Expert Consensus on Best Practices for Oral Selexipag Titration and Management of Expected Side Effects (SE) in the Treatment of Pulmonary Arterial Hypertension (PAH)

Sheryl Wu[1] , Gurinderpal Doad[2], Christina Benninger[2], Michelle Cho[2], Richard Perry[3], Daisy Bridge[3], Charlotte Oswald[3], Luis Val-Maranes[3], Paul Strachan[2]

[1]University of California, San Diego, La Jolla, CA
[2]Actelion Pharmaceuticals United States (US), Inc., a Johnson & Johnson company,Titusville, New Jersey, US
[3]Adelphi Values PROVE, Bollington, Cheshire, United Kingdom

Background

- Prostacyclin pathway agents are foundational for the treatment of PAH. These agents have demonstrated effects on exercise capacity, PAH hospitalization rates and mortality.
- Oral selexipag is a selective prostacyclin receptor agonist approved for patients with PAH to delay disease progression and reduce the risk of PAH-related hospitalizations, based on a robust evidence base that has been growing since GRIPHON, the largest PAH outcomes study to date.[1-3]
- Management of expected prostacyclin SE is necessary to find the most appropriate and effective dose and to improve treatment adherence and quality of life (QoL) for patients.
- However, there is significant variation on the approach for managing patients on oral selexipag, so this study aimed to provide expert recommendations to improve oral selexipag titration and SE management.

Objective

To reach consensus recommendations regarding titration and SE management by conducting a double-blinded Delphi panel of clinical experts with oral selexipag experience.

Methods

- The study was conducted between April and November 2023 using a double-blinded modified Delphi method (Figure 1): a structured communication method to elicit consensus from a range of opinions.
- The Delphi panel included a virtual consensus meeting that was held to discuss and revise any statements that did not reach consensus in the surveys (panel rounds 1 and 2).
- A nine-point Likert scale (from 1 [strongly disagree] to 9 [strongly agree]) was used to rate consensus.

Figure 1. Modified Delphi panel

Inclusion criteria
- ✓ US-based healthcare professionals (HCPs) actively treating patients with PAH
- ✓ Knowledge and experience of managing patients with oral selexipag

Recruitment of 17 panelists (11 physicians, 5 nurse practitioners (NPs) and 1 registered nurse (RN))

Delphi panel round 1: Online Questionnaire (n=17)

Analysis of **Delphi panel** Round 1 results

Delphi panel round 2: Online Questionnaire (n=17)

Analysis of **Delphi panel** Round 2 results

Delphi panel round 3: Consensus Meeting (n=11)
Attended by eight physicians, two NPs and one RN

Results

Panelists characteristics

- Most panelists (n=11/17) practice in accredited pulmonary hypertension centers.
- The average number of patients with PAH that the panel were treating with oral selexipag at the time of recruitment was 36 for physicians (n=11) and 35 for NPs and RN (n=6).

Clinical use of oral selexipag

- Oral selexipag is suitable for a large range of patients with PAH (according to panelists' clinical experience), including but not limited to, those in Table 1.

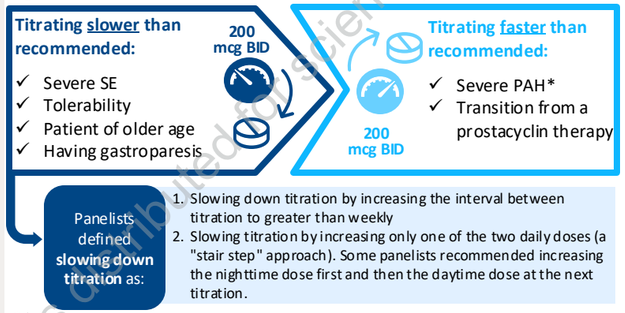
Table 1. Examples of clinical suitability of oral selexipag agreed by the panel

Intermediate risk status
A range of PAH-related symptoms, including fatigue, chest pain or edema
A range of comorbidities, including obesity, diabetes and hypertension
A range of connective tissue diseases (CTD) conditions
Prior non-PAH related hospitalisations

"Oral selexipag is appropriate across all age groups if the patient is able to tolerate it"
"Selexipag is suitable for intermediate risk patients to decrease their overall risk" – ***quotes from panelists on the suitability of oral selexipag***

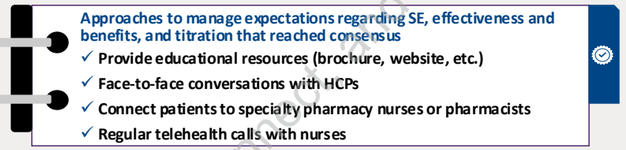
Titration of oral selexipag dose

Figure 2. Considerations that lead panelists to change the speed of titration



*Some panelists described severe PAH as patients with high risk or World Health Organisation (WHO) functional class (FC) III.

- The panel followed the approved Food and Drug Administration (FDA) dosing and titration recommendations for oral selexipag and agreed that the maintenance dose achieved is patient-specific.
- Some panelists noted that the maximum dose of oral selexipag may exceed the recommended 1600 mcg twice daily (BID) in some patients based on their clinical experience.



Expected SE management

- While panelists noted that the time to onset and resolution of expected SE can be variable and patient-specific, Figure 4 and Figure 5 show the typical time for expected SE to occur and resolve based on their clinical experience.

Figure 4. Time after first dose when patients typically experience SE (n=17)

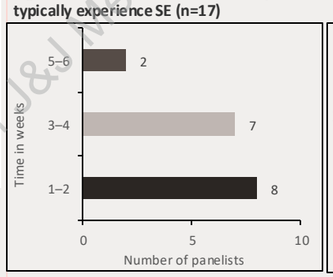
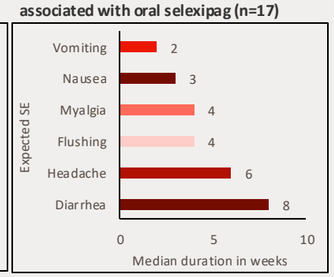


Figure 5. Median duration of expected SE associated with oral selexipag (n=17)



- Panelists noted that the time to onset and resolution of expected SE can be variable and patient-specific, but these often become manageable.

Table 2. Expected SE management approaches that reached consensus among the panel

Expected SE	Management approaches
Most common SE as agreed by the panel	
Headache	✓ Acetaminophen (Tylenol®)
Diarrhea	✓ Loperamide (Imodium®)
Occasionally occurring SE agreed by the panel	
Nausea	✓ Take oral selexipag with food (can mean 'take with a meal' and 'take with a small snack') ✓ Ondansetron (Zofran®)
Pain in extremity	✓ Screen for iron deficiency for restless legs ✓ Acetaminophen (Tylenol®)
Jaw pain	✓ No measures (reassure patient that this would get better with time)
Flushing	✓ Reassurance

"I counsel patients using the analogy about cancer and chemotherapy: this [PAH] is a severe disease and a life-threatening disease. It costs something to get the disease under control." – **quote from a panelist on SE management**

Presented at: at American Thoracic Society International Conference , May 2024

1. Janssen Submits New Drug Application (NDA) to U.S. FDA for UPTRAVI® (selexipag) Injection for Intravenous Use to Treat Pulmonary Arterial Hypertension (PAH). 2020; 2. Gaine S, et al. 2021;160(1):277-286. doi:https://doi.org/10.1016/j.chest.2021.01.066; 3.Panagiotidou E, et al. 2021;22(1):29-36. doi:10.1080/14656566.2020.1812579; 4. Sitbon O, et al. 2015;373(26):2522-2533. doi:10.1056/NEJMoa1503184 ; 5. FDA. UPTRAVI® (selexipag) tablets, for oral use. 2021.

Conclusions and Key Takeaways

- Selexipag is the only drug within the prostacyclin pathway indicated to delay disease progression and reduce PAH-related hospitalizations and is available as an oral twice daily option.
- This Delphi panel provides expert consensus recommendations on the real-world usage of oral selexipag outside of a clinical trial.
- These best practices provide additional granularity and insight (beyond current guidelines) on selexipag's dosing, titration, and SE management.
- Patient characteristics (including patient acceptability) were agreed to be the primary consideration for oral selexipag use and dictated clinical decision-making for oral selexipag.
- Findings show that the prescription and use of oral selexipag should be individualized for each patient and can be adapted through different dosing and titration methods to ensure optimal treatment and patient benefits in different patient populations with PAH.
- Despite expected SE being associated with oral selexipag, expert recommendations suggest these often become manageable over time.
- Informing patients on their disease, including discussing expected SE, treatment and titration plans, goals, and expectations is important when managing patients on oral selexipag.
- Findings may help improve management and titration of selexipag, leading to improved adherence to therapy.

Disclosures

SW is a member of the Speaker Bureau for Johnson & Johnson, as well as a member of Advisory Boards for Johnson & Johnson, Merck, and Liquidia. GD and PS employees and shareholders of Johnson & Johnson. CB and MC are employees of Johnson & Johnson. RP, DB, CO, and LVM are employees of Adelphi Values PROVE™, who were contracted by J&J to conduct this research.

Pulmonary Arterial Hypertension

Johnson&Johnson