Delphi study investigating the clinical use of oral selexipag to treat pulmonary arterial hypertension (PAH)

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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]
- Clinicians could benefit from guidelines with recommendations on the oral selexipag dosing and titration process and expected side effect management to optimize its clinical benefits and improve patients' experience.

Objective

To reach consensus on a best-practices recommendations to enhance patient care and assist with treatment 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 with 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) practiced 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, factors leading to:

Prescribe selexipag:
- ✓Difficulty managing prostacyclin therapies
- ✓Lack of access to resources necessary for parenteral formulations

Not prescribe selexipag:
- ✓Tolerability of selexipag versus other prostacyclin therapies.
- ✓Failure of other/previous therapy.

Titration of oral selexipag dose

- Panelists prescribed selexipag according to the FDA label, however noted that dosing and titration methods should be individualized for each patient to achieve their personalized dose to maximize treatment benefit.

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

Titrating slower than recommended: 200 mcg BID
- ✓ Severe side effect
- ✓ Tolerability
- ✓ Patient of older age
- ✓ Having gastroparesis

Titrating faster than recommended: 200 mcg BID
- ✓ Severe PAH*
- ✓ Transition from a prostacyclin therapy

Panelists defined **slowing down titration** as:
1. Slowing down titration by increasing the interval between titration to greater than weekly
2. Slowing titration by increasing only one of the two daily doses (a "stair step" approach). Some panelists recommended increasing the nighttime dose first and then the daytime dose at the next titration.

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

"I remind patients that they do not need to get to 1600 mcg, they just need to get to the maximum dose for them." ***– quote from panelist on managing patient expectations when started on oral selexipag***

Oral selexipag maximum dose

- Panelists noted that the maximum oral selexipag dose is primarily identified by the patients' tolerability to side effects.
- Prior treatment with parenteral prostacyclin therapy affected tolerability and some panelists suggested a higher selexipag dose is achievable by these patients.

Expected side effect management

- While panelists noted that the burden and duration of expected side effects can be variable and patient-specific, Figure 3 and Figure 4 show the side effects that are more clinically burdensome (selected by the panel) and the typical time for these to resolve based on their clinical experience.

Figure 3. Clinically burdensome side effects selected by the panel (n=17)

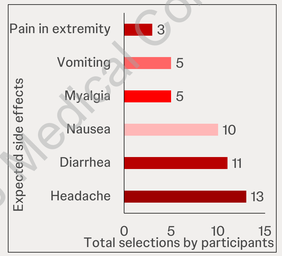
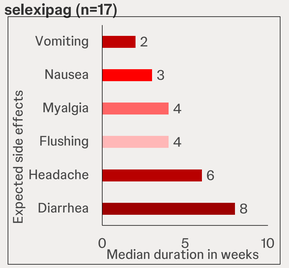


Figure 4. Median duration of expected side effects associated with oral selexipag (n=17)



- Panelists noted that side effects often become manageable with time.
- Panelists identified methods for managing each side effect (Table 2), agreeing that this should be proactive.

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

Expected side effect	Management approaches
Most common side effects as agreed by the panel	
Headache	✓ Acetaminophen (Tylenol®)
Diarrhea	✓ Loperamide (Imodium®)
Occasionally occurring side effects 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 side effect management**

- Panelists agreed that protocols that provide best practices for titration and dosing and guidance on monitoring patients on oral selexipag would be beneficial for oral selexipag expected side effect management.

Conclusions and Key Takeaways

- Selexipag is the only drug acting 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, including additional granularity and insight on dosing, titration, and side effect management.
- Panelists noted that the maximum selexipag dose should be individualized for each patient to optimize treatment, including higher doses for patients with good tolerability.
- The titration of oral selexipag should be individualized depending on the characteristics of each patient, with panelists identifying different methods for slowing down titration to adapt for patients suffering from severe side effects or lacking tolerability.
- Panelists identified common side effects associated with oral selexipag, which are typically experienced 2–4 weeks after the first dose, however it was highlighted that all these generally become manageable over time.
- Experts provided recommendations on methods for managing different oral selexipag side effects that can be included into guidelines. These may help improve clinical use and patients' experience 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

Presented at: PHA 2024 International PH Conference and Scientific Sessions

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.