Extended-release oral treprostinil in the management of pulmonary arterial hypertension: clinical evidence and experience

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Abstract: Treprostinil diolamine is the first oral prostacyclin approved for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity. Clinical studies have demonstrated modest benefit as monotherapy, whereas no difference in exercise capacity was observed with combination therapy. However, these trials were limited by subtherapeutic dosing owing to intolerable adverse effects. Prostacyclin-related adverse effects, such as nausea, diarrhea, headache, flushing, and jaw pain, are prevalent. More recent pharmacokinetic and clinical studies illustrate the dose–response relationship and the importance of achieving clinically effective doses. Therefore, efforts to improve tolerability are paramount. Oral treprostinil is recommended to be administered three times daily in order to facilitate more rapid titration, higher doses achieved, and improved tolerability. Oral treprostinil has also been studied in carefully selected, stable patients that transitioned from parenteral or inhaled therapy with close monitoring for late deterioration. Ongoing clinical trials will determine the long-term effects of higher doses of oral treprostinil on clinical outcomes. This review describes the clinical evidence and practical experience with the use of oral treprostinil for PAH.

Keywords: oral treprostinil, prostacyclins, pulmonary arterial hypertension, pulmonary hypertension, treprostinil diolamine

Introduction
Treprostinil diolamine was the first oral prostacyclin approved in 2013 for the management of patients with Group 1 pulmonary arterial hypertension (PAH) to improve exercise capacity. The development and approval of this medication represented a major step forward in PAH pharmacotherapy. PAH is a progressive and fatal disease with a 3-year survival rate in the modern era of approximately 58%.1 Prostacyclins are the proven treatment of choice in patients with advanced PAH, however, they remain underutilized for reasons that often include therapeutic complexity.2 The approval of oral treprostinil was made on the basis of the pivotal Oral Treprostinil for the Treatment of PAH (FREEDOM) trials, even though results from these studies were mixed.3–5 Its use as monotherapy led to a modest but significant improvement in exercise capacity, whereas no difference was found when studied as part of combination therapy. More recent data and postmarketing experience, however, have elucidated the contemporary use and evolving role of oral treprostinil in PAH management. Therefore, the purpose of this review is to describe clinical evidence and practical experience with the use of oral treprostinil for patients with PAH.

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activation in PAH results in reduced prostacyclin synthase and prostacyclin concentrations, and increased thromboxane A2 concentrations. The dysregulation and imbalance in this pathway mediates the pathogenesis of PAH, including vasoconstriction, vascular smooth muscle cell proliferation, and platelet aggregation. Consequently, the therapeutic use of exogenous prostacyclin represents a mainstay of therapy for advanced PAH. All prostacyclins bind to and stimulate the prostacyclin (IP) receptor, which then triggers a cascade of intracellular signaling leading to activation of adenylate cyclase, conversion of adenosine triphosphate to cyclic adenosine monophosphate, and activation of protein kinase A (Figure 1). The resulting pharmacologic effects are vasodilation of the pulmonary vasculature, inhibition of pulmonary artery smooth muscle cell proliferation, inhibition of platelet aggregation, and reversal of pulmonary artery remodeling. Prostacyclins improve exercise and functional capacity, hemodynamics, and symptoms, although only epoprostenol has improved survival in advanced PAH. Treprostinil is a second-generation prostanooid, which was developed to overcome some of the inherent limitations of epoprostenol, notably a longer half-life (4.5 h versus 4–6 min), stability at room temperature, and the commercial availability of multiple formulations (i.e. subcutaneous [SQ], intravenous [IV], inhaled, and oral). A comprehensive review of the experiences with treprostinil has been previously published.

Pharmacodynamics and pharmacokinetics of treprostinil diolamine

Treprostinil sodium is a tricyclic benzindene prostacyclin analog that is formulated as a controlled-release tablet that uses osmotic technology. Plasma protein binding is 96% and bioavailability is 17%. Sustained systemic exposure (AUC_{inf} [area under curve]) of the medication is improved during administration with a high-fat, high-calorie meal compared with the fasting state in healthy volunteers. However, oral treprostinil may be given with a meal containing as few as 250 calories and 30% fat without significantly affecting the overall bioavailability. Treprostinil is metabolized by the liver, primarily by the cytochrome P-450 (CYP) 2C8 isoenzyme and to a lesser extent by CYP 2C9. Consequently, dose adjustments are necessary for patients with Child–Pugh class A liver dysfunction whereas more advanced liver disease (class B and C) precludes use. In addition, concurrent use of a CYP2C8 inhibitor, such as gemfibrozil, results in the need for a lower dose of oral treprostinil.

The half-life is approximately 4.5 h with sustained concentrations for 8 h after a single dose. The relationship between dose and AUC (plasma concentration–time) is linear during chronic administration at doses up to 16 mg twice daily (BID). A 1 mg tablet of oral treprostinil provides a similar maximum concentration (C_{max}) to infusion treprostinil at a dose of 8–12 ng/kg/min. Smaller dosage strengths, including 0.25 mg tablets, are approximately equivalent to a dose of 2–3 ng/kg/min with regard to C_{max}. The sustained concentrations seen with oral treprostinil allow for BID administration, although a recent pharmacokinetic study of three times-daily (TID) administration in healthy volunteers demonstrated fewer peak-to-trough fluctuations in the concentration profile and the potential for improved patient tolerability. A small pharmacokinetic study of patients with PAH documented patient and physician-assessed improvement in adverse effects when transitioned from BID to TID dosing in 12 of the 13 patients evaluated. A recent study of 32 patients (n = 26 on TID dosing versus n = 6 on BID dosing) after 24 weeks of treatment with oral treprostinil confirmed the more favorable pharmacokinetic profile of TID administration. The BID group had higher peak concentrations, but greater than 2 h of subtherapeutic concentrations throughout the day. Conversely, the TID group had higher trough concentrations and a plasma

Figure 1. Mechanism of action of oral treprostinil. AC, adenylate cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; IP receptor, prostacyclin receptor; PKA, protein kinase A.
concentration–time profile that more closely resembled parenteral treprostinil. In fact, the authors observed that 1 mg oral treprostinil TID provides similar exposure (AUC, 0–12 h) to 6 ng/kg/min of infusion therapy in a 70 kg patient. Therefore, the authors recommended TID dosing to improve tolerability and facilitate dose up titration of oral treprostinil, however, these studies were conducted after the original clinical trials were designed using an oral treprostinil BID regimen.

### Clinical trials

The efficacy and safety of oral treprostinil for PAH was evaluated in the FREEDOM series of trials, both as monotherapy (Oral Treprostinil as Monotherapy for the Treatment of PAH [FREEDOM-M]) and when added to background therapy with an endothelin receptor antagonist (ERA), a phosphodiesterase type-5 inhibitor (PDE5I), or both (Oral Treprostinil in Combination with an ERA and/or a PDE5I for the Treatment of PAH [FREEDOM-C and FREEDOM-C2]). It should be noted that these studies enrolled primarily adult patients with PAH. A summary of these trials is presented in Table 1.

### Table 1. FREEDOM studies of oral treprostinil.

| PAH etiology, n/N (%) | WHO FC, n/N (%) | Study duration | Primary endpoint – change in 6MWD | Adverse effects occurring in > 50% of study population | Median dose | Premature discontinuation rate, n/N (%) |
|-----------------------|-----------------|----------------|-----------------------------------|------------------------------------------------------|-------------|----------------------------------------|
| **FREEDOM-C**         |                 |                |                                   |                                                      |             |                                        |
| IPAH/FPAH – 113/174 [65] CTD – 49/174 [28] | II – 41/174 [24] III – 127/174 [73] | 16 weeks | + 11 m [95% CI 0.0–22.0 m; p = 0.07] | Headache [86%] Nausea [64%] Diarrhea [61%] | 3.0 mg BID | 39/174 [22] |
| **FREEDOM-C2**        |                 |                |                                   |                                                      |             |                                        |
| IPAH/FPAH – 104/157 [66] CTD – 68/157 [31] | II – 43/157 [27] III – 110/157 [71] | 16 weeks | + 10 m [95% CI 2.0–22.0 m; p = 0.089] | Headache [71%] Diarrhea [55%] | 3.1 mg BID | 25/157 [16] |
| **FREEDOM-M**         |                 |                |                                   |                                                      |             |                                        |
| IPAH/FPAH – 114/151 [75] CTD – 26/151 [17] | II – 52/151 [34] III – 98/151 [65] | 12 weeks | +23.0 m [95% CI 4–41 m; p = 0.0125] | Headache [63%] | 3.4 mg BID | 26/151 [17] |

BID, twice-daily dosing; CI, confidence interval; CTD, connective tissue disease; FPAH, familial pulmonary arterial hypertension; FC, functional class; IPAH, idiopathic pulmonary arterial hypertension; 6MWD, 6-minute walk distance; PAH, pulmonary arterial hypertension; WHO, World Health Organization.
18 m improvement if the dose was 1.25–3.25 mg). Although this was not a prespecified end-point, the trend was suggestive of increased benefit with higher dose therapy. In addition, patients who had access to 0.25 mg tablets at randomization walked 29.5 m further compared with 7 m in patients with 0.5 mg and 1 mg tablets, and 5 m in those with 1 mg tablets only. Although the median dose at study completion for those with access to the 0.25 mg tablets was not reported, no patients in this group discontinued the study due to adverse events. These results showed that a more gradual titration resulted in better tolerability and higher rates of treatment continuation leading to improved clinical response.

Due to the frequent adverse drug effects and high rate of premature discontinuation of oral treprostinal in the FREEDOM-C trial, the FREEDOM-C2 trial sought to evaluate the effect of oral treprostinal when started at a lower dose of 0.25 mg BID. The FREEDOM-C2 trial randomized 310 patients to receive either oral treprostinal or placebo, with 53 patients (17%) on ERA monotherapy, 132 patients (43%) on PDE5I monotherapy, and 125 patients (40%) on combination therapy at study initiation. Despite reaching a similar median dose of 3.1 mg BID after 16 weeks of treatment compared with the FREEDOM-C trial, there was again no difference from baseline to week 16 in improvement in 6MWD compared with placebo. There was also no difference in the incidence of clinical worsening between groups. Premature discontinuation of the study drug due to adverse effects was also frequent in FREEDOM-C2, with 18 patients (11%) stopping therapy because of adverse effects. Taken together, the FREEDOM-C trials demonstrated that oral treprostinal, when added to background therapy, did not improve functional capacity in patients with PAH but it did contribute significantly to the development of adverse effects. A smaller proportion of patients in the FREEDOM-C2 trial taking ERA monotherapy and a higher proportion taking PDE5I monotherapy did little to change the tolerability profile of treprostinal. A limitation of both trials is the relative short period of follow up (16 weeks) and the use of low doses (median of approximately 3 mg BID).

A post-hoc analysis of FREEDOM-C and FREEDOM-C2 combined data from both trials (n = 660) to investigate further the efficacy of oral treprostinal as part of sequential combination therapy. Patient-level data was analyzed using a generally recognized imputation strategy. Overall, the authors reported a significant 10 m improvement in 6MWD, which was driven by patients that achieved the higher-dose group (> 3.5 mg). The median change in 6MWD at week 16 in this subgroup was ≥ 34 m versus the low-dose group (< 2 mg) (p ≤ 0.006). The authors concluded that there was little to no benefit at a total daily dose below 7 mg, and that clinicians should consider parenteral therapy for patients that cannot titrate beyond 6 mg of oral treprostinal (total daily dose).

The FREEDOM-M trial evaluated oral treprostinal as monotherapy in 349 patients with predominantly World Health Organization (WHO) functional class (FC) III symptoms. The primary analysis focused on the modified intention-to-treat population (mITT) of 228 patients who had access to low-dose 0.25 mg tablets. After 12 weeks of treatment and a median dose of 3.4 mg BID, patients in the mITT population had a 23 m improvement with treprostinal therapy, significantly greater than with placebo. There was no difference in clinical worsening between groups. A total of 23 patients (10%) discontinued treprostinal due to adverse effects, with headache, nausea, diarrhea, and jaw pain among the most common reasons for discontinuation. In the treprostinal-treated population, 94% of patients experienced an adverse effect.

An open-label extension study enrolled patients from the FREEDOM trials to evaluate long-term safety of higher doses and exercise capacity with oral treprostinal. A total of 824 patients had a mean exposure of 98 weeks with a maximum follow up of 5.7 years. Patients on background therapy represented 66% of the cohort, whereas 33% were not on any background therapy. Doses (mean ± standard deviation [SD]) achieved at 6, 12, and 24 months were 3.6 ± 2.7, 4.1 ± 3.1, and 5.0 ± 3.7 mg BID, respectively. Of the 522 patients (approximately 60% of the cohort) that completed 1 year of therapy, the average improvement in 6MWD from baseline was 24 m. Adverse effects experienced were similar to those seen in the FREEDOM trials, that is, headache (75%), diarrhea (61%), nausea (52%), flushing (42%), jaw pain (34%), and vomiting (34%).
Postmarketing experience
A single-center, open-label study of 37 patients enrolled into the FREEDOM extension study sought to evaluate 6MWD, FC, and hemodynamics associated with long-term oral treprostinil use. The primary endpoint was the change in pulmonary vascular resistance (PVR) at first follow-up catheterization. Patients received oral treprostinil for a median of 948 days at a dose (mean ± SD) of 4.3 ± 2.3 mg, 8.6 ± 3.2 mg, and 11.7 ± 5.8 mg per day at 3 months, 12 months, and 24 months, respectively. In contrast to the initial experience reported from the larger FREEDOM extension study, the authors of this study found no significant change in hemodynamics at first follow up, 6MWD at 3 months or 12 months, or FC at 12 months compared with baseline. However, there was a modest yet significant inverse relationship between dose and change in PVR. Change in PVR was also numerically improved among patients that achieved the highest dosing quartile. Dosing in this study was consistent with the FREEDOM trials in which dosing was started at 0.5 mg or 0.25 mg BID with the 0.125 mg dose added later in the protocol to improve tolerability. Dosing frequency was BID until 2013, when another protocol amendment allowed for TID dosing based on provider discretion. Six patients in this study transitioned to TID dosing, which led to an improvement in adverse effects but not an increase in the total daily dose achieved. In summary, the experience from this single-center study underscores the importance of achieving clinically effective doses with oral treprostinil in order to improve outcome.

A recent analysis of specialty pharmacy records (n = 1514) aimed to characterize the real-world dosing of oral treprostinil. The median total daily dose was 4.5 mg, 7.5 mg, and 9 mg at 3 months, 6 months, and 12 months. De novo patients achieved lower doses than transition patients at 6 months (6.75 mg versus 9 mg), and approximately 75% were on TID dosing. Median total daily dose was higher in the TID cohort versus BID cohort at 6 months (8.25 mg versus 4 mg). Treatment retention was higher among patients that received greater than 6 mg total daily dose at month 3 compared with those that did not. Treatment retention and dose acceleration rate were each also higher with TID dosing compared with the BID dosing regimen.

Transitions from parenteral or inhaled to oral treprostinil
Careful attention to dosing has spurred continued interest among clinicians and patients in the potential utility of oral treprostinil as an alternative to parenteral (IV or SQ) prostacyclin formulations. An open-label, multicenter, 24-week study recruited ‘low-risk’ patients on a stable dose of parenteral treprostinil (25–150 ng/kg/min) for transition to oral treprostinil. Patients had to have WHO FC I or II symptoms, acceptable hemodynamics (cardiac index > 2.2 L/min/m² and right atrial pressure < 11 mmHg), and demonstrated a durable/favorable response to parenteral therapy. All patients were on at least one background oral PAH therapy. The primary endpoint, defined as successful transition to oral therapy within 4 weeks and maintenance of clinical stability through week 24, was met in 31 of 33 patients. Two patients discontinued therapy as a result of adverse events and clinical worsening, respectively. In addition, the median change in 6MWD was +17 m. Hemodynamics did not change at study end, nor did PAH symptoms or WHO FC. However, the authors noted that a few patients had late deterioration, and that caution should be exercised among clinicians that supervise this transition. The median total daily dose of oral treprostinil achieved was 43.9 mg (range, 15.8–75 mg). A total of 26 participants received TID dosing, whereas only 7 were on BID dosing. The results of this seminal study demonstrated the feasibility of transitioning carefully selected, stable patients on background PAH therapy from parenteral to oral treprostinil.

Other reports of successful transition to oral treprostinil from parenteral and inhaled therapy have also been documented. A case series of nine patients described an inpatient transition over 4 days from parenteral treprostinil (n = 7) or inhaled treprostinil (n = 2) to oral treprostinil. Patient criteria for transition included: clinical stability with improved symptoms/functional capacity, intolerance of IV prostacyclin due to infection or SQ prostacyclin due to pain, and patient preference for transition in consideration of the aforementioned factors. In addition, each patient was on stable parenteral prostacyclin therapy for more than 30 days (median, 42 ng/kg/min). The median total daily doses (TID regimen) at discharge and after 47 weeks of follow up were 24 mg and 28 mg, respectively. Seven of the nine patients achieved a successful transition.
Two patients required conversion back to parenteral prostacyclin therapy. In one case, the patient experienced both clinical worsening and significant adverse events whereas the other patient had adverse events only. There were two patients whose dose after discharge had to be reduced to manage adverse events, whereas all others that successfully transitioned had an increase in dose.

Three patients from this cohort were switched from TID to four times-daily (QID) dosing due primarily to gastrointestinal adverse events which limited dosing up-titration in the outpatient setting.25 All three patients achieved a higher total daily dose, with lessening of adverse events, and maintenance of FC II symptoms with QID dosing compared with TID dosing. Two of the three patients had a 33% increase in total daily dose (40 mg versus 30 mg), whereas one patient had only a slight increase in dose (28 mg versus 27 mg). This novel dosing regimen was feasible and led to minimal change in 6MWD during follow up. However, caution should be exercised due to the potential for clinical deterioration. Therefore, close monitoring with echocardiographic and/or hemodynamic assessment is warranted.19 The pharmacokinetics and long-term clinical follow up with the QID dosing regimen need to be further evaluated.

An outpatient transition from SQ or inhaled to oral treprostinil was described in four patients.26 Two were on inhaled therapy that transitioned due to a persistent cough, while two on SQ therapy switched due to patient preference. Three of the four patients successfully transitioned. One patient had clinical worsening and returned to SQ treatment. The oral treprostinil dose achieved in follow up from the inhaled therapy was 3 mg TID, whereas one patient reached 14 mg TID.26 A single case report described a rapid initiation and titration of IV treprostinil with subsequent transition to oral treprostinil in a patient with severe PAH.27 The patient had been on triple therapy with sildenafil, ambrisentan, and inhaled treprostinil. The authors noted that parenteral treatment was not a suitable option in this patient at that time due to visual and auditory impairments. Once hemodynamic stability was reached with IV treprostinil (42 ng/kg/min by 96 h), the patient was then transitioned to oral treprostinil and up-titrated to a dose of 8 mg TID.27 Finally, a retrospective analysis of specialty pharmacy data found that 275 patients had oral treprostinil dispensed after a prescription for inhaled treprostinil. The mean initial dose of oral treprostinil prescribed was 1.34 ± 1.61 mg/day. There was no correlation between inhaled treprostinil dose or duration and initial oral treprostinil dose.28

Guideline recommendations
The Fifth World Symposium on Pulmonary Hypertension and American College of Chest Physician PAH guidelines were published prior to the availability of oral treprostinil.29,30 Therefore, recommendations on its role in current treatment were not addressed. However, the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) pulmonary hypertension treatment guidelines recommended consideration for use of oral treprostinil as monotherapy in patients with WHO FC III symptoms (Class IIb recommendation).31 The ESC/ERS guidelines did indicate preferential support to the use of oral agents in other drug classes including ERAs, PDE5I, and the IP receptor agonist, selexipag (Class 1A for sildenafil, ambrisentan, and bosentan; Class 1B for tadalafil, macitentan, riociguat, and selexipag). There was no recommendation for or against use of oral treprostinil in any other FC for patients. In addition, oral treprostinil was not included among the recommended combination therapy regimens in the treatment of PAH.31

Expert consensus
An expert consensus document was developed to integrate current evidence and opinions for the practical use of oral treprostinil.32 Best practice statements were vetted by FREEDOM trial investigators using the Delphi process. Final consensus recommendations related to initial dosing included the following: strong preference for TID dosing, starting dose of 0.125 mg for treatment-naïve patients (especially with relative hypotension, low tolerance for adverse effects, or less than 60 kg), administration of doses at least 5 h apart (ideally 6–8 h during awake hours), and titration by 0.125 mg dose increments. Dosing target recommendations were also provided based on time intervals, and included: a 3-month goal of 4 mg TID, 6-month goal of 6 mg TID, and a 12-month target of 8 mg TID. Maximum dosing, however, should ultimately be determined by patient tolerability. With regard to place in therapy, best practices advocate for the use of oral treprostinil in combination with other PAH-approved therapies in order to maintain disease stability. Oral treprostinil
may also be considered in patients that transition from parenteral prostacyclin treatment. However, these patients should receive background therapy and be carefully selected.\textsuperscript{19,32} Consensus recommendations were also presented for the management of adverse events with oral treprostinil. The authors advised aggressive use of antidiarrheal medication when necessary and provided specific recommendations for additional interventions based on adverse effects, which are discussed below.\textsuperscript{32}

**Adverse effects**

Drug intolerance is common with oral treprostinil, with 94–100\% of patients experiencing adverse effects in the FREEDOM trials.\textsuperscript{3–5} Furthermore, adverse effects leading to drug discontinuation occurred in up to 14\% of treprostinil-treated patients. Adverse effects typical of prostanooid therapy were commonly reported, including headache, nausea, diarrhea, flushing, and jaw pain.\textsuperscript{3–5} Slightly lower rates of adverse effects, including events leading to discontinuation, were seen in patients with access to lower starting doses (0.125 mg, 0.25 mg) of oral treprostinil, and is a strategy to improve tolerability while still achieving similar doses attained in clinical trials.

Postmarketing evaluations of oral treprostinil have confirmed the high rate of adverse effects. In two studies evaluating the transition from parenteral prostacyclin therapy to oral treprostinil, adverse effects were reported in eight out of nine patients (88\%) in one evaluation and 32 out of 33 patients (97\%) in another, with headache, nausea, diarrhea, flushing, and jaw pain.\textsuperscript{19,25} The high incidence of adverse effects in those evaluations is notable because all patients previously received prostacyclin therapy (the majority of whom transitioned from SQ to oral treprostinil). Therefore, a patient’s ability to tolerate a parenteral form of prostacyclin therapy does not necessarily predict tolerability with the oral formulation. Reasons for this are not entirely clear, but the preponderance of adverse events that were gastrointestinal in nature with oral treprostinil (particularly with BID dosing) offers a viable explanation.

Despite the frequency with which treatment-related adverse effects occur, little guidance for adverse effect management from clinical trials or from postmarketing experience exists. To address this, investigators from the FREEDOM series of trials created an expert consensus document that included recommendations from physicians with experience in prescribing oral treprostinil.\textsuperscript{32} Many adverse effects can be managed with adjunctive pharmacotherapy or modification of titration schedule. A summary of their recommendations for frequently encountered adverse effects with oral treprostinil is provided in Table 2.

**Future directions**

An ongoing Trial of the Early Combination of Oral Treprostinil with Background Oral Monotherapy in Subjects with Pulmonary Arterial Hypertension (FREEDOM-EV) (NCT 01560624) will provide important insights into the long-term clinical effects of higher doses of oral treprostinil. The primary outcome measure is time to first clinical worsening event from randomization to approximately 4 years. Change in 6MWD will also be assessed at 24 weeks. The study investigators aim to recruit an estimated 850 participants.\textsuperscript{33}

**Conclusion**

Treprostinil diolamine is the first oral prostacyclin to be approved and adds to the growing number of pharmacologic options for the treatment of PAH. Its precise application in PAH management is not yet certain, but postmarketing experience suggests clinical utility in the setting of sequential combination therapy with an ERA and/or a PDE5I. Data from the FREEDOM trials suggest that caution with combination therapy is warranted, however, the results were confounded by subtherapeutic dosing and suboptimal initial dosing titration that led to more prevalent adverse events.\textsuperscript{3–5} The introduction of smaller dosage strengths and use of TID dosing facilitates more rapid titration, higher doses achieved, and improved tolerability. In addition, transition to oral treprostinil from parenteral prostacyclin treatment in carefully selected, stable patients may also be considered. The clinical benefits of oral treprostinil are closely related to dose achieved, therefore efforts to improve tolerability are paramount. Ongoing clinical trials will determine long-term effects of oral treprostinil on important endpoints such as complications related to PAH (e.g. hospitalizations, disease progression) and safety.
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| Table 2. Consensus opinion for management of adverse effects with oral treprostinil.32 |
|-----------------------------------|-----------------------------------|
| **Adverse effect** | **Management** |
| Diarrhea | Dicycloverine  
Loperamide |
| Nausea | Take with food  
Ondansetron |
| Headache | Acetaminophen – first-line  
Tramadol – second-line  
Opiates in severe cases |
| Flushing | Reassurance  
Decrease rate of titration only if absolutely necessary |
| Jaw pain | No measures necessary  
Reassurance |
| Dizziness | Decrease antihypertensive doses  
Manage under-hydration or over-diuresis  
Close monitoring of blood pressure  
Decrease oral treprostinil dose |
| Hypotension | Stop or decrease antihypertensive medications  
Manage under-hydration or over-diuresis |
| Extremity pain | Gabapentin |
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