Clinical Policy Title:	tadalafil
Policy Number:	RxA.332
Drug(s) Applied:	Adcirca®, Alyq™, Tadliq®
Original Policy Date:	03/06/2020
Last Review Date:	04/13/2023
Line of Business Policy Applies to:	All lines of business

Background

Tadalafil (Adcirca®, Alyq™, Tadliq®) is a phosphodiesterase-5 inhibitor (PDE5).
Adcirca®, Alyq™ and Tadliq® are indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1) to improve exercise ability.

Studies establishing effectiveness included predominately patients with New York Heart Association (NYHA) Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
tadalafil (Adcirca®, Alyq™, Tadliq®)	PAH	40 mg orally once daily Renal Impairment: • Mild (creatinine clearance CrCl 51 to 80 mL/min) or moderate (CrCl 31 to 50 mL/min): 20 mg once daily. Increase to 40 mg (10 mL) once daily. Hepatic Impairment: • Mild or moderate (Child Pugh Class A or B): 20 mg (5 mL) once per day	40 mg/day

Dosage Forms

- Adcirca®, Alyq™: Tablets: 20 mg
- Tadliq®: Oral suspension: 20 mg/5 mL

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Pulmonary Arterial Hypertension (must meet all):

1. Diagnosis of PAH;
2. Prescribed by or in consultation with a cardiologist or a pulmonologist;
3. Failure of a calcium channel blocker (see Appendix B), unless member meets one of the following (a or b):
   a. Inadequate response or contraindication to acute vasodilator testing;
   b. Contraindication or clinically significant adverse effects to calcium channel blockers are experienced;
4. For Tadliq® request, member is unable to swallow tablets;
5. Dose does not exceed 40 mg per day.

Approval duration:
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. Pulmonary Arterial Hypertension (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria;
2. Member is responding positively to therapy;
3. For Tadliq® requests member is unable to swallow tablets;
4. If request is for a dose increase, new dose does not exceed 40 mg per day.

Approval duration
Commercial: 12 months
Medicaid: 12 months

III. APPENDICES

APPENDIX A: Abbreviation/Acronym Key
FC: Functional class
FDA: Food and Drug Administration
NYHA: New York Heart Association
PAH: pulmonary arterial hypertension
PH: pulmonary hypertension
WHO: World Health Organization
GC: guanylate cyclase
PDE5: phosphodiesterase-5 inhibitor

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
nifedipine (Adalat®CC, Procardia®, Procardia XL®)	60 mg orally once daily; may increase to 120 to 240 mg/day	240 mg/day
diltiazem (Dilt-XR®, Cardizem®CD, Cartia XT®, Tiazac®, Taztia XT®, Cardizem®LA,	Initial, 60 mg orally 3 times daily, usual dosage range in idiopathic	720 mg/day

Matzim® LA)	PAH: 240 to 720 mg/day	
amlodipine (Norvasc®)	5 mg orally once daily	10 mg/day

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):*
  - Concomitant organic nitrates;
  - Concomitant guanylate cyclase (GC) stimulators;
  - Hypersensitivity reactions.

  *Contraindications listed reflect direct statements made in the manufacturer's package insert; for additional uses, warnings, and precautions, please refer to clinical guidelines.

- Boxed Warning(s):
  - None reported.

APPENDIX D: General Information

- Pulmonary Hypertension: WHO Classification
  - Group 1: PAH (pulmonary arterial hypertension)
  - Group 2: PH due to left heart disease
  - Group 3: PH due to lung disease and/or hypoxemia
  - Group 4: CTEPH (chronic thromboembolic pulmonary hypertension)
  - Group 5: PH due to unclear multifactorial mechanisms
- Dividing the 40mg dose over the course of the day is not recommended.
- Renal Impairment for Tadliq® Severe (creatinine clearance <30 mL/min and on hemodialysis): Avoid use of Tadliq®
- Hepatic Impairment for Tadliq® Severe (Child Pugh Class C): Avoid use of Tadliq®

APPENDIX E: Pulmonary Hypertension: WHO/NYHA Functional Classes (FC)

Treatment Approach*	FC	Status at Rest	Tolerance of Physical Activity (PA)	PA Limitations	Heart Failure
Monitoring for progression of PH and treatment of co-existing conditions	I	Comfortable at rest	No limitation	Ordinary PA does not cause undue dyspnea or fatigue, chest pain, or near syncope.	
Advanced treatment of PH with PH-	II	Comfortable at rest	Slight limitation	Ordinary PA causes undue dyspnea or fatigue, chest pain, or near syncope.	

targeted therapy - *see Appendix F***	III	Comfortable at rest	Marked limitation	Less than ordinary PA causes undue dyspnea or fatigue, chest pain, or near syncope.	
	IV	Dyspnea or fatigue may be present at rest	Inability to carry out any PA without symptoms	Discomfort is increased by any PA.	Signs of right heart failure

*PH supportive measures may include diuretics, oxygen therapy, anticoagulation, digoxin, exercise, pneumococcal vaccination. **Advanced treatment options also include calcium channel blockers.

APPENDIX F: Pulmonary Hypertension: Targeted Therapies

Mechanism of Action	Drug Class	Drug Subclass	Drug	Brand/Generic Formulations
Reduction of pulmonary arterial pressure through vasodilation	Prostacyclin* pathway agonist **Member of the prostanoid class of fatty acid derivatives.*	Prostacyclin	Epoprostenol	Veletri (IV) Flolan (IV) Flolan generic (IV)
		Synthetic prostacyclin analog	Treprostinil	Orenitram (oral tablet) Remodulin (IV) Tyvaso (inhalation)
			Iloprost	Ventavis (inhalation)
		Non-prostanoid prostacyclin receptor (IP receptor) agonist	Selexipag	Uptravi (oral tablet)
	Endothelin receptor antagonist (ETRA)	Selective receptor antagonist	Ambrisentan	Letairis (oral tablet)
		Nonselective dual action receptor antagonist	Bosentan	Tracleer (oral tablet)
			Macitentan	Opsumit (oral tablet)
	Nitric oxide- cyclic guanosine monophosphate enhancer	Phosphodiesterase type 5 (PDE5) inhibitor	Sildenafil	Revatio (IV, oral tablet, oral suspension)
			Tadalafil	Adcirca® (oral tablet)
		Guanylate cyclase stimulant (sGC)	Riociguat	Adempas (oral tablet)

References

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Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established	01/2020	03/06/2020
Policy was reviewed: 1. Added alternative Authorized Generic (Alyq™) to the policy. 2. Continued Therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance..." 3. Approval Duration for commercial updated to 12 months.	07/09/2020	09/14/2020

4. Added maximum daily dosing. 5. References reviewed and updated.		
Policy was reviewed: 1. Statement about provider sample ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy. 2. Initial Approval Criteria and Continued Therapy Approval Criteria were updated to remove HIM approval duration. 3. Continued Therapy Approval Criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 4. Therapeutic Alternatives verbiage was rephrased to "Below are suggested therapeutic alternatives based on clinical guidance..". 5. Appendix B: Therapeutic Alternatives was updated to remove inactive/unavailable drugs Afeditab® CR and Dilacor XR®. 6. Statement about drug listing format in Appendix B is rephrased to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only". 7. Appendix D was updated to include “Dividing the 40mg dose over the course of the day is not recommended”. 8. References were reviewed and updated.	05/28/2021	09/14/2021
Policy was reviewed: 1. Initial Approval Criteria I.A.4 and Continued Approval Criteria II.B.3 updated to add requirement of trial of generic tadalafil before brand Adcirca® or Alyq™,unless contraindicated or clinically significant adverse effects are experienced. 2. Appendix B, Dosing Regimen, Updated: a. diltiazem: Updated dosing information from 720 to 960 mg PO once daily to Initial, 60 mg orally 3 times daily, usual	03/15/2022	07/18/2022

dosage range in idiopathic PAH: 240 to 720 mg/day for indication PAH b. amlodipine: Updated dosing information from 20 to 30 mg PO once daily to Initial, 2.5 mg orally once daily for indication PAH. 3. Appendix B, Maximum Dose, Updated: a. diltiazem: Updated maximum dose information from 960 mg/day to 720 mg/day for indication PAH. b. amlodipine: Updated maximum dose information from 30 mg/day to 20 mg/day for indication PAH 4. Disclaimer about contraindications "Contraindications listed reflect statements made in the manufacturer's package insert..." was added to Appendix C. 5. References were reviewed and updated.		
Policy was reviewed: 1. Clinical Policy Title, Drug(s) Applied: Updated to include new drug Tadliq®. 2. Background: Updated to include new Brand, Tadliq®. 3. Dosing Information, Drug Name: Updated to include new drug Tadliq®. 4. Dosing Information, Dosing Regimen, tadalafil (Adcirca®, Alyq™, Tadliq®): Updated to include hepatic and renal impairment dosing information for indication PAH. 5. Dosage Forms: Updated to include new brand dosage form, Tadliq®: Oral suspension: 20 mg/5 mL. 6. Initial Approval Criteria, I.A.4: Updated to remove prior trial and failure criteria "If request is for brand Adcirca® or Alyq™, member must use generic tadalafil, unless contraindicated or clinically significant adverse effects are experienced." 7. Initial Approval Criteria, I.A.4: Updated to include new drug request criteria, For Tadliq® request, member is unable to swallow tablets. 8. Continued Therapy Approval Criteria, II.A.3: Updated to remove prior trial and failure criteria "If request is for brand Adcirca® or	03/17/2023	04/13/2023

Alyq™, member must use generic tadalafil, unless contraindicated or clinically significant adverse effects are experienced." 9. Continued Therapy Approval Criteria, II.A.3: Updated to include new drug request criteria, For Tadliq® request, member is unable to swallow tablets. 10. Appendix A: Updated to include abbreviations GC & PDE5. 11. Appendix B, Dosing Regimen, amlodipine (Norvasc®): Updated dosing information from initial, 2.5 mg orally once daily to 5 mg orally once daily for indication PAH. 12. Appendix B, Maximum Dose, amlodipine (Norvasc®): Updated maximum dose information from 20 mg/day to 10 mg/day for indication PAH. 13. Appendix D, General Information: Updated to include new information regarding Renal Impairment and Hepatic Impairment. 14. References were reviewed and updated.		