25 January 2024
EMA/91623/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Uptravi

International non-proprietary name: selexipag

Procedure No. EMEA/H/C/003774/X/0038

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AUC	area under the concentration-time curve
AUC0 24h,ss	area under the concentration-time curve over the time interval 0 to 24 hours at steady state
AUC96-120h	area under the concentration-time curve over the time interval 96 to 120 hours
AUC0-inf	area under the concentration-time curve from time 0 to extrapolated infinity
AUCτ	area under the concentration-time curve during a dosing interval
AUCτ,ss	area under the concentration-time curve during a dosing interval at steady state
bid	twice daily
BMI	body mass index
Cmax	maximum plasma concentration
Cmax,ss	maximum concentration during a dosing interval
CYP	cytochrome P450
DDI	drug-drug interaction
EMA	European Medicines Agency
FOCE-I	first-order conditional estimation with interaction
qd	once daily
PAH	pulmonary arterial hypertension
PK	pharmacokinetics
SmPC	Summary of Product Characteristics
t1/2	elimination half-life
vs.	Versus

1. Background information on the procedure

1.1. Submission of the dossier

Janssen-Cilag International N.V. submitted on 24 January 2023 an extension of the marketing authorisation to add a new strength of 100 µg film-coated tablets in HDPE bottle. The RMP (version 10.1) is updated in accordance.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (c) - Extensions of marketing authorisations.

1.3. Information on Paediatric requirements

Not applicable.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise

The application was received by the EMA on	24 January 2023
The procedure started on	23 February 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 May 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	23 May 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to	8 June 2023

CHMP during the meeting on	
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	22 June 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	7 September 2023
The CHMP Rapporteur's Assessment Report on the responses to the List of Questions was circulated to all CHMP and PRAC members on	6 October 2023
The PRAC Rapporteur's Assessment Report on the responses to the List of Questions was circulated to all PRAC and CHMP members on	13 October 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	26 October 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	9 November 2023
The MAH submitted the responses to the CHMP List of Outstanding Issues on	20 December 2023
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	9 January 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Uptravi on	25 January 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Uptravi is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO functional class (FC) II–III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies.

Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease (see section 5.1).

2.1.2. Epidemiology and risk factors

It is estimated[1] that the overall prevalence of PAH in Europe to be about 20 cases per million. PAH can be further classified into subtypes according to aetiology. These are IPAH, heritable PAH, PAH induced by exposure to drugs and toxins, or PAH associated with other conditions, such as connective tissue disease (CTD-PAH) and congenital heart disease (CHD-PAH). For the most common PAH subtypes, incidences and prevalences per million population are reported in systematic national registries: for IPAH 2.6 to 7.6 and 9.0 to 18.3; CTD-PAH 2.8 and 10.0 to 13.0; and CHD-PAH 2.2 and 7.0 to 19.0, respectively (Peacock 2007[2], Skride 2018[3], NHS Digital 2021).

Any factor or condition that is suspected to play a predisposing or facilitating role in the development of the disease is defined as a risk factor. A number of risk factors for the development of PAH have been identified that include family history, drugs and chemicals, diseases, age, and sex (Simonneau 2019[4]).

2.1.3. Aetiology and pathogenesis

The pathophysiology of PAH is not fully understood but is thought to involve abnormal interactions between endothelial and smooth muscle cells, leading to vasoconstriction, vascular smooth muscle cell proliferation, vascular endothelial proliferation, and in situ thrombosis. Reduced prostacyclin synthase activity and variably reduced IP receptor expression, an up-regulated endothelin (ET-1) system, and abnormalities of the nitric oxide pathway are considered important mediators of these pathological changes and form the therapeutic targets for currently available PAH-specific therapies (Chin 2008[5], McGoon 2009[6]).

2.1.4. Clinical presentation

PAH is a disease of the small pulmonary arteries, characterized by vascular proliferation and remodelling. These vascular changes result in a progressive increase of pulmonary vascular resistance leading to right ventricular failure and premature death. There is currently no cure for PAH. Common symptoms of PAH are shortness of breath, fatigue, non-productive cough, angina pectoris, fainting or syncope, peripheral oedema, rarely haemoptysis, and other signs and symptoms of cardiovascular decompensation. With disease progression, exercise tolerance is markedly decreased, and life expectancy is reduced (Galiè 2015a[7]).

[1] 2021 Activity Report – Orphanet
[2] Peacock AJ, Murphy NF, McMurray JJ, Caballero L, Stewart S. An epidemiological study of pulmonary arterial hypertension. Eur Respir J. 2007 Jul;30(1):104-9. doi: 10.1183/09031936.00092306. Epub 2007 Mar 14. PMID: 17360728.
[3] Skride A, Sablinskis K, Lejnieks A, Rudzitis A, Lang I. Characteristics and survival data from Latvian pulmonary hypertension registry: comparison of prospective pulmonary hypertension registries in Europe. Pulm Circ. 2018 Jul-Sep;8(3):2045894018780521. doi: 10.1177/2045894018780521. Epub 2018 May 16. PMID: 29767576; PMCID: PMC6055319.
[4] Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019 Jan 24;53(1):1801913. doi: 10.1183/13993003.01913-2018. PMID: 30545968; PMCID: PMC6351336.
[5] Chin KM, Rubin LJ. Pulmonary arterial hypertension. J Am Coll Cardiol. 2008 Apr 22;51(16):1527-38. doi: 10.1016/j.jacc.2008.01.024. Erratum in: J Am Coll Cardiol. 2008 Jul 8;52(2):169. PMID: 18420094.
[6] McGoon MD, Kane GC. Pulmonary hypertension: diagnosis and management. Mayo Clin Proc. 2009 Feb;84(2):191-207. doi: 10.4065/84.2.191. Erratum in: Mayo Clin Proc. 2009 Apr;84(4):386. PMID: 19181654; PMCID: PMC2664591.
[7] Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 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 Respir J. 2015 Oct;46(4):903-75. doi: 10.1183/13993003.01032-2015. Epub 2015 Aug 29. Erratum in: Eur Respir J. 2015 Dec;46(6):1855-6. PMID: 26318161.

2.1.5. Management

A range of conventional therapies have been shown to provide some degree of symptomatic benefit to PAH patients. Among those conventional treatments are oxygen for patients with dyspnoea associated with PAH, anticoagulants to decrease the risk for intrapulmonary thrombosis and thromboembolism, diuretics for patients with decompensated RHF associated with PAH, and calcium channel blockers, which may be of benefit in PAH patients with a positive vasoreactive response during right heart catheterization (Simonneau 2019, Fuso 2011[8]).

PAH-specific therapies target one of three major pathways (known to be involved in the development of PAH: the prostacyclin and nitric oxide pathways, which are under expressed in patients with PAH, and the endothelin pathway, which is overexpressed. Route of administration varies between the medicinal products (IV, subcutaneous, oral, or inhaled). These PAH-specific therapies are either prescribed alone or in combination, which can be either provided as initial or sequential therapies (Galiè 2019[9]).

Available pharmacological therapies for PAH address the three target pathways mentioned above:

• Prostacyclin (epoprostenol) and its analogues relax and reduce proliferation of vascular smooth muscle cells.

• ERAs, by inhibiting the effects of elevated ET-1 levels, reduce vasoconstriction, smooth muscle cell proliferation and pulmonary vessel fibrosis.

• PDE-5 inhibitors and the soluble guanylate cyclase agonist, riociguat, potentiate the anti-platelet, antiproliferative, and vasodilatory effects of nitric oxide.

2.2. About the product

Selexipag is a selective and long-acting non-prostanoid agonist of the prostacyclin receptor. Enzymatic hydrolysis of selexipag yields JNJ-68006861 (also known as ACT-333679), the active metabolite of selexipag. Selexipag is approved in over 70 countries worldwide. In the EU, selexipag is indicated for the long-term treatment of PAH in adult patients with WHO FC II-III, either as combination therapy in patients insufficiently controlled with an ERA and/or a PDE-5 inhibitor, or as monotherapy in patients who are not candidates for these therapies.

2.3. Type of Application and aspects on development

2.3.1. Legal basis

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (c) - Extensions of marketing authorisations

[8] Fuso L, Baldi F, Di Perna A. Therapeutic strategies in pulmonary hypertension. Front Pharmacol. 2011 Apr 20;2:21. doi: 10.3389/fphar.2011.00021. PMID: 21687513; PMCID: PMC3108478.
[9] Galiè N, Channick RN, Frantz RP, Grünig E, Jing ZC, Moiseeva O, Preston IR, Pulido T, Safdar Z, Tamura Y, McLaughlin VV. Risk stratification and medical therapy of pulmonary arterial hypertension. Eur Respir J. 2019 Jan 24;53(1):1801889. doi: 10.1183/13993003.01889-2018. PMID: 30545971; PMCID: PMC6351343.

2.3.2. Similarity with orphan medicinal products

It is considered that Uptravi is not similar to Opsumit within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000 due to differences in chemical structure and mechanism of action.

2.4. Quality aspects

2.4.1. Introduction

This line extension application concerns the registration of a new 100 µg tablet strength for selexipag, to facilitate adult patients that require additional dosing flexibility.

Uptravi is already authorised as immediate release film-coated tablets containing 200 µg, 400 µg, 600 µg, 800 µg, 1000 µg, 1200 µg, 1400 µg, and 1600 µg selexipag.

The finished product is presented as an immediate release film-coated tablet for oral administration containing 100 µg of selexipag as active substance.

Other ingredients are:

Tablet core: mannitol (E421), maize starch, low substituted hydroxypropylcellulose, hydroxypropylcellulose, magnesium stearate;

Film coating: hypromellose (E464), propylene glycol (E1520), titanium dioxide (E171), iron oxide yellow (E172), iron oxide black (E172), carnauba wax, talc.

The product is available in high density polyethylene (HDPE) bottle with twist-off child-resistant closure, containing 1 g silica desiccant capsule in the cap, and a heat seal liner, as described in the SmPC (section 6.5).

2.4.2. Active Substance

Module 3.2.S has not been submitted with this line extension. It is confirmed that there are no changes to the active substance (AS) compared to the authorised dossier; this is acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product (FP) is an immediate release, film-coated tablet for oral administration, containing 100 µg selexipag (JNJ-67896049-AAA or ACT-293987). The tablet strength is identified by tablet size and unique debossing; the 100 µg tablet is a yellow, round, film-coated tablet of 3 mm in diameter, debossed with "1" on one side.

For the final 100 µg film-coated tablets formulation (G043), a yellow Opadry® coating has been selected and debossing with the number "1" was implemented. The combination of the debossment and the smaller size of the tablet, is considered to allow adequate differentiation of this strength from the currently approved formulations.

A suitable development program is performed based on the experience with the already approved finished product strengths. The same excipients as used in the commercially available Uptravi film-

coated tablets have been used for the development of the 100 µg film-coated tablet, except for the coating powder.

Excipients are well characterised cand widely used in pharmaceutical preparations. Coating powder is the only excipient not used in the already approved drug products and has suitably been documented.

The 100 µg dose strength was designed to be proportionally similar to the commercially available 800 µg tablet, and it is also considered proportionally similar to the 200 µg tablets (and the 50 µg development strength). The new strength is manufactured using the same process as the authorised Uptravi tablets.

Comparative dissolution data of 200 µg tablet and 2x100 µg tablets in three different media (0.1 N HCl pH 1.2, sodium acetate buffer pH 4.5, and phosphate buffer pH 6.8) was presented and similarity profiles was shown. A relative bioavailability study was performed comparing 5 0µg and 200 µg tablets and regarded transferrable to 100 µg tablets, since strengths are dose proportional. Reference is made to the clinical part of this report for details.

The dissolution method for the 100 µg strength is identical to the already approved method. Different analytical method is used and adequately described and validated. Average dissolution profiles are shown for three representative batches. Discriminatory power of the dissolution method could not be shown for the 100 µg strengths. This has been justified emphasising that manufacturing of "bad" batches is challenging due to high solubility of the AS and small tablet size. The tightened specification limit is acceptable.

The finished product is packed in bottles rather than blisters as the previously authorised dosage strengths. Limited data exists for finally proposed packaging material and it is still questionable that patients can easily remove one single tablet from the bottle. Further, the quality of the tablets is impaired by an increase in water and higher level of degradation products during use. From quality perspective, the bottle packaging is less suitable than blisters but there is a special situation since the additional strength is necessary from clinical point of view and has been requested as commitment during the type II variation EMEA/H/C/003774/II/0022. Against this background, the CHMP requested and the applicant committed to assess additional accessories, including dispensing devices that allow tablets to be removed individually (e.g. as available for sweetener or other marketed mini tablets) as an aid for the removal of the tablets from the bottle, and to perform usability studies accordingly. The applicant agreed to comply with the above recommendation and to provide a status update to the agency within an agreed timeframe (REC1).

The development of manufacturing process has been satisfactorily laid down in line with the other authorised strengths. Critical quality attributes (CQAs) derived from the Quality Target Product Profile (QTPP), Table 3, and patient impact (safety, efficacy, and therapy compliance).

Table 1. Quality Target Product Profile

Quality Target Product Profile		Drug Product Critical Quality Attribute
Drug Product Attribute	Target	
Route of Administration	Oral	Appearance
Dosage Form	film-coated tablet	Appearance
Dosage Strength	100 µg Selexipag	Appearance, identification, assay, uniformity of dosage units
Purity	Sufficiently low level of impurities/degradation products, complying with the ICH requirements	Chromatographic purity
Drug Release Profile	Immediate release	Dissolution
Microbial Purity	Sufficiently low level of microbial burden, complying with ICH requirements	Microbial purity
Container Closure System	HDPE Bottle with desiccant in the cap, child-resistant and tamper evident	Chromatographic purity, dissolution, microbial purity
Stability	Minimum 36 months shelf life	Appearance, assay, chromatographic purity, dissolution.

An overview of CQAs and the justification of their criticality was provided. CQAs impacted by process steps were summarized and a suitable control strategy has been established.

The container closure system for commercial FP is a 15 mL high density polyethylene (HDPE) bottle with twist-off child resistant (CR) closure containing 1 g silica desiccant capsule in the inner cap. The

materials of construction of the container closure system are compliant with the European Regulation for materials intended to come into contact with food EC 1935/2004, including Regulation (EU) No 10/2011 on Plastic Materials and Articles Intended to Come into Contact with Food.

2.4.3.1. Manufacture of the product and process controls

The FP manufacturing site and other sites involved in testing, packaging and labelling were stated. GMP certificates were provided and were acceptable.

The manufacturing process comprises nine steps including blending, granulation solution preparation, granulation and drying, final blending, compression, film-coating suspension, preparation, film-coating, polishing and packaging. The process is considered as standard process and is adequately described. A flow chart was presented. The manufacturing process for the new strength is the same process as the process used for the authorised Uptravi tablets.

Critical steps were described, the relevant critical process parameters were identified and suitable in-process control (IPCs) are in place. The manufacturing process has been validated by three consecutive batches of selexipag 100 µg film coated tablets. The results of the validation batches demonstrate that the manufacturing process of selexipag 100 µg film-coated tablets is robust, reproducible and able to produce product with the specified quality.

2.4.3.2. Product specification

The FP release and shelf life specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (UHPLC , UV), assay (UHPLC), chromatographic purity (UHPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), water content (Ph. Eur.) and microbial purity (Ph. Eur.).

The finished product release and shelf-life specification is acceptable. The limits for specified degradation products have been justified; justification is accepted that this limit is toxicologically qualified. Although it might generally be acceptable that limits are wider than the limits for already approved dosage strengths, the specification limits should be reconsidered when additional stability data for commercial scale batches in proposed primary packaging become available (REC3).

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Component approach is used for risk assessment of elemental impurities. The applicant has converted the 30% permitted daily exposure values to control thresholds for each component, and evaluated whether those components can contribute significantly to the elemental impurity levels in the finished product by comparing the calculated component control thresholds with information from component suppliers, batch screening results, historical screening data, published literature, and/or specifications. The conclusion is that the concentrations of all Class 1, Class 2A and Class 3 elemental impurities in all components are below the calculated control thresholds. The risk assessment concluded that none of the elemental impurities assessed are expected to exceed their control thresholds and that the manufacturing process and analytical controls in place are adequate to assure that the levels of the elemental impurities in the finished drug product do not exceed the permitted levels. Based on the risk assessment and the presented information it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC)

No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) Nº 726/2004 for nitrosamine impurities in human medicines (EMA/425645/2020).

Since secondary amines were identified in the AS and the formation of nitrosamine impurities (NDSRI as well as NMBA and NDMA) may be possible, a Major Objection (MO) was raised requesting the applicant to perform confirmatory testing unless otherwise justified. In response to the MO the applicant provided detailed purge calculation for relevant secondary amines present in the AS synthesis. Excipients as source of nitrite have adequately been considered. Overall, it is plausible that the potential combined exposure is therefore assessed to be far below 10% of the AI. In addition no degradation products have been identified and thus, risk of N-nitrosamine impurity formation over shelf life is considered low as well. Based on the information provided the MO was resolved and it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The information regarding the reference standards used is also satisfactory.

Batch analysis data were provided for 6 commercial scale manufactured at the proposed site. In addition data from another 9 development batches were presented. All results were within the proposed specifications and demonstrate consistency of the manufacturing process.

2.4.3.3. Stability of the product

Stability data from 4 (3 primary stability and one PPQ batch) commercial scale batches of finished product manufactured by the proposed site, stored for up to 12 months under both long-term storage conditions of 25 °C / 60% RH up to 18 months under intermediate condition 30 °C / 75% RH, and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Initially very limited stability data was provided (6 months) in the proposed commercial packaging and that was raised as a MO which was addressed by provision of additional long term and intermediate conditions stability data.

The 3 primary stability batches are not packaged in the proposed commercial container closure system (15ml HDPE bottle with a child-resistant closure with 1 g desiccant embedded in the cap and filled with either 60, or 140 tablets) but are packaged in 40 mL HDPE bottles, with a child-resistant closure with 2 g desiccant embedded in the cap and filled with 60 tablets. Both bottles are of the same composition and use the same cap. The amount of desiccant embedded in the cap is reduced to 1 g for the 15 mL bottle based on shelf life modelling, which demonstrated that the specific degradant will remain below the limit .

The fourth batch (PPQ) is packaged in the exact packaging as proposed for the commercial product.

Samples were tested for appearance, assay, chromatographic purity, dissolution, water content, Microbiological purity and water activity. The results were within specification for all monitored parameters through 12 months at both long-term storage conditions of 25°C/60%RH , 18 months intermediate condition 30 °C / 75% RH, and through 6 months of storage at the accelerated storage condition of 40 °C / 75% RH compared to the initial values.

However degradation products in the PPQ batch (packaged in the commercial packaging material), although remained within the specification limits increased at accelerated conditions compared with the 3 primary stability batches. A MO was raised in this regard about the suitability of the proposed

packaging and desiccant configuration, as it seemed that the package proposed for commercial use (15ml bottle and 1g desiccant) is not as protective as the package used for primary stability batches (40ml bottle and 2g desiccant). In response to the MO the impact of the smaller bottle size with a different amount of desiccant on the concentrations of both specified degradation products over a shelf-life, and the electrostatic behaviour of the 100 µg tablets, were evaluated. The choice of primary packaging material has thoroughly been discussed and justified. However, it is currently not clear that patients can easily remove one single tablet from the bottle. The tablets are very small and electrostatic behaviour is described that might complicate the removal of one single tablets. In this respect the applicant commitment to assess additional accessories, including dispensing devices that allow tablets to be removed individually, as an aid for the removal of the tablets from the bottle and to perform usability studies accordingly is accepted (REC1).

An in-use stability study has been performed on one batch packed as 60 and 140 tablets in the proposed commercial container closure system (15 mL HDPE bottle with 1 g desiccant) under long-term conditions (25 °C/60% RH and 30 °C/75% RH) at the initial time point of the stability studies. The in-use study will be repeated at the end of the proposed shelf-life. As expected, an increase of water content was observed through 3 months of in-use storage exceeding the initially proposed water content specification limit at all time points. However the increased water content induced only a slight increase of specified degradation product JNJ-68006861-AAA which remained within the proposed specification.

As a higher water content is neither causing a quality risk nor has an impact on the dispensing of the tablets from the bottles, the originally proposed shelf-life limit for water content was widened. The revised shelf-life limit for water content is considered appropriately justified based on the observed water content increase during storage and in-use testing, the maximum water sorption capacity of the tablets and allowing for analytical variation. The available real-time and in-use stability data, including predictive modelling, confirm that all finished product quality attributes are expected to remain within the proposed specification limits throughout the proposed shelf life.

With regard to the ongoing in use stability studies (240033 and 240034) at the end of shelf-life the applicant committed as requested to update the protocol to include all stability indicating parameters at each timepoint (i.e., A = Appearance, assay, chromatographic purity, dissolution, water content and hardness (hardness is tested for information only) and B = Microbial purity) in order to further confirm the physical stability of the tablets throughout the in-use period (REC2).

Overall the totality of the data supports the proposed in-use shelf-life of 3 months for the finished product packed as 60 and 140 count in the commercial primary packaging.

In addition the provided stability protocols and relevant commitments are acceptable.

Forced degradation studies under extreme stress conditions were performed on one commercial batch to test the effects of thermal acidic, thermal alkaline, oxidative, neutral, dry heat, humid heat, light (ICH Q1B) and metal ions conditions on the drug product as per ICH Q1B. These studies were also conducted to demonstrate that the proposed UHPLC chromatographic purity method is stability indicating. Photostability testing (as per ICH guideline Q1B) was considered during forced degradation study. It was found that coating gives suitable protection to light and the product is not prone to degradation under photolytic conditions.

Based on submitted stability data, the proposed shelf-life of 18 months without special storage conditions as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

2.4.3.4. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. No changes are applicable for the active substance compared to the authorised dossier and thus no new information for the Active Substance was presented in the dossier. The three Major Objections raised during the procedure related to the potential presence of nitrosamine impurities, the suitability of the container closure system and the limited stability data (to support the proposed shelf life) were resolved by provision of additional data and information.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to assessing additional accessories or dispensing devices to allow easier removal of individual tablets from the bottle, updating the in-use stability studies protocol and re-evaluating the shelf-life acceptance criteria for related substances.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. to assess additional accessories, including dispensing devices that allow tablets to be removed individually, as an aid for the removal of the tablets from the bottle and to perform usability studies accordingly. An assessment report, containing our proposed next steps, will be provided to the agency within an agreed timeframe.
2. to update the protocol for the ongoing in-use stability studies and at the end of shelf-life to include all stability indicating parameters at each timepoint to further confirm the physical stability of the tablets throughout the in-use period. The results of the in-use stability study at the end of shelf-life will be provided once available within an agreed timeframe.
3. to re-evaluate the shelf-life acceptance criteria for related substances (referred to as chromatographic purity in section 3.2.P.5.1) based on additional stability data on commercial drug product batches in the proposed commercial primary packaging within an agreed timeframe.

2.5. Non-clinical aspects

No new non-clinical data was submitted to support this application which was considered acceptable by CHMP.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

2.6.2. Clinical pharmacology

No new clinical studies were performed regarding the development of the 100-µg tablet (which is concerned by this application), and the MAH requested a biowaiver regarding the introduction of this new strength.

Therefore, the 100 µg film-coated selexipag tablet has not been evaluated in a clinical bioequivalence (BE) study.

The request for a biowaiver for a clinical bioequivalence study of the 100 µg formulation is supported by a comparative in vitro dissolution study (please refer to Quality section above) and the clinical relative bioavailability Study AC-065-112, conducted prior to the development of the 100-µg dose strength.

In addition, in the bioequivalence program completed as part of the initial MAA, which included bioequivalence Study AC-065-108 and comparison of the in vitro dissolution profiles, bioequivalence was demonstrated between 8×200 µg and 1×1600 µg film-coated tablets of selexipag i.e., the highest approved tablet strength.

Study AC-065-108 demonstrated the bioequivalence of 1600 µg selexipag administered either as 8 film-coated tablets of 200 µg or administered as a single 1600 µg film-coated tablet in healthy male participants. This study has been assessed at the time of the initial MA and allowed extrapolation of the "clinical study formulation" to all of the strengths marketed.

In-vitro dissolution was investigated comparing the dissolution of 4×50 µg, 2×100 µg, and 1×200 µg selexipag film-coated tablets in order to support a biowaiver for a clinical BE study with the 100-µg strength.

A waiver for a BE study for a new strength is in line with the criteria as set up in Guideline CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **.

These conditions can be applied for extrapolation from a higher established (i.e. 200 µg) to a lower strength in case of linear or more than linear dose related exposure which is the case. The pharmacokinetics of selexipag and the active metabolite, both after single- and multiple-dose administration, are dose-proportional up to a single dose of 800 micrograms and multiple doses of up to 1,800 micrograms twice daily.

The a.m. criteria for bridging of the 100-µg film-coated tablet (G043) to the commercial formulations are sufficiently met:

(1) the 100-µg film-coated tablet is manufactured using the same process as the commercial Uptravi adult tablets.

(2) the qualitative composition of the 100-µg film-coated tablet is similar to the 200 µg Uptravi adult tablet as the same excipients are used, except for the film-coating components.

(3) the 100-µg film-coated tablet is almost quantitatively proportionally to the 200 µg Uptravi adult tablet, minimal differences are not considered relevant and

(4) the in vitro dissolution behaviour of the 100-µg film-coated tablet (G043) was compared to the commercially available 200 µg film-coated tablet and f2 similarity criteria were met.

The in vitro dissolution profiles of all 3 formulations were found to be similar (f2 ≥50) in the 3 pharmacopeial buffers (ie, 0.1 N HCl pH 1.2, sodium acetate buffer pH 4.5, and phosphate buffer pH 6.8) when tested at the same dose of 200 µg (ie, 4×50 µg tablets, 2×100 µg tablets, or 1×200 µg tablet per vessel.

It should also be noted that the 100 µg selexipag tablet strength has the same pharmaceutical dosage form (film-coated tablet), qualitative composition, and manufacturing process as the currently marketed film-coated tablets. The 100-µg tablet has a proportionally similar composition to the currently marketed 800 µg tablet. In addition, the 100-µg tablet is considered proportionally similar to the currently marketed 200 µg tablet and to the 50-µg tablet (developed for clinical study use) used in the relative bioavailability Study AC-065-112).

2.6.3. Conclusions on clinical pharmacology

Based on the EMA guidance on the Investigation of Bioequivalence pertaining to a bridging approach (CHMP Guideline on the Investigation of Bioequivalence, 2010), the CHMP is of the opinion that a biowaiver for the 100-µg dose strength has been appropriately justified.

2.6.4. Clinical efficacy

No new clinical efficacy data was submitted in support of this application for a new 100 µg selexipag tablet strength as the efficacy profile of the 100-µg tablet strength is expected to be consistent with the already approved strengths. This was considered acceptable by CHMP.

2.6.5. Clinical safety

No new data on clinical safety were provided for the 100-µg strength which was considered acceptable by CHMP.

The CHMP took note of the safety data available from the comparative bioavailability study AC-065-112 (4 x 50 µg paediatric formulation vs. 200 µg film coated tablet (marketed formulation) including 20 male healthy volunteers (cross over design). No new safety issues were identified from this study.

2.6.6. Conclusions on the clinical safety

The safety profile of the 100-µg tablet strength is expected to be consistent with the other already approved strengths.

2.7. Risk Management Plan

2.7.1. Safety concerns

Important identified risks	Hypotension
	Anemia
	Hyperthyroidism
	Concomitant use with strong inhibitors of CYP2C8
Important potential risks	Pulmonary edema associated with PVOD
	MACE
	Renal functional impairment / acute renal failure
	Bleeding events
	Light-dependent non-melanoma skin malignancies
	Ophthalmological effects associated with retinal vascular system
	GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction)
	Medication error
Missing information	Use in pediatric patients
	Use in elderly over 75 years old
	Use during pregnancy and lactation
	Concomitant use with strong inhibitors of UGT1A3 and UGT2B7

2.7.2. Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
AC-065A401 EXPOSURE PASS: observational cohort study of PAH patients newly treated with either UPTRAVI®	To further characterize the safety profile in PAH patients treated with UPTRAVI in routine clinical practice; including additional experience of the use of	• Hypotension • Anemia • Hyperthyroidism • Pulmonary edema associated with PVOD • MACE	Annual updates	Progress reports on enrolment and intermediate analysis results will

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
(selexipag) or any other PAH-specific therapy, in clinical practice. Ongoing	UPTRAVI in patients over the age of 75 years; and to compare mortality and MACE rates with PAH patients not treated with UPTRAVI.	• Renal function impairment / acute renal failure • Bleeding events • Light-dependent non-melanoma skin malignancies •Ophthalmological effects associated with retinal vascular system • GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction) • Use in elderly over 75 years old	Final study report	be provided yearly, including mortality data. Submission of combined final study report of study results from EXPOSURE and EXTRACT for PRAC agreement: 2024. Final study report 12 months after PRAC agreement
67896049PAH0002 EXTRACT PASS: retrospective medical chart review of PAH patients newly treated with either UPTRAVI® (selexipag) or any other PAH-specific therapy. Planned	The purpose of this PASS is to complement EXPOSURE to further characterize the safety profile in PAH patients treated with UPTRAVI in routine clinical practice; including additional experience of the use of UPTRAVI in patients over the age of 75 years; and to describe mortality and MACE rates with PAH patients not treated with UPTRAVI.	• Hypotension • Anemia • Hyperthyroidism • Pulmonary edema associated with PVOD • MACE • Renal function impairment / acute renal failure • Bleeding events • Light-dependent non-melanoma skin malignancies •Ophthalmological effects associated with retinal vascular system • GI disturbances denoting intestinal	Final study report	Submission of combined final report of study results from EXPOSURE and EXTRACT for PRAC agreement: 2024

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
		intussusception (manifested as ileus or obstruction) • Use in elderly over 75 years old		
AC-065A403 EDUCATE **PASS** to evaluate risk minimization measures for medication errors with UPTRAVI during the titration phase in patients with pulmonary arterial hypertension (PAH) in clinical practice. Planned	The objectives of this study are to assess HCPs' and patients' awareness (process), knowledge (impact), and comprehension (impact) of the risk minimization materials and to record the occurrence of patient- reported "wrong dose" medication errors (outcome) at completion of titration or discontinuation of UPTRAVI during titration.	Occurrence of medication errors during the UPTRAVI titration phase.	Final study report	Final study report submission: 2024

2.7.3. Risk minimisation measures

Safety concern	Routine risk minimisation activities
Hypotension (important identified risk)	Routine risk communication: SmPC section 4.4: 'Special warnings and precautions for use'. SmPC section 4.8: 'Undesirable effects' in the ADR table as a common adverse reaction.

	PL section 2: 'What you need to know before you take UPTRAVI'. PL section 4: 'Possible side effects'. <u>Routine risk minimization activities recommending specific clinical measures to address the risk:</u> None <u>Other routine risk minimization measures beyond the Product Information:</u> Medicinal product subject to restricted medical prescription.
Anemia (important identified risk)	<u>Routine risk communication:</u> SmPC section 4.8: 'Undesirable effects' in the ADR table as a common adverse reaction based on data from the GRIPHON study. Section 4.8 of the SmPC also includes a description that anemia was reported at a higher frequency in the TRITON study. PL section 4: 'Possible side effects'. <u>Routine risk minimization activities recommending specific clinical measures to address the risk:</u> None Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription.
Hyperthyroidism (important identified risk)	<u>Routine risk communication:</u> SmPC section 4.4: 'Special warnings and precautions for use'. SmPC section 4.8: 'Undesirable effects' in the ADR table as a common adverse reaction. PL section 2: 'What you need to know before you take UPTRAVI'. PL section 4: 'Possible side effects'. <u>Routine risk minimization activities recommending specific clinical measures to address the risk:</u> None <u>Other routine risk minimization measures beyond the Product Information:</u> Legal status: Medicinal product subject to restricted medical prescription.
Concomitant use with strong inhibitors of CYP2C8 (important identified risk)	<u>Routine risk communication:</u> SmPC section 4.3: 'Contraindications'. SmPC section 4.5: 'Interaction with other medicinal products and other forms of interaction'. PL section 2: 'What you need to know before you take UPTRAVI'. <u>Routine risk minimization activities recommending specific clinical measures</u>

	to address the risk: None Other routine risk minimization measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription.
Pulmonary edema associated with PVOD (important potential risk)	Routine risk communication: SmPC section 4.4: 'Special warnings and precautions for use'. Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription.
MACE (important potential risk)	Routine risk communication: SmPC section 4.3: 'Contraindications'. PL section 2: 'What you need to know before you take UPTRAVI'. Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription.
Renal function impairment / acute renal failure (important potential risk)	Routine risk communication: SmPC section 4.2: 'Posology and method of administration'. SmPC section 4.4: 'Special warnings and precautions for use'. SmPC section 5.2: 'Pharmacokinetic properties'. PL section 2: 'What you need to know before you take UPTRAVI'. Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription.
Bleeding events (important potential risk)	Routine risk communication: SmPC section 4.5: 'Interaction with other medicinal products and other forms of interaction'. PL section 2: 'What you need to know before you take UPTRAVI'. Routine risk minimization activities recommending specific clinical measures

	to address the risk: None Other routine risk minimization measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription.
Light-dependent non melanoma skin malignancies (important potential risk)	Routine risk communication: None risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription.
Ophthalmological effects associated with retinal vascular system (important potential risk)	Routine risk communication: SmPC section 5.3: 'Preclinical safety data'. Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription.
GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction) (important potential risk)	Routine risk communication: SmPC section 4.2: 'Posology and method of administration'. SmPC section 5.3: 'Preclinical safety data'. PL section 2: 'What you need to know before you take UPTRAVI'. Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription.
Medication error (important potential risk)	Routine risk communication: SmPC section 4.2: 'Posology and method of administration'. PL section 2: 'What you need to know before you take UPTRAVI'. PL section 3: 'How to take UPTRAVI'. Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information:

	Legal status: Medicinal product subject to restricted medical prescription. The authorized pack size is chosen to ensure that the medicine is used correctly.
Missing information in use in pediatric patients	Routine risk communication: SmPC section 4.2: 'Posology and method of administration'. SmPC section 5.1: 'Pharmacodynamic properties'. PL section 2: 'What you need to know before you take UPTRAVI'. Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription.
Missing information in use in elderly over 75 years old	Routine risk communication: SmPC section 4.2: 'Posology and method of administration'. SmPC section 4.4: 'Special warnings and precautions for use'. PL section 2: 'What you need to know before you take UPTRAVI'. Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription.
Missing information in use during pregnancy and lactation	Routine risk communication: SmPC section 4.4: 'Special warnings and precautions for use'. SmPC section 4.6: 'Fertility, pregnancy and lactation'. SmPC section 5.3: 'Preclinical safety data'. PL section 2: 'What you need to know before you take UPTRAVI'. Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription.
Missing information in concomitant use with strong inhibitors of UGT1A3 and UGT2B7	Routine risk communication: SmPC section 4.5: 'Interactions with other medicinal products and other forms of interaction'. SmPC section 5.2: 'Pharmacokinetic properties'.

	Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription.

2.7.4. Conclusion

The CHMP considered that the risk management plan version 10.1 is acceptable.

The safety profile of selexipag remains unchanged. No new safety issues were identified during the assessment of data that were submitted in support of the authorisation of the 100-µg tablet strength. No changes to the summary of safety concerns are required.

However, the applicant should provide in future PSURs a cumulative review addressing the question whether an accurate removal of 100 µg tablets from the bottle is ensured in the real clinical practice, taking into account the small size of the tablets and considering their electrostatic behaviour.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

A User testing of the Package Leaflet was not submitted by the MAH. This is acceptable considering that changes are mainly restricted to dosing recommendations.

3. Benefit-Risk Balance

The benefit risk balance of Uptravi remains positive. Dose adapted bioequivalence of the newly proposed strength to the commercially available 200 µ strength has been demonstrated. A reduced bid dosing for patients receiving moderate CYP2C18 inhibitors is incorporated in the SmPC and PIL, a reduced qd dosing may be maintained for patients already sufficiently stabilized on qd administration or in cases an appropriate dose strength to establish a reduced bid dosing is not available.

3.1. Conclusions

The overall benefit/risk balance of Uptravi is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Uptravi is not similar to Opsumit within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix on similarity.

Outcome

Based on the CHMP review of data on quality, the CHMP considers by consensus that the benefit-risk balance of, Uptravi new strength is favourable in the following indication:

Uptravi is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO functional class (FC) II–III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies.

Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease (see section 5.1).

The CHMP therefore recommends the extension(s) of the marketing authorisation for Uptravi subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and

interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- **Additional risk minimisation measures**

Prior to the launch of Uptravi in each Member State, the MAH must agree on the content and format of the Controlled Access System with the National Competent Authority.

The Controlled Access System is aimed to facilitate the identification of prescribers, to approach them with the appropriate information on the safe and effective use of Uptravi, and to provide them with risk minimisation tools, especially regarding the potential risk of medication error. The Controlled Access System should include three key principles that will be incorporated within each system in all Member States. These are:

- The identification and maintenance of a list of all Uptravi prescribers;
- The distribution of kits to all identified prescribers to minimise the risks of medication error in particular;
- Tracking of the receipt of the kits by prescribers.

The MAH shall ensure that in each Member State where Uptravi is marketed, all healthcare professionals who are expected to prescribe and/or dispense Uptravi are provided with a Prescriber Kit containing the following:

- The Summary of Product Characteristics for Uptravi;
- Cover letter to the healthcare professional;
- Healthcare professional A4 laminated titration guide(s);
- Patient titration guide(s);
- Patient Leaflet.

The cover letter to the healthcare professional should explain that the purpose of the educational materials is to reduce the risk of medication error due to the availability of multiple tablets and dose strengths, and it should provide a list of the contents of the Prescriber Kit.

The healthcare professional A4 laminated titration guides for selexipag starting doses of 100 micrograms and 200 micrograms are intended to reduce the risk of medication error due to the titration phase at treatment initiation with Uptravi and it should contain the following key elements:

- The dosing and titration concept;
- The move to the maintenance dose (titration phase);

- Expectations and management of adverse reactions during the titration phase;
- Encouragement and guidance for healthcare professionals to communicate clearly with the patient during their first visit, as well as to take responsibility to contact the patient during the titration phase, facilitating communication between healthcare professional and the patient (need for contact and to schedule telephone calls).

Patient titration guides for selexipag starting doses of 100 micrograms and 200 micrograms are available. The patient titration guide to be used by the healthcare professionals during discussions with the patient should contain the following key elements:

- Lay language version of the healthcare professional A4 laminated titration guide;
- Diary to facilitate Uptravi use and serve as a reminder for the patients (e.g., to contact her/his doctor), and a place to record intake of tablets;
- Information about the safe and effective use of Uptravi in lay language.

The patient titration guide corresponding to the patient's selexipag starting dose of 100 micrograms or 200 micrograms along with the Patient Information Leaflet should be given to the patient after the demonstration. Patients will receive a titration guide and Patient Leaflet in their titration packs of Uptravi.