

Thrombopoietin Agonists
Eltrombopag (Promacta®) for Use for Hepatitis C Related Thrombocytopenia
Criteria for Use
May 2013

**VA Pharmacy Benefits Management Services, Medical Advisory Panel,
VISN Pharmacist Executives and Office of Public Health**

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient. Individual cases that are outside the recommendations should be adjudicated at the local facility according to the policy and procedures of its P&T Committee and Pharmacy Services.

EXCLUSION CRITERIA (If any are selected below, patient is not eligible for either drug)

- Anticipated antiviral treatment includes a direct-acting antiviral (DAA) for the treatment of chronic hepatitis C virus (HCV) infection (see Issues for Consideration)**
- Patient currently receiving peginterferon and ribavirin with or without DAA for chronic HCV infection (eltrombopag was only studied prior to the initiation of peginterferon and ribavirin and then maintenance on peginterferon and ribavirin).**
- Any contraindications to peginterferon and ribavirin apply since eltrombopag will be administered with peginterferon and ribavirin if platelets goal is reached (refer to VA HCRC and PSHG HCV Treatment Recommendations for contraindications specific to peginterferon and ribavirin; <http://vaww.hepatitis.va.gov>)
- Active malignancy or stem cell disorder
- Prior history of arterial or venous thrombosis **and** ≥ 2 of the following risk factors: hereditary thrombophilic disorders (e.g., Factor V Leiden, antithrombin III deficiency, etc.); estrogen hormone replacement therapy; systemic contraception therapy (containing estrogen); smoking; diabetes; hypercholesterolemia; medication for hypertension; or cancer
- Serious cardiac, cerebrovascular, or pulmonary disease
- Any disease condition associated with active bleeding or requiring anticoagulation with heparin or warfarin
- Known hypersensitivity, intolerance or allergy to peginterferon and ribavirin, eltrombopag tablets or any of their ingredients
- Evidence of decompensated liver disease (i.e., Child-Pugh score ≥ 7 and/or clinical manifestations)
- Patient infected with HIV (No safety and efficacy data)

INCLUSION CRITERIA (The answers to all of the following must be fulfilled in order to meet criteria)

- Under care of and/or in collaboration with an experienced VA HCV practitioner
- Provider has discussed with patient the potential risks and benefits of eltrombopag, HCV therapy and progression of HCV disease and a shared decision has been made for use
- Patient has diagnosis of chronic HCV infection
- Baseline platelet count $< 75,000/\mu\text{L}$
- Patients are appropriate candidates for peginterferon and ribavirin combination antiviral therapy
- Treatment with peginterferon and ribavirin (i.e., only dual therapy) is anticipated after reaching target platelet goal
- Abdominal imaging negative for portal vein thrombosis within the past 3 months

DOSAGE AND ADMINISTRATION

Eltrombopag should be initiated prior to peginterferon and ribavirin therapy to obtain target platelet count. If target platelet count is achieved and patient is still eligible for peginterferon and ribavirin therapy, then peginterferon and ribavirin may be initiated with the continuation of eltrombopag.

- Initiate eltrombopag at a dose of 25mg once daily. Eltrombopag should be taken on an empty stomach (1 hour before or 2 hours after a meal). Refer to Issues for Consideration for drug-drug and drug-food interactions.
- Adjust eltrombopag by 25mg increments every 2 weeks as necessary to achieve target platelet count required to initiate antiviral therapy; target platelet count should be $\geq 90,000/\mu\text{L}$ if using peginterferon alfa-2a and $\geq 100,000/\mu\text{L}$ if using peginterferon alfa-2b. **Use the lowest dose of eltrombopag to achieve and maintain a platelet count necessary to initiate and maintain peginterferon and ribavirin.**
- At the end of the pre-treatment phase (i.e., prior to peginterferon and ribavirin), the same dose of eltrombopag should be maintained when starting antiviral therapy. Eltrombopag while on antiviral therapy may be modified to maintain platelet counts; **target platelet count on HCV treatment should be between 50,000-150,000.**
- Please note that dose reduction is NOT needed solely based upon ethnicity (i.e., in patients of East Asian ethnicity) with the use of eltrombopag for chronic hepatitis C.

PBM Recommendations for Initial and Adjustments of Eltrombopag for Patients with HCV

Initial dose of eltrombopag	25 mg orally once daily
Dose Adjustment based on platelet count <i>Please note that the dosage adjustment recommended below differs from FDA prescribing information. The below recommendations are based upon hepatology experts in the VA that recommend to maintain target platelet counts between 50,000/μL to 150,000/μL to reduce potential thrombotic complications.</i>	
<50,000/μL following at least 2 weeks of eltrombopag	Increase daily dose by 25 mg; wait 2 weeks to assess the effects of this and any subsequent dose adjustments. Please note that maximum dose is 100 mg/day.
\geq150,000/μL to 200,000/μL at any time	Decrease daily dose by 25mg; wait 2 weeks to assess the effects of this and any subsequent dose adjustments
>200,000/μL at any time	Stop eltrombopag ; increase the frequency of platelet monitoring to twice weekly. Once platelet count is <100,000/ μ L, reinstitute therapy at daily dose reduced by 25 mg. For patients taking 25mg once daily, reinstitute therapy at a daily dose of 12.5 mg.
Maximum dose	100 mg/day
Discontinuation	Eltrombopag should be discontinued when antiviral therapy is discontinued.

RECOMMENDED MONITORING

Monitoring prior to initiation of eltrombopag therapy

- CBC with differential (including platelet count)
- Ocular exam for detection of cataracts
- Liver Function Panel (Total and Direct bilirubin, AST, ALT, albumin, total protein)

Monitoring during eltrombopag therapy

- CBC weekly until stable, then monthly
- Serum liver tests (ALT, AST, and bilirubin) every 2 weeks during adjustment phase, then monthly
 - If bilirubin is elevated, perform fractionation.
 - If abnormal levels are detected, repeat the tests within 3 to 5 days. If abnormalities are confirmed, monitor serum liver tests weekly until abnormality(ies) resolve, stabilize, or return to baseline levels.
- Ocular exams and regularly monitor for signs and symptoms of cataracts

Monitoring upon discontinuation of eltrombopag therapy

- CBCs weekly for at least four weeks

Discontinuation of Eltrombopag for hepatotoxicity

- If ALT levels increase to \geq 3X ULN in patients with normal liver function or \geq 3X baseline in patients with pre-treatment elevations in transaminases and are:
 - Progressive, or
 - Persistent for \geq 4 weeks, or
 - Accompanied by increased direct bilirubin, or
 - Accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation

ISSUES FOR CONSIDERATION

Treatment Considerations

- FDA Approved Indication: Treatment of thrombocytopenia in patients with chronic hepatitis C to allow patients to initiate and maintain interferon-based therapy. **The approval was based upon efficacy and safety of eltrombopag in HCV patients being treated with only peginterferon and ribavirin; therefore, the efficacy and safety of eltrombopag with DAA-containing regimens has not been established.** Thus, dose reduction of peginterferon alfa-2a and peginterferon alfa-2b according to prescribing information should be considered for patients with thrombocytopenia (<50,000/ μ L) who are currently receiving peginterferon and ribavirin with or without DAA for chronic HCV infection. Please note that the peginterferon prescribing information recommends discontinuation of treatment when platelets are <25,000/ μ L; this should include discontinuation of ALL antiviral therapy including ribavirin and DAA.
 - The use of eltrombopag may be considered in carefully selected HCV-GT1 infected patients with advanced hepatic fibrosis from whom therapy for HCV with a DAA in combination with peginterferon-ribavirin is indicated but cannot be safely initiated because of thrombocytopenia. The decision to approve such therapy requires thoughtful local adjudication.
- FDA Limitations of Use: 1) Eltrombopag should not be used to normalize platelet counts; 2) Eltrombopag should only be used in patients with HCV whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits

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the ability to maintain interferon-based therapy.

Safety

- Eltrombopag labeling contains **Box Warnings** for hepatotoxicity and risk of hepatic decompensation. Both ENABLE 1 and ENABLE 2 revealed more events suggestive of hepatic decompensation in subjects taking eltrombopag compared to subjects taking placebo, 13% vs 8% in ENABLE 1 and 13 vs 6% in ENABLE 2, respectively. Patients with albumin <3.5g/dL or MELD scores ≥10 at baseline had the greatest risk of hepatic decompensation. Events suggestive of hepatic decompensation are ascites, hepatic encephalopathy, variceal hemorrhage, spontaneous bacterial peritonitis, hepatocellular carcinoma, or death. Follow monitoring guidelines above for discontinuation of eltrombopag for hepatotoxicity.
- Patients considered high risk for thromboembolism: Eltrombopag may further increase risk for thrombotic complications. Consider risk of potential thromboembolic event vs. benefit of reducing bleed risk in these cases. In ENABLE 1 and ENABLE 2, 3% (31/955) of patients treated with eltrombopag experienced a thrombotic event compared to 1% (5/484) receiving placebo. These events were observed at low and at normal platelet counts and included both venous and arterial events.
- In the ENABLE 1 and ENABLE 2, cataracts developed or worsened in 8% patients treated with eltrombopag and 5% patients treated with placebo.

Use in Specific Populations (refer to Prescribing Information for comprehensive list of use in specific populations):

- HIV: No safety or efficacy data available in this population and limited drug-drug interactions studies have been performed.
- Renal insufficiency: Eltrombopag safety and efficacy have not been studied in those with renal insufficiency (CrCl<50ml/min); use with caution in those with renal impairment.
- Hepatic insufficiency: Eltrombopag clearance was reduced in moderate-severe hepatic impairment; initial dose should be reduced to 25mg orally daily; monitor serum liver function tests as recommended
- Pregnancy: Pregnancy Category C; Consider potential risks and benefits to mother and fetus. When exposure or use during pregnancy occurs, discuss patient enrollment in the Promacta Pregnancy Registry (1-888-483-5249), <http://pregnancyregistry.gsk.com/Promatcta.html>

Drug-drug/Drug-food interactions

- Eltrombopag is a substrate of CYP1A2 and CYP2C8; an inhibitor of OATP1B1; an inhibitor of UDP-glucuronosyltransferases (UGTs); and chelates polyvalent cations. Multiple drug interactions have been reported with eltrombopag. Refer to prescribing information for details of interactions and management.
- Eltrombopag administration should be separated from medications, supplements or ingestion of food containing iron, calcium, aluminum, magnesium, selenium and zinc by at least 4 hours.

Discontinuation Considerations

- Non-response to eltrombopag: Consider discontinuing eltrombopag after 9 weeks at maximum dose (100 mg/day) if platelet count has not increased to a sufficient level to initiate antiviral therapy with pegylated interferon and ribavirin
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