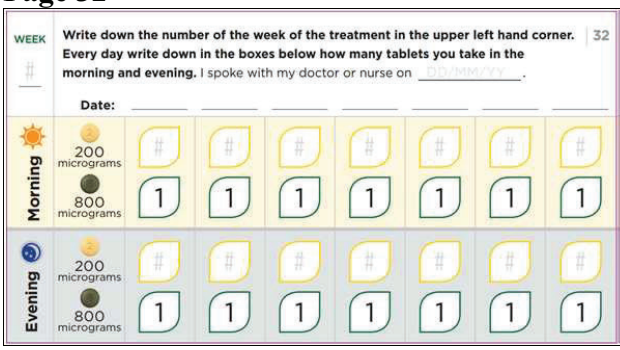

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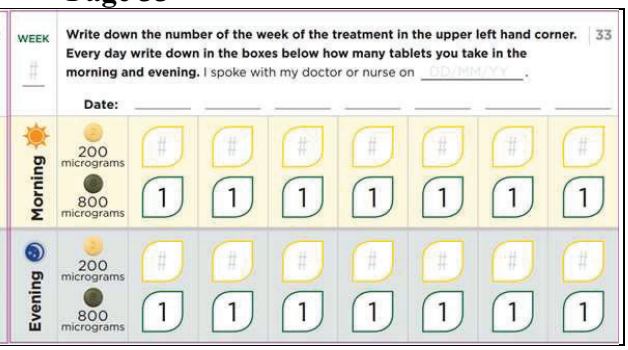

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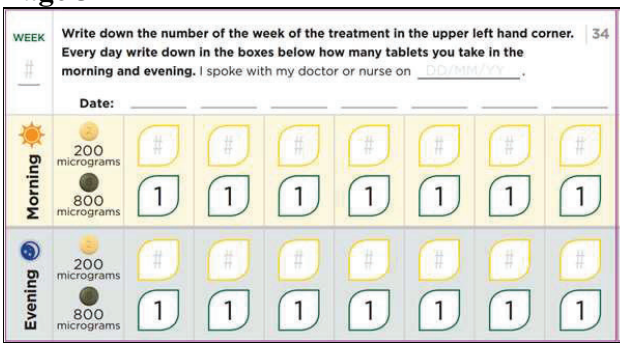

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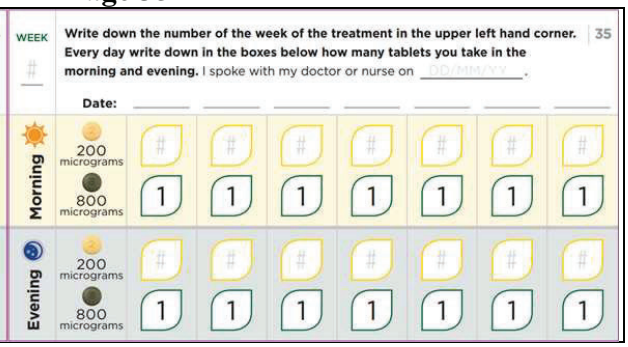

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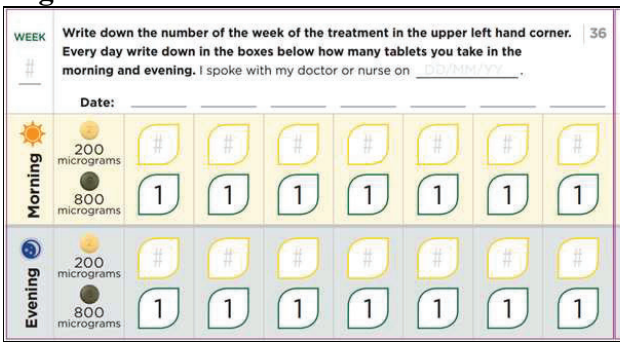

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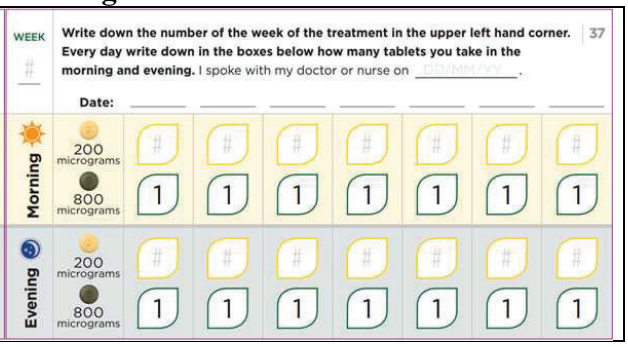

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ANNEX 4: DEFINITIONS OF ADVERSE EVENTS

Adverse event or adverse experience

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding or lack of expected pharmacological action), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product [EMA 2012].

A treatment-emergent AE is any AE with onset date after the first dose date, or earlier onset but worsening the severity, independently of being associated to the use of the Uptravi.

AEs include:

- Recurrence or worsening of a pre-existing disease.
- Increase in frequency or intensity of symptoms of a pre-existing disease or medical condition.
- Continuous persistent disease or symptoms present at enrolment/initiation of treatment that worsen following the start of the study.
- Abnormal assessments, eg, vital signs, or physical examination findings, if they represent a clinically significant finding that was not present at enrolment/initiation of treatment or worsened during the course of the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which were not present at enrolment/initiation of treatment or worsened during the course of the study or led to interruption or permanent discontinuation of Uptravi.

In addition to AEs, exposure during pregnancy or lactation, product complaints, medication errors, overdose, misuse, abuse, occupational exposure and transmission of an infectious agent via Uptravi and the identification of a potential counterfeit medicinal product needs to be reported.

Reports of Uptravi off-label use without an associated AE collected within non-interventional studies shall be included in final study reports.

AEs do not include:

- Medical procedures such as surgery, endoscopy, tooth extraction. However, the event that led to the intervention is considered an AE.

Situations in which no undesirable change occurred, such as hospitalisation for cosmetic surgery or for social reasons.

Adverse drug reaction

- An adverse drug reaction (ADR) is defined as a response to a medicinal (investigational or noninvestigational) product that is noxious and unintended. The phrase “response to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. The phrase “a reasonable possibility” means

that there are facts, evidence, or arguments to support a causal association with the medicinal product.

- An ADR, in contrast to an adverse event, is characterised by the fact that a causal relationship between the medicinal product and the occurrence is suspected. All adverse events judged by either the reporting physician or the sponsor as having a reasonable causal relationship to a medicinal product qualify as ADRs.

Serious adverse events (SAE)

An SAE is defined by the International Council for Harmonisation guidelines as any AE fulfilling at least one of the following criteria:

- Fatal.
- Life-threatening: refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.
- Requiring inpatient hospitalisation, or prolongation of existing hospitalisation.
- Resulting in persistent or significant disability or incapacity.
- Is a suspected transmission of any infectious agent via a medicinal product.
- Congenital anomaly or birth defect.
- Medically significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalisation but may be considered to be SAEs when, based upon appropriate medical judgement, they may jeopardise the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The following reasons for **hospitalisations** are exempted from being reported:

- Hospitalisations for cosmetic elective surgery, or social and/or convenience reasons.
- Hospitalisation for pre-planned (prior to enrolment) standard monitoring of a pre-existing disease (present at enrolment) or medical condition that did not worsen, eg, hospitalisation for coronary angiography in a patient with stable angina pectoris.
- Hospitalisations for elective treatment of a pre-existing disease (present at enrolment) or medical condition that did not worsen, eg, elective hip replacement for arthritis.

However, complications that occur during such hospitalisations are AEs or SAEs (for example, if a complication prolongs hospitalisation) and should be reported as described below.

Relationship to the use of Uptravi

Each AE must be assessed by the physician as to whether or not there is a reasonable possibility of causal relationship to Uptravi that was ongoing at the time of AE onset and reported as either related or unrelated. The determination of the likelihood that Uptravi caused the AE shall be provided by an investigator who is a qualified physician.

Product Quality Complaints

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labelling, or packaging, ie, any dissatisfaction relative to the identity quality, durability, reliability, or performance of a distributed product, including its labelling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system. For the PAH-specific marketed products from the MAH, PQCs are to be reported.

For PQC in patients not receiving any PAH-specific products from the MAH, it is the prescriber's/investigator's responsibility to report these PQCs to the corresponding manufacturer, as applicable.

Overdose

For this study, any dose of sponsor-marketed medication higher than the planned total daily dose in a single day according to approved medication label will be considered an overdose.

PARTICIPATING PHYSICIAN AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the conduct of the study and the obligations of confidentiality.

Sponsor's Responsible Party (Main Author):

Name (typed or printed): PPD

Institution: Actelion Pharmaceutical Ltd and Janssen Research and Development, a Division of Janssen Pharmaceutica NV

Signature: [electronic signature appended at the end of the protocol] Date: _____

(Day Month Year)

Note: If the address or telephone number of the participating physician changes during the course of the study, written notification will be provided to the sponsor; a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	22-Mar-2024 08:06:35 (GMT)	Document Approval
Oster-Gozet Laurence PPD	22-Mar-2024 11:09:48 (GMT)	Document Approval
PPD	22-Mar-2024 17:41:36 (GMT)	Document Approval