Safety Guide for REVOLADE ™ (eltrombopag) in chronic hepatitis C-associated thrombocytopenia (HCVaT)

Important safety information for healthcare professionals regarding the monitoring and management of patients prescribed eltrombopag

Revolade is indicated in patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia to:

- Enable the initiation of interferon based therapy.
- Optimize interferon based therapy.

This guide forms part of the risk management programme for eltrombopag and is based on the approved SmPC. For safety information on the use of eltrombopag to treat chronic hepatitis C-associated thrombocytopenia (HCVaT), please refer to the safety guide for eltrombopag in HCVaT.

Prescribing Information is available at the end of this document.

NOVARTIS

Eltrombopag – FOR THE TREATMENT OF THROMBOCYTOPENIA IN ADULTS WITH HEPATITIS C

Eltrombopag indicated in patients with chronic hepatitis C virus (HCV) infection for The treatment of thrombocytopenia to: Enable the initiation of interferon based therapy. Optimize interferon based therapy. Where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based thearpy. The active ingredient, eltrombopag, is an oral thrombopoietin (TPO)-receptor agonist that stimulates platelet production by increasing differentiation and proliferation of megakaryocytes.[1] The aim of treatment with eltrombopag should be to achieve platelet counts sufficient to initiate antiviral therapy and, once antiviral therapy has begun, to maintain platelet counts at a level which prevents the risk of bleeding ,normally around 50,000-75,000/µl.

The safety and tolerability of eltrombopag have been evaluated in 1,576 patients with HCV in the eltrombopag clinical development programme.[2,3]

Summary of eltrombopag clinical studies in patients with HCV[1–3]

Study	Phase	N	Design	Dosing group	Study aim and status
2357	II	**Part 1:** Eltrombopag:56 Placebo: 18 **Part 2:** Eltrombopag:45 Placebo: 4	16-week double blind,randomised, placebocontrolled parallelgroupstudy	**Part 1:** Eltrombopag30mg,50mg, 75 mg or placebo **Part 2:** Eltrombopag30mg,50mg, 75 mg or placebo; inconjunctionwithpIFN (alfa 2a or alfa 2b) and ribavirinantiviraltherapy	Dose-ranging efficacy,safetyand pharmacokinetics Completed
ENABLE-1	III	**Part 1:** Eltrombopag: 716 **Part 2:** Eltrombopag: 449 Placebo: 232	**Part 1:** Open-label,dose escalation **Part 2:** 48-week double-blind, randomised, placebocontrolled	**Part 1:** Eltrombopag25mg,50mg, 75 mg and 100 mg **Part 2:** Eltrombopagdosefrom Part 1 or placebo; in conjunction with pIFN (alfa 2a) and ribavirin antiviral therapy	Efficacyandsafety Completed
ENABLE-2	III	**Part 1:** Eltrombopag: 805 **Part 2**: Eltrombopag: 506 Placebo: 252	**Part 1:** Open-label,dose escalation **Part 2:** 48-week double-blind, randomised, placebocontrolled	**Part 1:** Eltrombopag25mg,50mg, 75 mg and 100 mg **Part 2:** Eltrombopagdosefrom Part 1 or placebo; in conjunction with pIFN (alfa 2b) and ribavirin antiviral therapy	Efficacyandsafety Completed

N = total study population

Eltrombopag is generally well-tolerated. Phase III trials showed a similar incidence of the most common adverse events in patients treated with eltrombopag, and those treated with placebo.[3] The most common adverse events included headache, anemia, decreased appetite, insomnia, cough, nausea diarrhoea, alopecia, pruritis, myalgia, pyrexia, fatigue, influenza-like illness, asthenia, chills and peripheral oedema. Here we discuss some important safety issues identified during the clinical development programme and provide guidance on best practice management of these issues should they arise.

HEPATIC DECOMPENSATION

Chronic HCV patients suffering from cirrhosis may have a higher risk of hepatic decompensation when receiving alfa interferon antiviral therapy.[1] In Phase III trials, the incidence of hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, and spontaneous bacterial peritonitis) was higher in patients treated with eltrombopag than those treated with placebo.[1] Early treatment of events suggestive of hepatic decompensation is recommended.

Incidence

Across the Phase III trials, ascites, hepatic malignant neoplasms, and hepatic encephalopathy were classified as "common", occurring in at least 1% but less than 10% of patients.[1] Hepatic decompensation was reported in 11% of HCV patients treated with eltrombopag, in comparison with 6% of HCV patients treated with placebo.[1]

Who is at risk?

Chronic HCV patients suffering from cirrhosis may have a higher risk of hepatic decompensation when receiving alfa interferon therapy. In patients with advanced liver disease (defined by low albumin levels [≤35 g/L] or a Model for End-Stage Liver Disease [MELD] score ≥10 at baseline), Phase III trials with eltrombopag showed the risk of hepatic decompensation increased three fold; these patients also had a higher risk of fatal adverse events.[1] In addition, eltrombopag treatment in this population was only modestly more likely to achieve sustained virologic response (SVR) compared with placebo, while treatment had a larger benefit in the group overall.[1] In HCV patients with advanced chronic liver disease, eltrombopag should only be administered by physicians experienced in the management of advanced HCV, and after careful consideration of the expected benefits in comparison with the risks. Patients with advanced chronic liver disease should be closely monitored.[1]

Treatment

Patients with symptoms suggestive of hepatic decompensation should stop treatment with eltrombopag.[1] Treatment with eltrombopag should be discontinued if antiviral therapy is terminated for hepatic decompensation.[1]

THROMBOEMBOLIC EVENTS

Thromboembolic events (TEEs) may be more likely to occur in patients with chronic HCV, and patients with advanced liver disease have an increased risk of portal vein thrombosis.[3]

Incidence

In Phase III trials, TEEs were experienced by 4% of patients treated with eltrombopag, in comparison with 1% of patients treated with placebo.[1] No specific temporal relationship between the start of treatment and TEE event was found.[1] Portal vein thrombosis was the most common TEE reported, occurring in 2% of patients treated with eltrombopag, and <1% of patients treated with placebo.[1]

Who is at risk?

Patients with increased risk for TEEs include, but are not limited to, those with inherited (e.g. Factor V Leiden) or acquired risk factors (e.g. ATIII deficiency, antiphospholipid syndrome), advanced age, long periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity, and smoking.[1] In Phase III trials, patients with low albumin levels (≤35 g/L) or MELD ≥10 had a two-fold greater risk of TEEs than those with higher albumin levels; similarly, patients aged 60 or older had a two-fold greater risk of TEEs compared to younger patients.[1] Before administering eltrombopag, careful consideration of the expected benefits in comparison to the risks should be given, and at-risk patients should be closely monitored. Overdose with eltrombopag may increase platelet counts excessively and increase the risk of TEEs.[1]

Additional monitoring

During treatment with eltrombopag, the patient's platelet count should be monitored weekly until a stable count has been achieved (usually about 50,000-75,000/µL) and monthly thereafter.[1] The daily eltrombopag dose should be reduced by 25 mg if the platelet count rises above 100,000/µL, and interrupted altogether if it rises above 150,000/µL.[1] Treatment can be reinitiated at a reduced dose once the platelet count reaches ≤100,000/µL.[1]

Treatment

Eltrombopag therapy should be withdrawn immediately from patients experiencing symptoms of a TEE.[1] Such patients should be managed in Liver Units with experience in management of cirrhotic patients experiencing a portal vein thrombosis or other TEE. Treatment for TEEs includes Vitamin K antagonists or low molecular weight heparin and/or interventional re-vascularisation. Eltrombopag therapy should be re-initiated at the lowest possible dose following careful clinical assessment and after careful consideration of the expected benefits of continuing eltrombopag therapy in comparison with the risks of further TEEs and/or other adverse events.

HEPATOTOXICITY

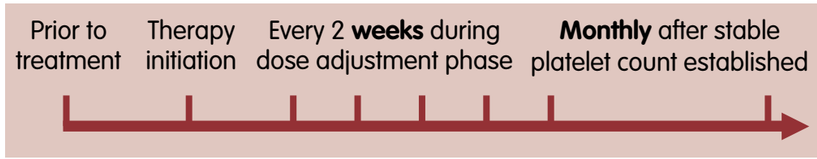
Clinical trials have shown that eltrombopag can cause changes in hepatobiliary function.[1] Most patients receiving eltrombopag with antiviral therapy will experience indirect hyperbilirubinemia, and patients should be educated on the potential for abnormal liver function, the importance of laboratory monitoring, and the signs and symptoms of hepatotoxicity (e.g. jaundice).[1,4]

Incidence

The frequency of hyperbilirubinemia and jaundice was classified as "common" in the eltrombopag clinical development programme, occurring in at least 1% but less than 10% of patients.[1] In Phase III trials, total bilirubin ≥1.5 × upper limit of normal (ULN) was reported in 76% of eltrombopag treated patients, and 50% of placebo treated patients.[1]

Additional monitoring

Patients receiving eltrombopag require regular monitoring of liver function:[1]



If abnormal levels are detected, repeat the tests within **3 to 5 days**. If the abnormalities are confirmed, monitor serum liver tests until the abnormalities resolve, stabilise or return to baseline levels.

Patients should discontinue eltrombopag if ALT reaches at least 3x ULN and elevated levels:

- persist for at least 4 weeks;
- are accompanied by increased direct bilirubin;
- progressively increase; or
- are in conjunction with clinical evidence of liver damage or hepatic decompensation

OCULAR CHANGES

In clinical studies in patients with HCV receiving interferon-based therapy, progression of pre-existing baseline cataracts or incident cataracts was reported in 8% of patients receiving eltrombopag and 5% of patients receiving placebo.[1] Retinal haemorrhages, mostly Grade 1 or 2, have been reported in patients receiving eltrombopag and pIFN-based therapy.[1] All patients receiving eltrombopag should have routine ophthalmologic monitoring.

BLEEDING FOLLOWING DISCONTINUATION

In Phase III trials, gastrointestinal bleeding was reported following discontinuation of pIFN, ribavirin, and eltrombopag.[1] Some of these cases were serious and fatal.[1] After therapy is discontinued, patients should be monitored for any signs or symptoms of gastrointestinal bleeding. Platelet counts should be monitored weekly for four weeks following discontinuation of eltrombopag.

BONE MARROW RETICULIN FORMATION AND RISK FOR BONE MARROW FIBROSIS

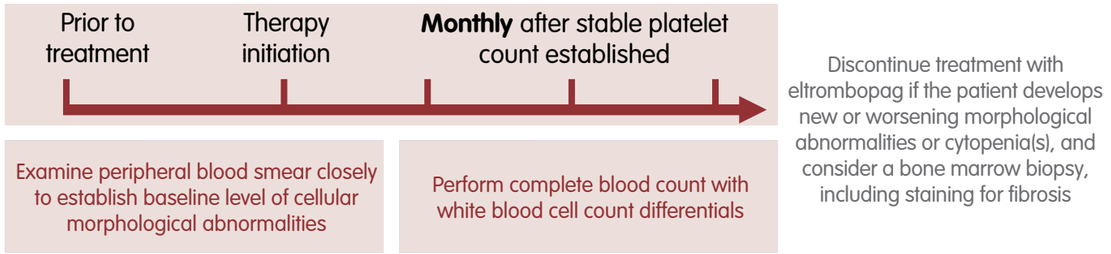
Eltrombopag may increase the risk for development or progression of reticulin fibres within the bone marrow.[1]

Incidence

In studies of patients with HCV taking eltrombopag, there was no evidence of clinically relevant bone marrow abnormalities or clinical findings that would indicate bone marrow dysfunction.[1]

Additional monitoring

Patients receiving eltrombopag require regular blood count monitoring:[1]



If immature or dysplastic cells are observed, peripheral blood smears should be examined.[1]

FATAL ADVERSE EVENTS

Thrombocytopenic patients with chronic HCV who receive pIFN-based therapy in combination with eltrombopag may be at greater risk of fatal adverse events.[1]

Patients with the poorest prognosis (i.e. albumin ≤35 g/L, or MELD score ≥10) should be educated on the risk of fatal adverse events, in particular hepatic decompensation (hepatic failure, ascites, encephalopathy and bleeding varices), infections, and ischaemic complications.

Who is at risk?

Patients at highest risk are those with the poorest prognosis, such as advanced liver disease (MELD score ≥10 or albumin levels ≤35 g/L).[1]

Treatment

In Phase III trials, the benefits of treatment with eltrombopag were modest in patients with the poorest prognosis (especially those with baseline albumin ≤35 g/L) compared with the group overall.[1] Treatment with eltrombopag in these patients should only be initiated by physicians experienced in managing advanced HCV, and only when the risks of thrombocytopenia or withholding antiviral therapy outweigh the risks of treatment with eltrombopag.[1] Treatment with eltrombopag should be stopped if signs and symptoms suggestive of TEEs events or hepatic decompensation occur (see sections on hepatic decompensation and TEEs).[1]

OTHER CONSIDERATIONS WHEN PRESCRIBING ELTROMBOPAG

Eltrombopag treatment should be initiated and remain under the supervision of a physician experienced in the management of chronic HCV and its complications. Eltrombopag should not be used outside the context of its license unless in a clinical trial setting.[1]

Who is not suitable for Eltrombopag therapy?

Eltrombopag is not suitable for use in HCV patients who the physician has deemed will not benefit from interferon-based therapy. The risk-benefit of using eltrombopag to treat thrombocytopenia outside of the registered indication has not been established.[1] Eltrombopag is not recommended for use in children or adolescents aged less than 18 years.[1] Eltrombopag is also not recommended during pregnancy or in women of childbearing potential who are not using contraception.[1]

It is not known whether the active ingredient or metabolites of eltrombopag are excreted in human milk; a risk to the nursing child cannot be excluded.[1] Physician and patient must decide whether to discontinue breast-feeding or to abstain from eltrombopag therapy, taking into account the benefit of breast-feeding for the child and benefit of eltrombopag therapy for the woman.

Are there any dose adjustments for specific populations?

Plasma eltrombopag exposure has been found to be higher in patients with East Asian ancestry (such as Japanese, Chinese, Taiwanese, Korean, and Thai).[1] but no specific dose adjustments are required for this population.[1] Similarly, no dose adjustments are required for patients with renal impairment or mild hepatic impairment.

What dose adjustments are required?

Use the lowest dose of eltrombopag to achieve and maintain a platelet count necessary to initiate and maintain antiviral therapy.[1] After initiating eltrombopag, or after any subsequent dose increase, 2 weeks should pass before a dose adjustment is considered again.[1] The daily dose of eltrombopag should not exceed 100mg.

* On initiation of antiviral therapy, platelet count may fall, so immediate dose reductions should be avoided
† For patients taking 25 mg once daily, consider reinitiating dosing at 25 mg every other day

DOES ELTROMBOPAG HAVE ANY SIGNIFICANT MEDICINAL OR FOOD INTERACTIONS?

HMG CoA reductase inhibitors

Eltrombopag is an inhibitor of the OATP1B1 transporter, and a breast cancer resistance protein (BCRP) substrate and inhibitor.[1] Care should be taken when co-administering eltrombopag with HMG CoA reductase inhibitors such as rosuvastatin, pravastatin, simvastatin, and lovastatin, as exposure to these may be increased.[1] A reduced dose of statins should be considered when they are co-administered with eltrombopag, and patients should be carefully monitored for statin adverse reactions..[1]

OATP1B1 and BCRP substrates

Co-administration of eltrombopag and OATP1B1 and BCRP substrates (e.g. methotrexate and topotecan) should be undertaken with caution.[1]

CYP1A2 and CYP2C8 inhibitors and inducers

Medicinal products that inhibit or induce multiple metabolic pathways have the potential to increase (e.g. fluvoxamine) or decrease (e.g. rifampicin) eltrombopag exposure.[1]

Lopinavir/ritonavir

Co-administration of eltrombopag with lopinavir or ritonavir may decrease plasma concentration of eltrombopag. Caution must be used when co-administering these products, and platelet counts should be closely monitored when lopinavir/ritonavir therapy is initiated or discontinued.[1]

Polyvalent cations

Polyvalent cations, including iron, calcium, magnesium, aluminium, selenium and zinc significantly reduce absorption of eltrombopag.[1] Antacids and other products containing polyvalent cations, such as dairy products and mineral supplements, must not be administered 4 hours before or after taking eltrombopag.[1] For patients requiring an antacid, you may wish to consider an alternative timing or non-heavy metal containing antacid, such as an H2 blocker or proton pump inhibitor.[5]

Food interactions

Food with moderate or high levels of calcium has been shown to reduce exposure to eltrombopag.[1] In the 4 hours before or after taking eltrombopag, patients should be advised to consume food containing little (<50 mg) or no calcium.[1] It may be useful to assist your patients in developing an individualised plan to administer eltrombopag at a time each day that fits into their daily schedule.

ELTROMBOPAG – SAFETY MANAGEMENT ESSENTIALS

INDICATION: Adult patients with chronic HCV infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy.[1]

DOSING AND DOSE ADJUSTMENT

Initiate eltrombopag at a dose of 25 mg/day.[1] Adjust dose every two weeks up to a maximum of 100 mg/day as needed in order to achieve a platelet count sufficient to initiate antiviral therapy.[1] Use the minimum dose necessary to achieve the target platelet count required to start antiviral therapy. During interferon-based therapy, use the lowest dose of eltrombopag needed to maintain platelet counts at a level to prevent bleeding or reductions in antiviral therapy.[1] Platelet counts >75,000/µL should be avoided.[1] eltrombopag should not be used to normalise platelet counts.[1]

REGULAR MONITORING

Pre-treatment Phase	ELTROMBOPAG initiated	Dose-adjustment Phase	Stable-dose Phase
CBC		CBC (weekly)	CBC and WBC differential (monthly)†
Liver function tests (LFTs)*		LFTs (every two weeks)	LFTs (monthly)
Peripheral blood smears		Peripheral blood smears (weekly)	Peripheral blood smears (monthly)

*Liver: Serum ALT, AST and bilirubin. CBC = complete blood count including platelets.
†Platelet counts should be monitored weekly for 4 weeks following discontinuation of eltrombopag therapy. Platelet counts may remain elevated for several weeks before returning to pre-treatment levels.

INTERACTIONS

Caution should be used when co-administering eltrombopag with:	
HMG CoA reductase inhibitors	Polyvalent cations
OATP1B1 and BCRP substrates	Lopinavir/ritonavir
CYP1A2 and CYP2C8 inhibitors and inducers	

OVERDOSE

Patient overdose → Consider administering metal cation preparation* orally to limit absorption → Closely monitor patient platelet counts → Reinitiate treatment in line with eltrombopag administration guidelines

*Preparations containing metal cations, such as calcium, magnesium or aluminium, chelate with eltrombopag and prevent absorption.

STOPPING

Eltrombopag treatment should be stopped when antiviral therapy is discontinued unless otherwise justified. Excessive platelet count responses or important liver test abnormalities also necessitate discontinuation. If after 2 weeks' therapy with eltrombopag at a dose of 100 mg, platelet counts sufficient to initiate antiviral therapy are not achieved, eltrombopag should be discontinued.[1] Platelet counts return to baseline levels within 2 weeks of discontinuing treatment with eltrombopag in most patients, which may increase the risk of bleeding.

PRESCRIBING INFORMATION

REVOLADE®

Important note: Before prescribing, consult full prescribing information.

Presentation: Film-coated tablets containing eltrombopag olamine equivalent to 25 mg, or 50 mg of eltrombopag free acid.

Indications: Eltrombopag is indicated for the treatment of previously treated patients with chronic idiopathic thrombocytopenic purpura (ITP) to increase platelet counts and reduce or prevent bleeding.

Dosage and administration: Dosing regimens must be individualized based on the patient's platelet counts.Dose regimen: Starting dose between 25 to 50 mg once daily. Monitoring and individual dose adjustment. Maintenance doses with maximum daily doses between 75 to 150 mg depending on patient population and indication.

Special populations: Elderly: No clinically significant differences in safety. Renal impairment: Caution and close monitoring recommended. Hepatic impairment: Caution and close monitoring, starting dose 25 mg once daily.

Contraindications: None.

Warnings and precautions:Hepatic monitoring. Hepatic decompensation Close monitoring for signs and symptoms of hepatic decompensation. Thrombotic/thromboembolic complications: Use with caution in patients with known risk factors for thromboembolism. Monitoring of platelet counts and potentially dose reduction or discontinuation. Increased risk for bleeding after discontinuation of treatment. Monitoring weekly for 4 weeks following discontinuation. Risk for malignancies and progression of malignancies. Patient with cataracts: Routine monitoring.

Women of child-bearing potential, pregnancy: Should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

Breast-feeding: Not recommended unless the expected benefit justifies the potential risk to the infant.

Adverse drug reactions (by highest reporting frequency):

ITP study population: Very common (≥10%): Nausea, diarrhea. Common (1 to 10%): Pharyngitis, urinary tract infection, dry mouth, vomiting, increased aspartate aminotransferase, increased alanine aminotransferase, alopecia, rash, back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia.

ITP pediatric study population (1 to 17 years of age) – Additional ADRs: Very common (≥10%): Nasopharyngitis, upper respiratory tract infection. Common (1 to 10%): Rhinitis, abdominal pain, toothache, cough, oropharyngeal pain, rhinorrhea, pyrexia.

Adverse reaction from spontaneous reports: Rare (0.01 to 0.1%): Thrombotic microangiopathy with acute renal failure.

For a complete list of ADRs, consult full prescribing information.

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Interactions: Rosuvastatin: Dose reduction and monitoring. Other OATP1B1 and BCRP substrates to be used with caution. Cyclosporine (BCRP inhibitor): monitoring weekly for 2 to 3 weeks, eltrombopag dose may need to be increased: Polyvalent cations (chelation): staggered administration. Food interactions. Lopinavir/ritonavir: Caution and monitoring of platelet count weekly for 2 to 3 weeks.

REFERENCES

1. Eltrombopag Summary of Product Characteristics, July 2013.
2. McHutchison JG, et al. *N Engl J Med* 2007;357:2227–2236.
3. Canadian Agency for Drugs and Technologies in Health. Clinical Review Report, Eltrombopag (Revolade), August 2015.
4. Ribavirin Summary of Product Characteristics, May 2009.
5. Williams DD, et al. *Clin Ther* 2009; 31: 764–776.

You can report any problem or adverse events through:

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Or by online: https://ade.sfda.gov.sa

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