MEDICATION POLICY:

Endothelin Antagonists

Generic Name: Endothelin Antagonists

Therapeutic Class or Brand Name: Endothelin Antagonists

Applicable Drugs (if Therapeutic Class): Letairis® (ambrisentan), Opsumit® (macitentan), Tracleer® (bosentan)

GPI Code: 4016000700, 4016001500, 4016005000

Preferred: N/A

Non-preferred: N/A

Date of Origin: 2/1/2013

Date Last Reviewed / Revised: 2/5/2019

Prior Authorization Criteria

(May be considered medically necessary when criteria I through IV are met)

I. Documented diagnosis of Pulmonary Arterial Hypertension (PAH), WHO Group I (see Appendix).

II. Documented failure, intolerance, or contraindication to sildenafil.

III. Minimum age requirement: 3 years old (Tracleer®)/18 years old (Letairis® & Opsumit®).

IV. Patient must be under the care or referral of a cardiologist or pulmonologist.

Exclusion Criteria

- Women who are or may become pregnant.
- Letairis®: patients with Idiopathic Pulmonary Fibrosis (IPF).
- Tracleer®: concomitant use with cyclosporine or glyburide.

Other Criteria

- Letairis®, Opsumit®, and Tracleer® are available only through restricted programs. More information about these programs is provided in the table below:

Drug Name	Restricted Program Name	Reason For Restricted Program	Website Address/Phone Number For Further Information
Letairis®	Letairis Risk Evaluation and Mitigation Strategy (REMS) Program	Risk of embryo-fetal toxicity	www.letairisrems.com/ 1-866-664-5327
Opsumit®	Opsumit REMS Program		www.OPSUMITREMS.com/ 1-866-228-3546
Tracleer®	Tracleer Risk Evaluation and Mitigation Strategy (REMS)	Risks of hepatotoxicity and birth defects	www.tracleerrems.com/ 1-866-228-3546

QUANTITY / DAYS SUPPLY RESTRICTIONS

- Letairis®: 30 tablets per 30 days.
- Opsumit®: 30 tablets per 30 days.
- Tracleer®:
    - Patients > 12 years old: 60 film-coated tablets per 30 days.
    - Patients < 12 years old:
        - Weight 4 to 8 kg: 30 tablets for suspension per 30 days.
        - Weight > 8 to 16 kg: 60 tablets for suspension per 30 days.
        - Weight >16 to 24 kg: 90 tablets for suspension per 30 days.
        - Weight > 24 to 40 kg: 120 tablets for suspension per 30 days.

APPROVAL LENGTH

- **Authorization:** 1 year.
- **Re-Authorization:** An updated letter of medical necessity or progress notes confirming the current medical necessity criteria are met and showing the medication is effective.

APPENDIX

Revised WHO Classification of Pulmonary Hypertension – Group 1:

- Idiopathic (IPAH).
- Familial (FPAH).
- Associated with (APAH):*
    - Connective tissue disorder (e.g. rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma, systemic sclerosis (formerly known as CREST syndrome)).
    - Congenital systemic-to-pulmonary shunts (e.g. congenital heart disease (CHD), including atrial or ventricular septal defect, patent ductus arteriosus (PDA), patent foramen ovale (PFO), truncus arteriosus, Eisenmenger syndrome, tetralogy of Fallot, transposition of the great vessels).
    - Portal hypertension.
    - HIV infection.
    - Drugs and toxins (e.g. anorexic agents, cocaine, methamphetamine, L-tryptophan).
    - Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies (e.g. sickle cell anemia, thalassemia), chronic myeloproliferative disorders, splenectomy).
- Associated with significant venous or capillary involvement:
    - Pulmonary veno-occlusive disease (PVOD).
    - Pulmonary capillary hemangiomatosis (PCH).
- Persistent pulmonary hypertension of the newborn.

* Diagnoses, include, but are not limited to these common diagnoses.

REFERENCES

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4137591/ .
2. http://www.bcbsnc.com/assets/services/public/pdfs/formulary/pah_endothelin_antagonists_um_criteria.pdf .
3. Medi-Span®.
4. http://www.gilead.com/~/media/Files/pdfs/medicines/cardiovascular/letairis/letairis_pi.pdf .
5. http://www.tracleer.com/assets/PDFs/Tracleer_Full_Prescribing_Information.pdf .
6. http://opsumit.com/sites/opsumit/files/OPSUMIT-Full-Prescribing-Information.pdf .

HISTORICAL TRACKING OF CHANGES MADE TO POLICY

Date	Notes/Changes
2/5/2019	1. **Changed under Quantities/Days Supply Restrictions** to account for bosentan pediatric indications **from** "Tracleer®: 60 tablets per 30 days" **to**: • Tracleer®: o Patients > 12 years old: 60 film-coated tablets per 30 days. o Patients < 12 years old: ▪ Weight 4 to 8 kg: 30 tablets for suspension per 30 days. ▪ Weight > 8 to 16 kg: 60 tablets for suspension per 30 days. ▪ Weight >16 to 24 kg: 90 tablets for suspension per 30 days. ▪ Weight > 24 to 40 kg: 120 tablets for suspension per 30 days. 2. **Deleted** obsolete URLs **under References items** #3 and #4: • http://blue.regence.com/trgmedpol/drugs/dru218.pdf. • http://blue.regence.com/trgmedpol/drugs/dru324.pdf. • ttp://blue.regence.com/trgmedpol/drugs/dru219.pdf. 2. **Replaced under References** item #1 http://journal.publications.chestnet.org/article.aspx?articleid=1881654 **with** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4137591 .
12/19/2017	1. **Changed** "III. Minimum age requirement: 18 years old" **to** "III. Minimum age requirement: 3 years old (Tracleer®)/18 years old (Letairis® & Opsumit®)" **under Prior Authorization Criteria**.
10/6/2016	1. **Added** "II. Documented failure, intolerance, or contraindication to sildenafil" **under Prior Authorization Criteria**. 2. **Changed** "Tracleer Access Program (T.A.P.)" **to** "Tracleer Risk Evaluation and Mitigation Strategy (REMS)" **under Other Criteria**. 3. **Updated** "http://www.tracleer.com/docs/Tracleer_Full_Prescribing_Information.pdf" **to**

<table>
<tr><td></td><td>"http://www.tracleer.com/assets/PDFs/Tracleer_Full_Prescribing_Information.pdf" under References.</td></tr>
<tr><td>4/21/2015</td><td>
1. Changed "Letairis® (ambrisentan) and Tracleer® (bosentan)" to "Letairis® (ambrisentan), Opsumit® (macitentan), Tracleer® (bosentan)" under Applicable Drugs
2. Changed GPI Code from "4016000700, 4016-001500" to "4016000700, 4016001500, 4016005000".
3. Removed "Letairis® and Tracleer® are only to be used in combination with other PAH therapies when treatment with one PAH agent failed to adequately control the patient's symptoms" from Exclusion Criteria.
4. Changed "Tracleer®: concomitant use of Tracleer® and Cyclosporine or Glyburide" to "Tracleer®: concomitant use with cyclosporine or glyburide" under Exclusion Criteria.
5. Changed "Because of the risks of hepatotoxicity and birth defects, Tracleer® is available only through a restricted program called the Tracleer Access Program (T.A.P.). As a component of the Tracleer REMS, prescribers, patients, and pharmacies must enroll in the program. Further information about Tracleer and T.A.P. is available at www.tracleerrems.com or 1-866-228-3546" and "Because of the risk of embryo-fetal toxicity, Letairis® is available only through a special restricted distribution program called the Letairis Risk Evaluation and Mitigation Strategy (REMS) program. Only prescribers and pharmacies certified with REMS may prescribe and distribute Letairis®. All female patients must enroll in the REMS program. Male patients are not enrolled in REMS. Further information is available at www.letairisrems.com or 1-866-664-5327" to "More information about these programs is provided in the table below:
<table>
<tr><th>Drug Name</th><th>Restricted Program Name</th><th>Reason For Restricted Program</th><th>Website Address/Phone Number For Further Information</th></tr>
<tr><td>Letairis®</td><td>Letairis Risk Evaluation and Mitigation Strategy (REMS) Program</td><td rowspan="2">Risk of embryo-fetal toxicity</td><td>www.letairisrems.com/ 1-866-664-5327</td></tr>
<tr><td>Opsumit®</td><td>Opsumit REMS Program</td><td>www.OPSUMITREMS.com/ 1-866-228-3546</td></tr>
<tr><td>Tracleer®</td><td>Tracleer Access Program (T.A.P.)</td><td>Risks of hepatotoxicity and birth defects</td><td>www.tracleerrems.com/ 1-866-228-3546</td></tr>
</table>
6. Added "Opsumit®: 30 tablets per 30 days" under Quantity/Days Supply Restrictions.
7. Added "http://journal.publications.chestnet.org/article.aspx?articleid=1881654", "http://blue.regence.com/trgmedpol/drugs/dru324.pdf", and "http://opsumit.com/sites/opsumit/files/OPSUMIT-Full-Prescribing-Information.pdf" under References.
</td></tr>
<tr><td>12/23/2013</td><td>
1. Adapted policy to new format.
2. Added GPI codes.
3. Added "Minimum Age Requirement: 18 years old" under Prior Authorization Criteria.
4. Added "Letairis®: patients with Idiopathic Pulmonary Fibrosis (IPF)" under Exclusion Criteria.
</td></tr>
</table>

to Plan for individual adoption of specific Medication Policies. Providers are expected to exercise their medical judgement in providing the most appropriate care for their patients.