

Drugs & Therapy

B ♦ U ♦ L ♦ L ♦ E ♦ T ♦ I ♦ N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met March 18 and April 15, 2014. 3 drugs were added in the *Formulary*, 1 drug class had criteria for use changes, 1 drug was designated non-formulary high priority, and 1 drug was designated non-formulary and not available.

◆ ADDED

Macitentan (Opsumit®)*

*Female patients must enroll in the REMS program. All patients must demonstrate financial ability to continue therapy in the outpatient setting prior to initiation of therapy.

Perampanel (Fycompa®)

Riociguat (Adempas®)*

*Female patients must enroll in the REMS program. All patients must demonstrate financial ability to continue therapy in the outpatient setting prior to initiation of therapy.

◆ CRITERIA FOR USE CHANGES

Fluoroquinolone Class

Criteria for use modified

◆ HIGH-PRIORITY NON-FORMULARY

Tresprostinil diolamine (Orenitram®)*

*Restricted to continuation of home therapy only

◆ NON-FORMULARY AND NOT AVAILABLE

Tasimelteon (Hetlioz®)^

^Patient may use their own

◆ DELETED

None

◆ THERAPEUTIC INTERCHANGES

None

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THERAPEUTIC UPDATE

ACC/AHA New Cholesterol Guidelines

In November 2013, the American College of Cardiology and the American Heart Association released a new Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.^[1] Prior to November, the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (published in 2002 and updated in 2004) served as the primary guide to patient therapy.^[2] These previous guidelines outlined therapeutic targets for patients with varying risk factors (i.e. LDL-C < 100 for patient with diabetes) as well as how targeted goals may best be achieved.

The newly-formed Blood Cholesterol Expert Panel (previously known as the Adult Treatment Panel or ATP IV), was appointed by the National Heart, Lung, and Blood Institute (NHLBI), and focused on three critical questions when drafting the new guidelines:

- What evidence supports LDL-C goals for primary prevention?
- What evidence supports LDL-C goals for secondary prevention?
- What is the impact of the major cholesterol drugs on efficacy and safety?

Major differences in the new guidelines include a new focus on atherosclerotic cardiovascular disease (ASCVD) reduction, a change in perspective on LDL-C and non-HDL-C treatment goals, and the inclusion of a new global ASCVD risk assessment tool for primary prevention.^[1] Perhaps the most significant change is that there no longer is a recommendation to support treating to a target LDL-C or non-HDL-C goal. This change is secondary to a lack of clinical

trial data showing reductions in ASCVD associated with target LDL-C and non-HDL-C attainment.

The new recommendations focus on selection of an appropriate intensity of statin treatment to reduce ASCVD risk in patients most likely to benefit from therapy. The major recommendations for statin therapy for ASCVD prevention include four statin groups, where the benefit of statin therapy outweighs the risk of adverse events. Patients identified in these four groups should then be treated with a low-, moderate-, or high-intensity statin, as determined by benefit group, age, and ASCVD risk. In addition, a new Global Risk Assessment for Primary Prevention of ASCVD tool was created which is more comprehensive than the previously utilized Framingham 10-year Risk Tool. The tool predicts the occurrence of stroke as well as myocardial infarction. While it does include components of the Framingham tool, it also considers the patient's race and whether or not they are diabetic.^[3]

Treatment Groups:

- Clinical ASCVD (defined as Acute Coronary Syndrome or history of MI, angina, coronary or other arterial revascularization, stroke, TIA, or peripheral artery disease presumed to be of atherosclerotic origin)
 - **Age ≤75 years:** High-intensity statin (Moderate intensity if not a candidate for high-intensity)

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Macitentan is a dual endothelin-receptor antagonist that prevents the binding of endothelin-1 (ET-1) to both endothelin receptor types A and B (ETA and ETB). Macitentan is structurally similar to bosentan (Tracleer®), but with advertised improvements in safety and efficacy.

Macitentan is an oral tablet that can be taken with or without food. This medication has an active metabolite, which can account for approximately 40% of the total pharmacological activity. The elimination half-lives of macitentan and its active metabolite are approximately 16 hours and 48 hours, respectively. In comparison to bosentan, macitentan has a longer half-life. This can be attributed to its slower receptor dissociation kinetics in pulmonary arterial smooth muscle cells.

Macitentan was predominantly studied for usage in pulmonary arterial hypertension (PAH) patients with WHO Functional Class II and III with or without the concomitant treatment of PDE-5 inhibitors or oral/inhaled prostanoids. The recommended dosage of macitentan for PAH is 10 mg once daily. Macitentan does not require renal or hepatic impairment dosage adjustments.

The Phase III SERAPHIN trial showed that macitentan significantly reduced hospitalizations due to PAH and improved worsening of PAH in comparison to placebo. Macitentan also showed an improvement in 6-minute walk distance; however this improvement is not as impressive as those seen in the Phase III trials for either bosentan or ambrisentan.

Macitentan is Pregnancy Category X and contraindicated during pregnancy. Because of this contraindication, all female patients must be enrolled in the Opsumit® REMS program. Additionally, macitentan may cause a decrease in spermatogenesis although a formal REMS program is not required for this adverse effect. The most common side effects seen with this medication in clinical trials included nasopharyngitis, anemia, bronchitis, and headaches. Macitentan can also cause pulmonary veno-occlusive disease, which can lead to pulmonary edema. While taking this medication, patients should have hemoglobin/hematocrit and liver function tests measured at baseline and throughout therapy to assess

for anemia and hepatotoxicity.

The Pharmacy and Therapeutics Committee voted to add macitentan in the *Formulary*. Female patients are required to enroll in the Opsumit® REMS program. All patients must show the financial ability to continue therapy as an outpatient prior to initiation of therapy.

Perampanel was requested by the Department of Neurology for use in the treatment of refractory complex partial seizures. As this medication is a controlled substance, patients are unable to use their own home medication per UF Health Shands Hospital Patient's Own Medication Policy.

Perampanel was approved by the FDA in October 2012 for the treatment of partial onset seizures in patients 12 years of age or older. Drug approval was based upon 3 Phase III clinical trials conducted worldwide. Perampanel carries a black box warning which describes the risk of serious neuropsychiatric events including but not limited to irritability, aggression, anger, anxiety, paranoia, euphoric mood, agitation, and mental status changes.

In clinical trials, perampanel was shown to be safe and effective for the adjunct treatment of partial-onset seizures. The most commonly described adverse events were dizziness, drowsiness, fatigue, irritability, and loss of muscle coordination. Monitoring for these adverse events is exceedingly important especially during periods of dose titration.

Perampanel is dosed once-daily and is available as 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg tablets with the most commonly utilized dosing regimen ranging from 8-12 mg daily. It was recommended that this agent be added in the *Formulary* for the treatment of partial onset seizures. With alternative therapies available at significantly lower cost, this medication is recommended to be reserved for use in patients who are medically refractory to therapies with other anti-epileptic agents.

Riociguat is a member of a novel class of drugs, the soluble guanylate cyclase stimulators for the treatment of pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH).

Soluble guanylate cyclase stimulators produce vasodilation through enriched signaling within the nitric oxide-cyclic GMP pathway in the absence of nitric oxide. Riociguat has a labeled indication to improve exercise capacity in patients with CTEPH either post operatively or in patients who are unable to undergo surgery. Riociguat is also indicated for patients with PAH of unknown causes, inherited, or associated with connective

tissue diseases, to improve their exercise capacity and to delay clinical worsening.

Riociguat has a relatively high bioavailability. The labeled dosage is to initiate treatment at 1 mg by mouth three times daily, titrating the dose by 0.5 mg three times daily based on the systolic blood pressure and signs or symptoms of hypotension to a max dosage of 2.5 mg three times daily.

Efficacy data are limited and have only been measured in two large, Phase III, multicenter, randomized, double-blind, placebo-controlled trials for use in PAH and CTEPH. Data suggests that riociguat is effective showing improvements in exercise capacity, pulmonary vascular resistance (PVR), and WHO functional class in patients with PAH and CTEPH, as well as decreasing the time to clinical worsening in patients with PAH. The improvements for PAH were seen in both treatment naïve patients as well as those receiving co-administration with prostanoids and endothelin-receptor antagonists. Of note, this is the first drug of any class to show an improvement in patients with CTEPH.

The most common side effects of riociguat include signs and symptoms of hypotension and gastrointestinal effects. Teratogenicity was seen in animal models, leading to the formulation of the Adempas® REMS Program. Long-term safety data is not yet available, however extension trials of both the CHEST-1 and PATENT-1 studies are aiming to collect additional information to evaluate safety and tolerability of riociguat therapy.

The Pharmacy and Therapeutics Committee voted to add riociguat in the *Formulary*. Female patients are required to enroll in the Adempas® REMS program. All patients must show the financial ability to continue therapy as an outpatient prior to initiation of therapy.

Tasimelteon is a melatonin receptor agonist which is indicated for the treatment of non-24 hour sleep-wake disorder in blind patients. This disorder is the result of light not entering the eyes which makes it difficult to synchronize a body clock to a 24 hour light-dark cycle. This oral tablet is dosed 20 mg prior to bedtime at the same time every night.

It was recommended that this agent be designated non-formulary and not available with patients able to take their own medication. The P&T Committee agreed with this recommendation.

Treprostinil diolamine is an oral extended-release osmotic tablet that
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Formulary update, from page 2

is FDA-approved for the treatment of pulmonary arterial hypertension (PAH) in World Health Organization (WHO) group 1 patients to improve exercise capacity. Treprostinil is a stable prostacyclin analog that causes direct vasodilation of the pulmonary and systemic arterial vascular beds. Other major pharmacologic actions include inhibition of platelet aggregation and inhibition of smooth muscle cell proliferation.

Oral treprostinil is administered every 12-hours and the dose depends on response and tolerability. In PAH, prostacyclins are typically reserved for last-line treatment to improve quality of life and exercise capacity. Prior to the approval of the oral formulation, treprostinil only existed as intravenous, subcutaneous, and inhaled forms dosed as continuous infusions or 4 times per day. Oral treprostinil allows twice daily dosing in a more convenient dosage form.

Efficacy data are limited and have only been measured in 3 large, Phase III, multicenter randomized, double-blind, placebo-controlled trials for use in PAH. Two trials assessed the efficacy in patients receiving combination therapy with endothelin receptor antagonists (ERAs), phosphodiester-

ase-5 inhibitors (PDE-5Is), or both. One trial assessed the efficacy of oral treprostinil used as monotherapy. Data suggests that when oral treprostinil is used as the sole vasodilator, the effect on exercise is small. Oral treprostinil has not been shown to add to other vasodilatory therapy.

Patients taking oral treprostinil should not have therapy discontinued abruptly. Patients temporarily unable to take oral medications may receive an infusion of subcutaneous or intravenous treprostinil. To calculate the total daily dose of treprostinil for the parenteral route, divide the oral total daily dose (mg) by 5.

It was recommended that treprostinil diolamine be designated as non-formulary high-priority for continuation of home therapy only with patients able to use their own supply. If unable to supply the product, the medication will be provided for inpatient use.

The **Fluoroquinolone Class** was evaluated by the Pharmacy and Therapeutics Committee in conjunction with the Anti-Infective Subcommittee in January 2014. The results of this evaluation were published in the February 2014 Drugs and Therapy Bulletin. As an addendum to that evaluation, the fluoroquinolone class was evaluated for utilization in patients receiving leech therapy as well as for

prophylaxis of spontaneous bacterial peritonitis (SBP) in high-risk patients.

Published evidence does not support the utilization of ciprofloxacin in leech therapy. The Anti-infective subcommittee recommended that first-line therapy for this indication remain sulfamethoxazole/trimethoprim. The Pharmacy and Therapeutics Committee agreed with this recommendation.

Literature evaluating the use of ciprofloxacin for the prevention of SBP in high risk patients yielded appropriate support for this indication. The Anti-infective subcommittee recommended an expansion of previously reported criteria to include this indication. The Pharmacy and Therapeutics Committee voted to approve this indication.

Insulin,

from page 1

– **Age >75 years:** Moderate-intensity

- Individuals with primary elevations of LDL-C \geq 190 mg/dL

– High-intensity statin (Moderate intensity if not a candidate for high-intensity)

- Individuals 40-75 years of age with diabetes with LDL-C between 70-189 mg/dL

– Moderate-intensity statin

– If estimated 10-year ASCVD risk \geq 7.5%: High-intensity statin

- Individuals 40-75 years of age with out clinical ASCVD and a LDL-C between 70-189 mg/dL and an estimated 10 year ASCVD risk \geq 7.5%

– Moderate-to-high intensity statin

The ASCVD prevention benefit of statin therapy is not as clear in patients not falling into one of the aforementioned groups, but may be considered in patients with additional risk factors including family history

Category	High Intensity	Moderate Intensity	Low Intensity
LDL-C lowering potential	Daily dose lowers LDL-C on average \geq 50%	Daily dose lowers LDL-C on average 30-50%	Daily dose lowers LDL-C on average < 30%
Recommended Statin Therapy	Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Lovastatin 40 mg Pitavastatin 2-4 mg Pravastatin 40-80 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg	Fluvastatin 20-40 mg Lovastatin 20 mg Pitavastatin 1 mg Pravastatin 10-20 mg Simvastatin 10 mg
UF Health Shands Formulary Options	Atorvastatin 40-80 mg	Atorvastatin 10-20 mg Lovastatin 40 mg	Lovastatin 20 mg

of early onset ASCVD or presence of genetic hyperlipidemia.

In regards to patient safety, the new guidelines recommend measuring baseline hepatic transaminase levels prior to initiation of statin therapy. In patients predisposed to statin-related adverse events (presence of multiple serious comorbidities, history of statin intolerance, unexplained ALT $>$ 3x the upper limit of normal, concomitant use

of drugs affecting statin metabolism, or $>$ 75 years old), the panel recommends using moderate-intensity statin therapy where high-intensity statin would otherwise be preferred. Fasting lipid panels should be obtained 4-12 weeks after initiation or dose adjustment, then every 3-12 months afterwards. The guidelines do not make any

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Insulin,

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recommendation related to the initiation or discontinuation of statins in heart failure or hemodialysis patients.

– Ginger Gamble, PharmD

REFERENCES

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3. 2013 Prevention Guidelines Tools: CV Risk Calculator. American Heart Association Website. Available from: <http://my.americanheart.org/cvrisk-calculator>. Accessed: January 1, 2014.

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