Template Letters | Appeal a Denied Claim

(From Provider to Payer)
This letter is only an example. *Please edit the letter to suit your needs and replace* ***[bold]*** *sections with the appropriate information.*

[PH CENTER LETTERHEAD]

[TODAY'S DATE]

[INSURANCE COMPANY]
[ADDRESS]
[PHONE/FAX]

Re: **[PATIENT NAME, DOB]**
[MEMBER ID]

Dear Claims Representative:

I am writing on behalf of my patient **[PATIENT NAME AND POLICY NUMBER]** to request reconsideration of payment of a denied claim for **[NAME OF TREATMENT]**.

You have indicated that **[NAME OF TREATMENT]** is not covered by **[INSERT PAYER NAME]** because of **[INSERT REASON GIVEN]**. This medication has been prescribed for **[PATIENT NAME]** based on their diagnosis of **[INSERT DIAGNOSIS INFORMATION]**.

Pulmonary hypertension (PH) is a condition characterized by increased blood pressure in the pulmonary artery. PH is considered in five clinical classification groups as defined by the World Symposium on PH (WSPH)[1]:

- WSPH Group 1 PH: Pulmonary Arterial Hypertension (PAH).
- WSPH Group 2 PH: PH due to Left Heart Disease.
- WSPH Group 3 PH: PH due to Lung Diseases and/or Hypoxia.
- WSPH Group 4 PH: PH due to Pulmonary Artery Obstructions (Chronic Thromboembolic Pulmonary Hypertension).
- WSPH Group 5 PH: PH with Unclear and/or Multifactorial Mechanisms.

When PAH occurs in the absence of a known cause, it is referred to as idiopathic pulmonary arterial hypertension (IPAH). IPAH is extremely rare, with new cases occurring in about one

[1] Simonneau G, et al. *Eur Respir J.* 2018; DOI :10.1183/13993003.01913-2018

person per million population per year.[2,3] PAH can also occur in association with other diseases and exposures, including historical anorexigen exposure, methamphetamine use, collagen vascular diseases, HIV infection, portal hypertension, and congenital heart diseases. PAH is an incurable, progressive illness with FDA-approved oral, inhaled, and parenteral targeted treatment options. **[INSERT NAME OF TREATMENT]** has been shown to significantly improve prognosis.

[CONSIDER INSERTION OF CLINICAL TRIAL RESULTS FOR TREATMENT. SEE "APPENDIX 1: CLINICAL TRIAL INFORMATION]

History and Diagnosis

[INSERT INFORMATION REGARDING PATIENT'S HISTORY WITH THIS DISEASE, DIAGNOSTIC RESULTS FROM THE MOST RECENT OFFICE VISIT OR RHC, INCLUDING PREVIOUSLY ATTEMPTED TREATMENTS (DRUG CLASSES FOR EACH AGENT, START DATE AND DISCONTINUATION DATE AND REASONS FOR ANY CHANGES E.G SIDE EFFECTS, AND RESULTS.] MAY ALSO INCLUDE THE REASONS WHY RELEVANT LOWER-TIER MEDICATIONS WERE SKIPPED.[4]

Based on the above information, I would appreciate your reconsideration of coverage for these submitted charges. **[INSERT NAME OF TREATMENT]** is medically necessary in order to treat this patient's diagnosis of **[INSERT DIAGNOSIS INFORMATION].** If you require any additional information, please contact me at **[INSERT PHYSICIAN'S TELEPHONE NUMBER AND CONTACT INFORMATION]**.

Sincerely,
[PROVIDER'S NAME]

[2] Humbert M, et al. *Am J Respir Crit Care Med.* 2006; 173(9):1023-1030
[3] Escribano-Subias P, et al. *Eur Respir J*. 2012; 40(3):596-603
[4] Brown, A. *Adv in Pulmonary Hypertension*. 2018; 17 (3):126-131

Clinical Trial Information

Epoprostenol

A 12-week prospective, randomized, multicenter open trial of continuously infused epoprostenol + conventional therapy compared to conventional therapy alone was completed in 81 patients with what was then called primary pulmonary hypertension (PPH) who were in New York Heart Association (NYHA) functional class III or IV. The primary endpoint of the clinical trial was change in exercise capacity as assessed by 6-minute walk distance. The primary reinforcing endpoints included hemodynamic changes and survival.

In 1996, Barst, et al. reported that patients on epoprostenol had a 6-minute walk distance increase of 31m after 12 weeks of therapy, compared to a decrease of 29m in the patients on conventional therapy alone (p <0.002). This difference remained statistically significant after adjustment for hemodynamics and 6-minute walk distance and treatment at baseline. Epoprostenol-treated patients demonstrated statistically significant hemodynamic improvements, including decreases in mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR). Eight patients died during the study, each of whom had been randomized to the conventional therapy arm.

Citation: Barst RJ, et al. *N Eng J Med*. 1996; 334:296-301

Treprostinil (Subcutaneous)

A 12-week prospective, randomized, double-blind, placebo-controlled, multi-center clinical trial of continuous subcutaneous (SQ) treprostinil was completed in 470 patients with several types of pulmonary arterial hypertension (PAH). The primary endpoint of the clinical trial was improvement in exercise capacity as assessed by 6-minute walk distance. Principal reinforcing endpoints were signs and symptoms of PAH; dyspnea-fatigue rating; and clinical deterioration, transplantation, and death. Secondary endpoints were hemodynamics, quality of life, and tolerability/safety.

In 2002, Simonneau, et al. reported that patients on SQ treprostinil had significantly improved exercise capacity, with a difference between groups in median distance walked of 16m (95% CI, 4.4m to 27.6, p=0.006) after 12 weeks. The treprostinil treatment arm also demonstrated significant improvements in the composite score of "signs and symptoms of pulmonary arterial hypertension," Dyspnea-Fatigue rating, Borg Dyspnea Score, cardiopulmonary hemodynamics (mean RA pressure [RAP], mean pulmonary artery pressure [mPAP], cardiac index [CI], pulmonary vascular resistance index, and mixed venous oxygen saturation), and quality of life as assessed by the Minnesota Living with Heart Failure Questionnaire.

Citation: Simonneau G, et al. *Am J Respir Crit Care Med*. 2002; 165(6): 800-4

Bosentan

Primary pulmonary hypertension (PPH) is a progressive disease with high mortality. Administration of i.v. epoprostenol has demonstrated improved exercise tolerance, haemodynamics, and survival. The

orally active, dual endothelin receptor antagonist bosentan improves exercise endurance, haemodynamics, and functional class over the short term. To determine the effect of first-line bosentan therapy on survival, this study followed 169 patients with PPH treated with bosentan in two placebo-controlled trials and their extensions. Data on survival and alternative treatments were collected from September 1999 (start of the first placebo-controlled study) to December 31, 2002. Observed survival up to 36 months was reported as Kaplan-Meier estimates and compared with predicted survival as determined for each patient by the National Institutes of Health Registry formula. Kaplan-Meier survival estimates were 96% at 12 months and 89% at 24 months. In contrast, predicted survival was 69% and 57%, respectively. In addition, at the end of 12 and 24 months, 85% and 70% of patients, respectively, remained alive and on bosentan monotherapy. Factors that predicted a worse outcome included World Health Organization Functional Class IV and 6-min walk distance below the median (358 m) at baseline. First-line bosentan therapy was found to improve survival in patients with advanced primary pulmonary hypertension.

Citation: McLaughlin V, et al. *Eur Respir J*. 2005; 25(2):244-9

Iloprost

In the AIR-1 clinical trial, a comparison of repeated daily inhalations of 2.5 or 5.0 microg of iloprost (six or nine times per day; median inhaled dose, 30 microg per day) with inhalation of placebo. A total of 203 patients with selected forms of severe pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension (New York Heart Association [NYHA] functional class III or IV) were included. The primary end point was met if, after week 12, the NYHA class and distance walked in six minutes were improved by at least one class and at least 10 percent, respectively, in the absence of clinical deterioration according to predefined criteria and death.

Citation: Olschewski H, et al. *N engl J Med.* 2002; 347(5):322-9

Sildenafil

A 12-week prospective, randomized, double-blind, placebo-controlled, multi-center clinical trial of oral sildenafil citrate was completed in 278 patients with several types of pulmonary arterial hypertension (PAH). The primary endpoint of the **S**ildenafil **U**se in **P**ulmonary Art**E**rial Hype**R**tension (SUPER) clinical trial was change in exercise capacity as assessed by 6-minute walk distance. Secondary endpoints were changes in mean pulmonary artery pressure (mPAP), Borg dyspnea score, WHO functional classification, and signs of clinical worsening defined *a priori*.

In 2005, Galiè, et al. reported that patients in the sildenafil trial arm had significant improved 6-minute walk distance (placebo-corrected differences of 45m, 46m, and 50m for the 20, 40, and 80mg of sildenafil being trialed, respectively). All sildenafil arms demonstrated significant reductions in mean pulmonary artery pressure (mPAP), and WHO functional classification improvements compared to placebo.

Citation: Galiè N, et al. *N Engl J Med*. 2005; 353:2148-57

Ambrisentan

Ambrisentan is a propanoic acid-based, A-selective endothelin receptor antagonist for the once-daily treatment of pulmonary arterial hypertension.

Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study 1 and 2 (ARIES-1 and ARIES-2) were concurrent, double-blind, placebo-controlled studies that randomized 202 and 192 patients with pulmonary arterial hypertension, respectively, to placebo or ambrisentan (ARIES-1, 5 or 10 mg; ARIES-2, 2.5 or 5 mg) orally once daily for 12 weeks. The 6-minute walk distance increased in all ambrisentan groups; mean placebo-corrected treatment effects were 31 m (P=0.008) and 51 m (P<0.001) in ARIES-1 for 5 and 10 mg ambrisentan, respectively, and 32 m (P=0.022) and 59 m (P<0.001) in ARIES-2 for 2.5 and 5 mg ambrisentan, respectively. Improvements in time to clinical worsening (ARIES-2), World Health Organization functional class (ARIES-1), Short Form-36 score (ARIES-2), Borg dyspnea score (both studies), and B-type natriuretic peptide (both studies) were observed. No patient treated with ambrisentan developed aminotransferase concentrations >3 times the upper limit of normal. In 280 patients completing 48 weeks of treatment with ambrisentan monotherapy, the improvement from baseline in 6-minute walk at 48 weeks was 39 m. Ambrisentan is known to improve exercise capacity in patients with pulmonary arterial hypertension. It is well tolerated and is associated with a low risk of aminotransferase abnormalities.

Citation: Galiè N, et al. *Circulation*. 2008; 117:3010–19

Tadalafil

Treatment options for pulmonary arterial hypertension target the prostacyclin, endothelin, or nitric oxide pathways. Tadalafil, a phosphodiesterase type-5 inhibitor, increases cGMP, the final mediator in the nitric oxide pathway.

In this 16-week, double-blind, placebo-controlled study, known as the PHIRST-1 trial, 405 patients with pulmonary arterial hypertension (idiopathic or associated), either treatment-naive or on background therapy with the endothelin receptor antagonist bosentan, were randomized to placebo or tadalafil 2.5, 10, 20, or 40 mg orally once daily. Tadalafil increased the distance walked in 6 minutes in a dose-dependent manner; only the 40-mg dose met the prespecified level of statistical significance (P<0.01). Overall, the mean placebo-corrected treatment effect was 33 m (95% confidence interval, 15 to 50 m). In the bosentan-naive group, the treatment effect was 44 m (95% confidence interval, 20 to 69 m) compared with 23 m (95% confidence interval, −2 to 48 m) in patients on background bosentan therapy. Tadalafil 40 mg improved the time to clinical worsening (P=0.041), incidence of clinical worsening (68% relative risk reduction; P=0.038), and health-related quality of life. The most common treatment-related adverse events reported with tadalafil were headache, myalgia, and flushing. In patients with pulmonary arterial hypertension, tadalafil 40 mg was well tolerated and improved exercise capacity and quality of life measures and reduced clinical worsening.

Citation: Galie N, et al. *Circulation* 2009; 119(22):2894-903

Treprostinil (Inhaled)

TRIUMPH I, was a 12-week, randomized, double-blind, placebo-controlled multi-center study of patients with PAH. The study population included 235 clinically stable subjects with pulmonary arterial hypertension (WHO Group 1), nearly all with NYHA Class III (98%) symptoms who were receiving either bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase-5 inhibitor) for at least three months prior to study initiation. Concomitant therapy also could have included anticoagulants, other vasodilators (e.g., calcium channel blockers), diuretics, oxygen, and digitalis, but not a prostacyclin. These patients were administered either placebo or Tyvaso in four daily treatment sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study. Patients were predominantly female (82%), had the origin of PAH as idiopathic/heritable (56%), secondary to connective tissue diseases (33%) or secondary to HIV or previous use of anorexigens (12%); bosentan was the concomitant oral medication in 70% of those enrolled, sildenafil in 30%.

The primary efficacy endpoint of the trial was the change in six-minute walk distance (6MWD) relative to baseline at 12 weeks. 6MWD was measured at peak exposure (between 10 and 60 minutes after dosing), and 3-5 hours after bosentan or 0.5-2 hours after sildenafil. Patients receiving Tyvaso had a placebo-corrected median change from baseline in peak 6MWD of 20 meters at Week 12 ($p<0.001$). The distribution of these 6MWD changes from baseline at Week 12 were plotted across the range of observed values (Figure 1). 6MWD measured at trough exposure (defined as measurement of 6MWD at least 4 hours after dosing) improved by 14 meters. There were no placebo-controlled 6MWD assessments made after 12 weeks.

Citation: McLaughlin V, et al. *J Am Coll Cardiol*. 2010; 55(18):1915-22

Treprostinil (Oral)

Study 1 (effect seen with no background vasodilator) FREEDOM-M

Study 1 was a 12-week, randomized (2:1 Orenitram to placebo), double-blind, placebo-controlled, international efficacy and safety study of Orenitram in patients with WHO Group 1 PAH not currently receiving PAH therapy. The primary efficacy endpoint was placebo-corrected change in six-minute walk distance (6MWD) from Baseline to Week 12. Study drug dose was titrated to a maximum of 12 mg BID based on clinical response and study drug tolerability. Study 1 enrolled 349 patients (overall analysis population) who were not receiving any PAH medication. At the beginning of the study, subjects were dosed with only the 1 mg tablets with 0.5 and 0.25 mg tablets introduced at sequentially later dates during the study. The primary analysis population consisted of the 228 patients who had access to the0.25 mg tablet at the time of randomization. Patients were administered Orenitram or placebo twice daily, with the doses titrated to effect over the course of the 12-week trial. Patients were in W HO functional class II (~33%) and class III (~66%) with either idiopathic or heritable PAH (~75%), collagen vascular disease associated PAH (~19%), or PAH associated with HIV (1%) or congenital heart defect (5%) or other conditions (~6%). The patients' mean baseline 6MWD was approximately 330 meters. In the primary analysis population, 17% of patients discontinued Orenitram compared to 14% of patients on placebo.

The primary efficacy endpoint of the trial was the change in 6MWD at 12 weeks for the primary analysis population. Analysis of Study 1 results demonstrated that those patients receiving Orenitram compared to patients receiving placebo improved their median 6MWD by approximately +23 meters (Hodges-Lehmann estimate; p=0.013, non-parametric analysis of covariance in accordance with the pre-specified statistical analysis plan) as compared to patients receiving placebo as demonstrated in (Figure 2). The within group median change from baseline was +25 meters for Orenitram and 5 meters for placebo at week 12 (N=228). Mean dose (±SD) in the Orenitram group was 2.3 ± 1.3, 3.2 ± 1.9, and 3.4 ± 1.9 mg BID at W eeks 4, 8, and 12, respectively, with a maximum dose of 12 mg BID. The distribution of the 6MWD change from baseline at Week 12 was also plotted across the range of observed values (Figure 3).

Studies 2 and 3 (no effect on a background of ERA, PDE-5 inhibitor, or both) FREEDOM-C

Studies 2 (N=350) and 3 (N=310) were 16-week, randomized, double-blind, placebo-controlled, international efficacy and safety studies of Orenitram in patients with WHO Group 1 PAH. The primary efficacy endpoint was placebo-corrected change in 6MWD from Baseline to Week 16. Patients were in WHO functional class II (~23%) and class III (~77%) with either idiopathic or heritable PAH (~66%), collagen vascular disease associated PAH (~29%), or PAH associated with HIV (1%) or congenital heart defect (4%). The patients' mean baseline 6MWD was approximately 340 meters. Approximately 40% were receiving both an ERA and a PDE-5 inhibitor. The results did not demonstrate a benefit in exercise testing with median 6MWD at Week 16 (11 meters [Hodges-Lehmann estimate; p=0.072] and 10 meters [Hodges-Lehmann estimate; p=0.089], respectively).

Long-Term Treatment of Pulmonary Hypertension

Patients (N=824) from the placebo-controlled studies entered a long-term, uncontrolled, open-label extension study. The average exposure to Orenitram was approximately 2 years with a maximum exposure of approximately 6 years. The dose of Orenitram continued to increase over time with doses (mean ± SD) of 3.6 ± 2.7, 4.2 ± 3.1, and 5 ± 3.7 mg BID at 6 (n=649), 12 (n=433), and 24 months (n=238), respectively, with a maximum dose of 21 mg BID. Reasons for discontinuation from the study included adverse event (16%), progression of disease (15%), death (13%), and withdrawn consent (7%). In the 522 subjects that completed the 12-month efficacy assessment, their mean 6MW D improved by 24 meters compared to baseline (30 meters in monotherapy patients and 20 meters when Orenitram was used in combination with an ERA and/or a PDE-5 inhibitor). Of the patients that remained in the study, overall survival was 92%, 87%, and 82% at the end of 1, 2, and 3-years, respectively, with progression-free survival (progression defined as death, discontinuation or addition of a PAH therapy) of 74%, 61%, and 47%. Without a control group, these data must be interpreted cautiously.

Citation: Jing ZC, et al. *Circulation*. 2013; 127:624–633

FREEDOM – EV should be released soon*

Riociguat

Riociguat, a soluble guanylate cyclase stimulator, has been shown in a phase 2 trial to be beneficial in the treatment of pulmonary arterial hypertension. Trials conducted were PATENT-1 and PATENT-2.

In the phase 3, double-blind study, they randomly assigned 443 patients with symptomatic pulmonary arterial hypertension to receive placebo, riociguat in individually adjusted doses of up to 2.5 mg three times daily (2.5 mg–maximum group), or riociguat in individually adjusted doses that were capped at 1.5 mg three times daily (1.5 mg–maximum group). The 1.5 mg–maximum group was included for exploratory purposes, and the data from that group were analyzed descriptively. Patients who were receiving no other treatment for pulmonary arterial hypertension and patients who were receiving endothelin-receptor antagonists or (nonintravenous) prostanoids were eligible.

By week 12, the 6-minute walk distance had increased by a mean of 30 m in the 2.5 mg–maximum group and had decreased by a mean of 6 m in the placebo group (least-squares mean difference, 36 m; 95% confidence interval, 20 to 52; P<0.001). Prespecified subgroup analyses showed that riociguat improved the 6-minute walk distance both in patients who were receiving no other treatment for the disease and in those who were receiving endothelin-receptor antagonists or prostanoids. There were significant improvements in pulmonary vascular resistance (P<0.001), NT-proBNP levels (P<0.001), WHO functional class (P=0.003), time to clinical worsening (P=0.005), and Borg dyspnea score (P=0.002). The most common serious adverse event in the placebo group and the 2.5 mg–maximum group was syncope (4% and 1%, respectively).
Riociguat significantly improved exercise capacity and secondary efficacy end points in patients with pulmonary arterial hypertension.

Citation: Ghofrani et al. *N Engl J Med* 2013; 369:330-340

Macitentan

SERAPHIN is a multi-center, double-blind, randomized, placebo-controlled, event driven, phase III clinical trial. Patients were randomly assigned 250 patients to placebo, 250 patients to the 3 mg macitentan dose and 242 to the 10 mg macitentan dose. Worsening of pulmonary arterial hypertension was the most frequent primary end-point event. The effect of macitentan on this end point was observed regardless of whether the patient was receiving therapy for pulmonary arterial hypertension at baseline. The primary end point occurred in 46.4%, 38%, and 31.4% of the patients in these groups respectively. Adverse events more frequently associated with macitentan compared to placebo were headache, nasopharyngitis and anemia. Macitentan significantly reduced morbidity and mortality among patients with pulmonary arterial hypertension in this event-driven study.

Citation: Pulido T, et al. *N Engl J Med.* 2013; 369:809-18

Selexipag

GRIPHON was a global, double-blind, randomized, placebo-controlled, event driven phase III trial. 1156 patients were enrolled with 1:1 randomization to receive selexipag or placebo. During the 12 week titration period, the study drug was initiate at 200 mcg BID and titrated weekly in increments of 200 mcg BID to the highest tolerated dose. The maximum dose allowed was 1600 mcg BID. Patients received double-blind treatment until they experienced a primary endpoint event, prematurely discontinued the study drug or the study ended.

In the GRIPHON study, selexipag treatment was well tolerated and delayed the progression of PAH irrespective of the subtype of CTD and baseline PAH therapy. The data supports use of multiple PAH therapies when treating patients with PAH-CTD and emphasized that this treatment strategy can yield benefits to this difficult to treat population.

Citation: Gaine S, et al. *Eur Respir J.* 2017; 50:1602493.