CLINICAL UPDATE

Brand Name	Tadliq®
Generic Name	tadalafil
Drug Manufacturer	CMP Development, LLC

Clinical Update

TYPE OF CLINICAL UPDATE

New Brand/Dosage Form

FDA APPROVAL DATE

June 17, 2022

LAUNCH DATE

September 16, 2022

REVIEW DESIGNATION

Standard

TYPE OF REVIEW

Type 5 - New Formulation or New Manufacturer; New Drug Application (NDA): 214522

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Tadliq® is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II – III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

MECHANISMS OF ACTION

Tadalafil is an inhibitor of phosphodiesterase type 5 (PDE5), the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP). Pulmonary arterial hypertension is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations in the pulmonary vascular smooth muscle. PDE5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 by tadalafil increases the concentrations of cGMP resulting in relaxation of pulmonary vascular smooth muscle cells and vasodilation of the pulmonary vascular bed.

Studies in vitro have demonstrated that tadalafil is a selective inhibitor of PDE5. PDE5 is found in pulmonary vascular smooth muscle, visceral smooth muscle, corpus cavernosum, skeletal muscle, platelets, kidney, lung, cerebellum, and pancreas.

DOSAGE FORM(S) AND STRENGTH(S)

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Oral Suspension: 20 mg/5 mL

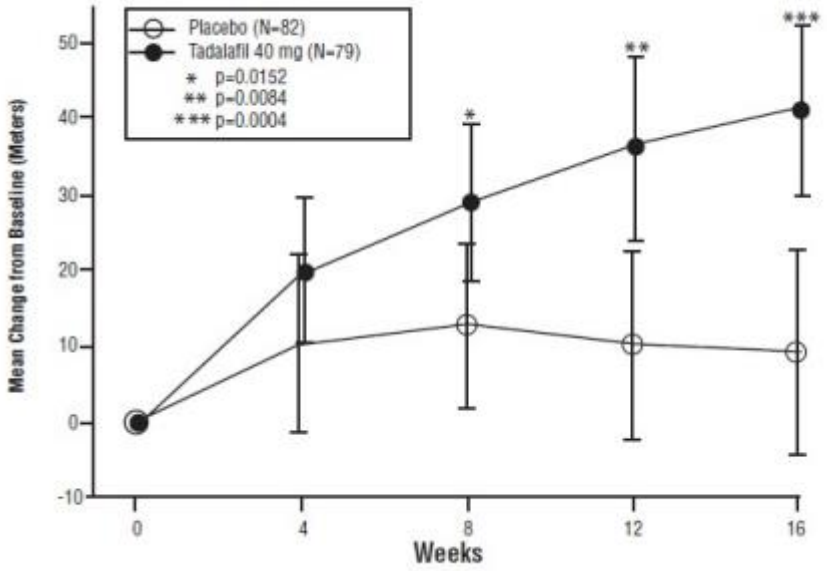
DOSE & ADMINISTRATION

- 40 mg (10 mL) once daily, with or without food.
- Use with ritonavir requires dosage adjustments.

EFFICACY

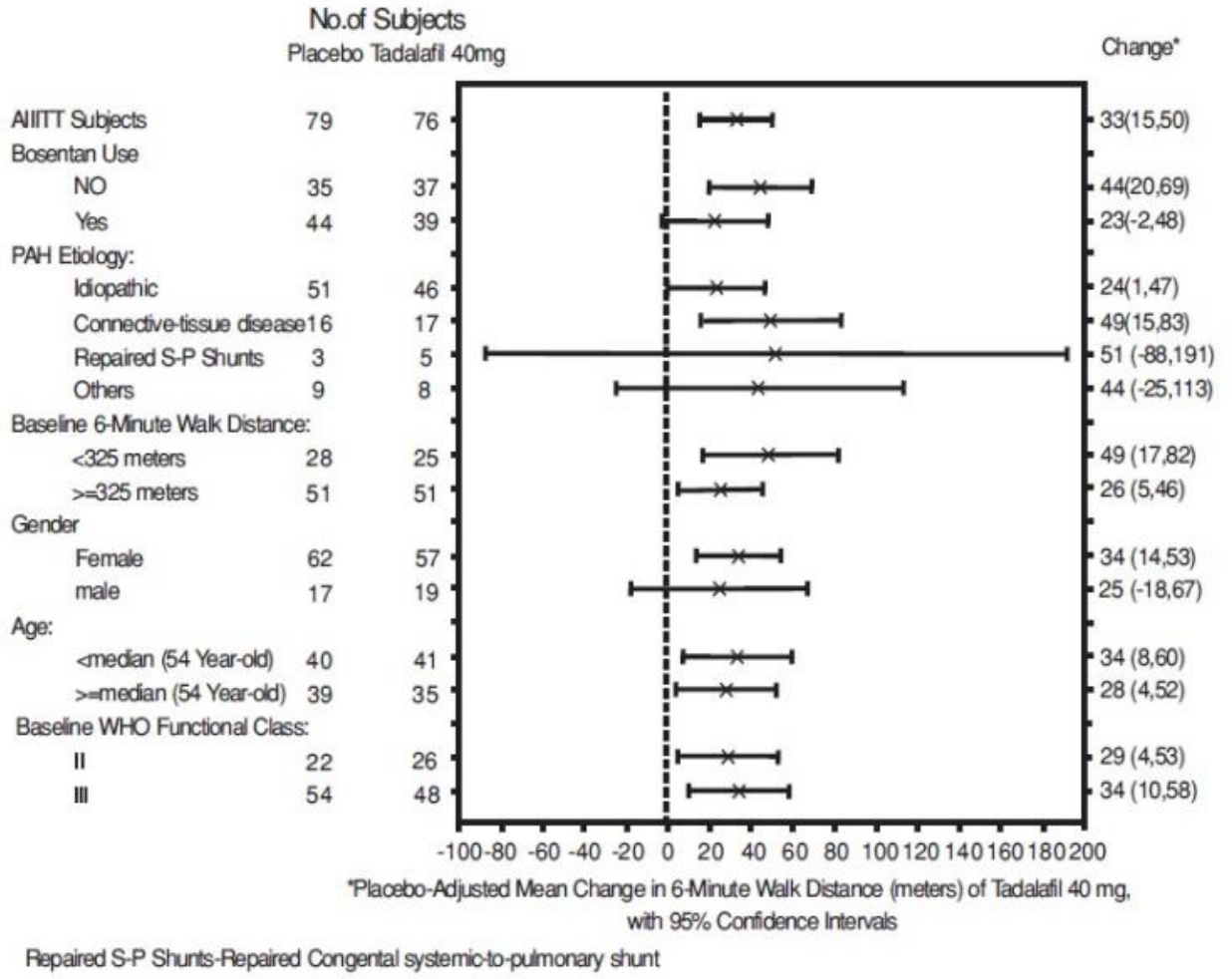
Tadalafil for Pulmonary Arterial Hypertension A randomized, double-blind, 16-week placebo-controlled study was conducted in 405 patients with pulmonary arterial hypertension, defined as a resting mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg, pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg, and pulmonary vascular resistance (PVR) ≥ 3 Wood units via right heart catheterization. Allowed background therapy included bosentan (maintenance dosing up to 125 mg twice daily) and chronic anticoagulation. The use of prostacyclin or analogue, L–arginine, phosphodiesterase inhibitor, or other chronic PAH medications were not permitted. Subjects were randomly assigned to 1 of 5 treatment groups (tadalafil 2.5, 10, 20, 40 mg, or placebo) in a 1:1:1:1:1 ratio. Subjects had to be at least 12 years of age and had a diagnosis of PAH that was idiopathic, heritable, related to connective tissue disease, anorexigen use, human immunodeficiency virus (HIV) infection, associated with an atrial-septal defect, or associated with surgical repair of a congenital systemic-to-pulmonary shunt of least 1 year in duration (for example, ventricular septal defect, patent ductus arteriosus). Patients with a history of left-sided heart disease, severe renal insufficiency, or pulmonary hypertension related to conditions other than specified in the inclusion criteria were not eligible for enrollment. The mean age of all subjects was 54 years (range 14 - 90 years) with the majority of subjects being Caucasian (81%) and female (78%). PAH etiologies were predominantly idiopathic or heritable PAH (61%) and related to connective tissue disease (23%). More than half (53%) of the subjects in the study were receiving concomitant bosentan therapy. The majority of subjects had a World Health Organization (WHO) Functional Class III (65%) or II (32%). The mean baseline 6-minute walk distance (6-MWD) was 343 meters. Of the 405 subjects, 341 completed the study. The primary efficacy endpoint was the change from baseline at week 16 in 6-MWD.In the tadalafil 40 mg treatment group, the placebo-adjusted mean change increase in 6-MWD was 33 meters (95% C.I. 15-50 meters; p=0.0004). The improvement in 6-MWD was apparent at 8 weeks of treatment and then maintained at week 12 and week 16.

Figure 1- Minute Walk Distance (meters) Mean Change from Baseline, with 95% Confidence Intervals



Placebo-adjusted changes in 6-MWD at 16 weeks were evaluated in subgroups. In patients taking only 40 mg of tadalafil (i.e., without concomitant bosentan), the placebo-adjusted mean change in 6- MWD was 44 meters. In patients taking 40 mg of tadalafil and concomitant bosentan therapy, the placebo adjusted mean change in 6-MWD was 23 meters.

Figure 2: Placebo- adjusted Mean Change in 6- Minute Walk Distance (meters) of Tadalafil 40 mg, with 95% Confidence Intervals

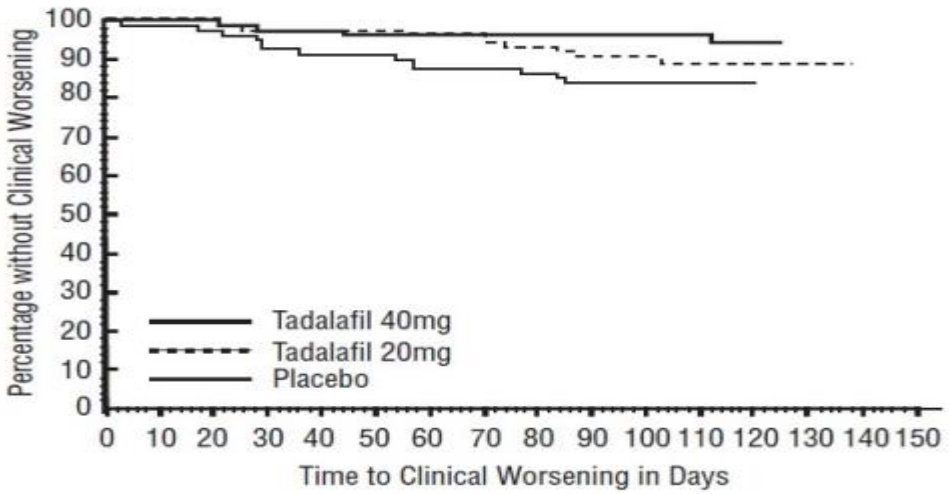


Repaired S-P Shunts-Repaired Congental systemic-to-pulmonary shunt

There was less clinical worsening (defined as death, lung transplantation, atrial septostomy, hospitalization because of worsening PAH, initiation of new PAH therapy [prostacyclin or analog, endothelin receptor antagonist, PDE5 inhibitor], or worsening WHO functional class) in the Tadalafil 40 mg group compared to the placebo group and the groups that used lower doses of tadalafil.

Table 1: Number (percent) with Clinical Worsening[a]					
			Tadalafil		
	Placebo N=82	2.5 mg N=82	10 mg N=80	20 mg N=82	40 mg N=79
Total with clinical worsening	13 (16)	10 (12)	7 (9)	8 (10)	4 (5)
Death	1	0	1	0	0
Hospitalization for worsening PAH	2	2	3	0	1
New PAH therapy	0	1	0	2	1
Worsening WHO class	11	10	6	6	3

Figure 3: Kaplan- Meier Plot of Time to Clinical Worsening



Long-Term Treatment of Pulmonary Arterial Hypertension

Patients (N=357) from the placebo-controlled study entered a long-term extension study. Of these, 311 patients have been treated with tadalafil for at least 6 months and 182 for 1 year (median exposure 356 days; range 2 days to 415 days). The survival rate in the extension study was 96.5 per 100 patient years. Without a control group, these data must be interpreted cautiously.