Once daily oral therapy

REVOLADE™
(eltrombopag olamine)

Safety Guide for *REVOLADE*™ (eltrombopag) in chronic immune thrombocytopenia (ITP)

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

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INTRODUCTION

ADVERSE EVENTS OF SPECIAL INTEREST:

1. Hepatotoxicity
2. Thrombotic/thromboembolic complications
3. Bone marrow reticulin formation and risk for bone marrow fibrosis
4. Haematological malignancies
5. Post therapy thrombocytopenia

OTHER CONSIDERATIONS

SUMMARY

- Safety management essentials

REVOLADE™ – for the treatment of adults with chronic idiopathic thrombocytopenic purpura (ITP)[1]

REVOLADE (eltrombopag) is indicated for adult chronic immune thrombocytopenia (ITP) in splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). *REVOLADE* may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated.[1] The active ingredient, eltrombopag, is an oral, thrombopoietin (TPO)-receptor agonist that maintains platelet counts at a haemostatic level by stimulating differentiation and proliferation of cells in the megakaryocyte lineage.[1,2] The objective of treatment with *REVOLADE* should not be to normalise platelet counts but to maintain platelet counts above the level for haemorrhagic risk (>50,000/μL).[1]

The safety and tolerability of *REVOLADE* have been evaluated in approximately 500 patients with chronic ITP in the *REVOLADE* clinical development programme.[1–6] At the most recent data cut-off point of the ongoing EXTEND study (February 2012), 253 patients had been treated for up to 6 months, with 217, 176, 59 and 10 patients for up to 1, 2, 4 and 5 years, respectively.[6]

Summary of *REVOLADE* clinical studies in patients with chronic ITP:

Study	Phase	N (n)	Design	Dosing group	Study aim and status
773A[2]	II	117 (88)	6-week randomized, double-blind, placebo-controlled study*	*REVOLADE* 30 mg, 50 mg, 75 mg, and placebo	Dose-ranging efficacy and safety *Completed*
773B[3]	III	114 (76)	6-week randomized, double-blind, placebo-controlled study*	*REVOLADE* 50 mg starting dose, and placebo	Short-term efficacy and safety *Completed*
RAISE[4]	III	197 (135)	6-month randomized, double-blind, placebo-controlled study*	*REVOLADE* 50 mg starting dose and placebo	6-month efficacy and safety *Completed*
REPEAT[5]	II	66 (66)	Open-label, repeat-dose, Phase II study	*REVOLADE* 50 mg starting dose	Repeated intermittent use efficacy and safety (3 x 6-week cycles, 4-week washout between cycles) *Completed*
EXTEND[6,7]	III	302	Open-label, long-term, extension study	*REVOLADE* 50 mg starting dose	Long-term safety and efficacy *Ongoing (enrolment completed)*
Bone marrow study[8,9]	IV	167†	Two-year, open-label, multi-centre study	*REVOLADE* 50 mg starting dose (25 mg in patients of East Asian ancestry)	To evaluate the long-term effect of *REVOLADE* on bone marrow reticulin and/or collagen fibers *Ongoing*
LENS[10]	IV	164	Observational study monitoring ocular safety in subjects previously enrolled in a *REVOLADE* trial and who received either *REVOLADE* or placebo	N/A – observational only	Long-term ocular safety with respect to changes in the lens *Completed*

N = total study population; n = number of patients who received *REVOLADE*.

*The use of standard-of-care (SOC) in addition to *REVOLADE* or placebo was permitted in these studies.

~ 25 mg dose adjustments were permitted in these studies.

†Number of patients enrolled in the study by the 2-year interim analysis

Study ID numbers: TRA100**773A**, TRA100**773B** and **RAISE** [TRA102537], **REPEAT** [TRA108057], and **EXTEND** [TRA105325] and **Bone marrow study** [TRA11294001]

Results showed that *REVOLADE* was generally well tolerated in patients with chronic ITP compared to placebo, with a low rate of mild-to-moderate, transient adverse events.[2–4,6,7] Here we draw attention to some important safety issues that were identified during the clinical development programme and provide guidance on best practice management of these issues should they arise.

1. HEPATOTOXICITY[1]

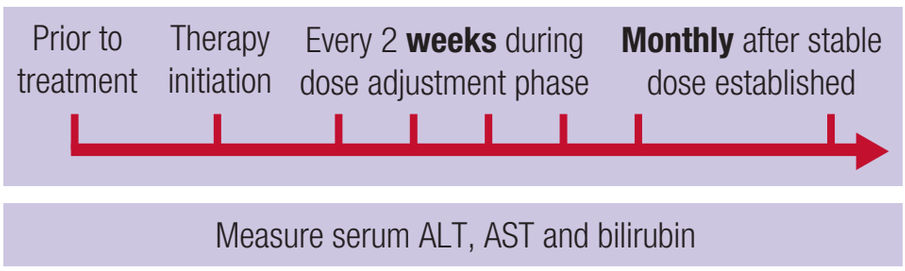
Clinical trials have shown that *REVOLADE* can cause changes in hepatobiliary function indicated by increases in liver function parameters. Patients should be educated about the potential for abnormal liver function and the importance of laboratory monitoring of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin. They should also be reassured that, when they occur, hepatobiliary abnormalities are usually mild (grade 1–2), reversible and without clinical sequelae. *REVOLADE* should not be used in ITP patients with hepatic impairment (Child–Pugh score ≥5) unless the expected benefit outweighs the identified risk of portal venous thrombosis, in which case the starting dose of *REVOLADE* must be 25 mg once daily. After initiating the dose of *REVOLADE* in patients with hepatic impairment, wait 3 weeks before increasing the dose.

Incidence of hepatotoxicity with *REVOLADE*

The frequency of increases in ALT, AST and bilirubin was classified as 'common' with *REVOLADE* in the overall clinical development programme, occurring in at least 1% but less than 10% of patients.[1]

The potential for hepatotoxicity with *REVOLADE* is being assessed in the ongoing long-term EXTEND study, an open-label extension including patients who had completed a previous *REVOLADE* ITP study (TRA100773A/B, RAISE and REPEAT).[7] Analysis of 302 patients with ITP treated with *REVOLADE* for a median of 121 weeks (range, 2 days–285 weeks [5.5 years]), revealed that a total of 36 patients (12%) experienced hepatobiliary laboratory abnormalities (HBLAs).[6] Most HBLAs were mild, reversible, and without associated symptoms of impaired liver function; a total of eight patients (3%) discontinued *REVOLADE* therapy owing to hepatobiliary adverse events.[6]

Patients receiving *REVOLADE* require regular monitoring of serum liver tests[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.

When should *REVOLADE* be discontinued?

Discontinue *REVOLADE* if ALT levels increase to three-times upper limit of normal or greater and are:

Progressive	**OR**	Persistent for ≥4 weeks	**OR**	Accompanied by increased direct bilirubin	**OR**	Accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation

Can *REVOLADE* be administered to patients with hepatic impairment?

In ITP patients with hepatic impairment (Child–Pugh score ≥5), *REVOLADE* should not be used unless the expected benefit outweighs the identified risk of portal venous thrombosis, in which case the starting dose of *REVOLADE* must be 25 mg once daily. After initiating the dose of *REVOLADE* in patients with hepatic impairment, wait 3 weeks before increasing the dose.

2. THROMBOTIC/THROMBOEMBOLIC COMPLICATIONS

Thromboembolic events (TEEs) may occur in patients with ITP[1]; approximately 5% of patients with chronic ITP are reported to have experienced a TEE.[11] Thus, there is a potential concern that thrombotic or thromboembolic complications may occur in these patients as a result of excessive increases in platelet counts.[1] As a consequence, *REVOLADE* should be used with caution in patients with known risk factors for thromboembolism, and these patients should be educated about the potential risks associated with *REVOLADE* treatment.

Incidence of thrombotic/thromboembolic complications with *REVOLADE*[1]

In 3 controlled and 2 uncontrolled clinical studies, among adult chronic ITP patients receiving *REVOLADE* (n=446), 17 subjects experienced a total of 19 TEEs, which included (in descending order of occurrence) deep vein thrombosis (n=6), pulmonary embolism (n=6), acute myocardial infarction (n=2), cerebral infarction (n=2), embolism (n=1).[1] In the ongoing long-term EXTEND study, where patients have been treated with *REVOLADE* for up to 5.5 years, the incidence of thromboembolic events is 2.70 per 100 patient-years (95% CI: 1.62–4.21),[6] with no increased incidence observed with longer duration of therapy.[12] No relationship between thromboembolic events and elevated platelet counts has been observed.[6]

The risk of TEEs has been found to be increased in thrombocytopenic patients (platelet count <50,000/μL) with chronic liver disease (CLD), without concomitant ITP.[1] In a placebo-controlled study (n=288, safety population), following 2 weeks of treatment in preparation for invasive procedures, six of 143 (4%) adult patients with CLD, receiving *REVOLADE* experienced seven TEEs of the portal venous system and two of 145 (1%) subjects in the placebo group experienced three TEEs.[1] Five of the six patients treated with *REVOLADE* experienced the TEE at a platelet count >200,000/μL.[1] *REVOLADE* should not be used in ITP patients with hepatic impairment (Child–Pugh score ≥5) unless the expected benefit outweighs the identified risk of portal venous

thrombosis.[1] If the use of *REVOLADE* is deemed necessary for ITP patients with hepatic impairment, the starting dose of *REVOLADE* must be 25 mg once daily.[1] After initiating the dose of *REVOLADE* in patients with hepatic impairment, wait 3 weeks before increasing the dose.[1]

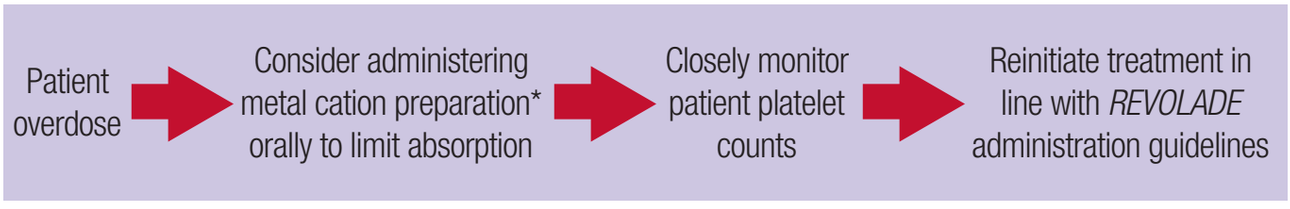
What are the risk factors for thromboembolism?

Risk factors for thromboembolism include, but are not limited to, inherited (e.g. Factor V Leiden) or acquired risk factors (e.g. ATIII deficiency, antiphospholipid syndrome), advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking.[1] The risk of TEEs has been found to be increased in thrombocytopenic patients (platelet count <50,000/μL) with CLD, without concomitant ITP, treated with 75 mg *REVOLADE* once daily for 2 weeks in preparation for invasive procedures. No specific risk factors were identified in those subjects who experienced a TEE with the exception of platelet counts ≥200,000/μL.[1] Analysis of data from the 446 patients with chronic ITP treated with *REVOLADE* across the ITP clinical trial programme, observed no correlation between high platelet counts and the incidence of TEEs.[13] Physicians considering prescribing *REVOLADE* to patients presenting with these risk factors should weigh up the relative risks and benefits of treatment.

How can the risk of thrombotic/thromboembolic complications be minimised?

To minimise the risk for thrombotic/thromboembolic complications, the platelet count should be monitored weekly during treatment until a stable count has been achieved.[1] Thereafter they should be monitored monthly.[1] The *REVOLADE* dose should be reduced if the platelet count rises above 150,000/μL, or discontinued if it rises above 250,000/μL.[1] The risk–benefit balance should be considered in patients at risk of TEEs of any aetiology.[1]

Overdose with *REVOLADE* may increase platelet counts excessively and increase the risk of thrombotic/thromboembolic complications. In the event of overdose, follow the steps outlined below:[1]



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

3. BONE MARROW RETICULIN FORMATION AND RISK FOR BONE MARROW FIBROSIS

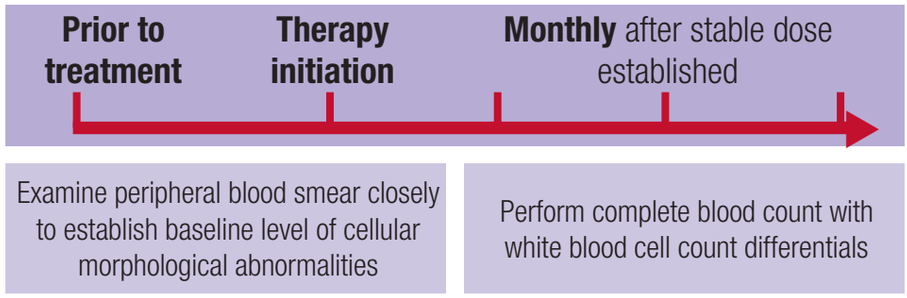
REVOLADE, as with other TPO-receptor agonists, may increase the risk for development or progression of reticulin fibers within the bone marrow.[1] Interpretation of the impact of the TPO-receptor agonists on reticulin changes is complicated by the fact that patients with ITP are at an increased risk of bone marrow reticulin formation prior to treatment. A retrospective study of bone marrow samples from 40 such ITP patients with ITP identified 67% with grade 1–2 reticulin.[14]

Across the overall clinical ITP programme, no patients receiving *REVOLADE* demonstrated clinically relevant bone marrow abnormalities or signs of bone marrow dysfunction. *REVOLADE* treatment was discontinued in one patient owing to bone marrow reticulin.[1]

From the most recent analysis of bone marrow data from patients treated with *REVOLADE* in the ongoing open-label EXTEND study, there was no clinically relevant increase in bone marrow reticulin deposition in patients treated with *REVOLADE* for up to 4.75 years (n=113).[6]

In an ongoing, Phase IV, 2-year, prospective bone marrow study, bone marrow biopsies are collected at baseline (pre-treatment) and at 1 and 2 years of treatment.[9] At the 2-year interim analysis, there was no increase in bone marrow reticulin in 73% (33/45) of patients, an increase of 1 grade in 16% (7/45) of patients and a 2-grade increase in 2% (1/45) of patients.[9] No patient with an increase to MF-2 at 2 years had adverse events or haematological abnormalities considered to be related to impaired bone marrow function and none withdrew due to bone marrow findings.[9] Analysis from this prospective study indicated that at baseline, approximately 11% of adult chronic ITP patients may have MF-1 reticulin in their bone marrow.[9] The effects of *REVOLADE*, as with other TPO-receptor agonists, on bone marrow reticulin formation are continuing to be monitored.

Patients receiving *REVOLADE* require regular blood count monitoring[1]



If the patient develops new or worsening morphological abnormalities or cytopenia(s), discontinue treatment and consider a bone marrow biopsy, including staining for fibrosis.

4. HAEMATOLOGICAL MALIGNANCIES

TPO-receptor agonists are growth factors that lead to thrombopoietic progenitor cell expansion, differentiation and platelet production. The TPO receptor is predominantly expressed on the surface of cells of the myeloid lineage and there is a concern that TPO-receptor agonists may stimulate the progression of existing haematopoietic malignancies, such as myelodysplastic syndrome (MDS).[1] Studies have shown that patients with autoimmune disorders, including ITP, have a significantly increased risk of developing haematological malignancies irrespective of treatment.[15]

- In clinical studies with a TPO-receptor agonist in patients with MDS, cases of transient increases in blast cell counts were observed and cases of MDS disease progression to acute myeloid leukaemia (AML) were reported. Patients should, therefore, be informed that a concern exists that TPO-receptor agonists may stimulate the progression of existing haematopoietic malignancies, such as MDS
- The diagnosis of ITP in adults and elderly patients should be confirmed by excluding other clinical entities with thrombocytopenia. In all patients and especially the elderly, the diagnosis of ITP should be confirmed by exclusion of other clinical conditions which may present with thrombocytopenia. A diagnosis of MDS must be expressly excluded.
  - Physicians should consider performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age and in those with systemic symptoms or abnormal signs such as increased peripheral blast cells.
- *REVOLADE* should not be used outside the context of its licence unless in a clinical trial setting.

In a randomized, double-blind, placebo-controlled, Phase III study (RAISE) of *REVOLADE* in 197 patients with ITP, malignancies were reported for one patient in the *REVOLADE* group (1%) and one patient in the placebo group (2%).[4] Two patients were diagnosed with lymphoma (one diffuse large B-cell and one non-Hodgkin) during the 622 patient-years of *REVOLADE* exposure during an open-label extension study (EXTEND) (as of February 2011 cut-off date).[16]

5. POST THERAPY THROMBOCYTOPENIA[1]

Platelet counts return to baseline levels within 2 weeks of discontinuing treatment with *REVOLADE* in most patients, which may increase the risk of bleeding. In three controlled clinical studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 8% and 8% of the *REVOLADE* and placebo groups, respectively.

This risk of post therapy thrombocytopenia is increased if *REVOLADE* treatment is discontinued in the presence of anticoagulants or anti-platelet agents. It is recommended that, if treatment with *REVOLADE* is discontinued, ITP treatment be restarted according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or anti-platelet therapy, reversal of anticoagulation, or platelet support.

Patients should be informed of the risk of bleeding and platelet count should be monitored weekly for 4 weeks following discontinuation of *REVOLADE*.

OTHER CONSIDERATIONS

Are there any dose adjustment recommendations for specific populations?[1]

Plasma *REVOLADE* exposure was shown to be 87% higher in a pharmacokinetic study of ITP patients with East Asian ancestry (such as Japanese, Chinese, Taiwanese and Korean) compared with non-East Asian (predominantly Caucasian) patients. Therefore, a lower starting dose of 25 mg once daily should be considered for these patients. Patients of East Asian ancestry should be monitored closely, and the *REVOLADE* dose increased by 25 mg to a maximum of 75 mg if platelet counts remain below 50,000/μL following at least 2 weeks of therapy.

REVOLADE should not be used in ITP patients with hepatic impairment (Child–Pugh score ≥5) unless the expected benefit outweighs the identified risk of portal venous thrombosis, in which case the starting dose of *REVOLADE* must be 25 mg once daily. After initiating the dose of *REVOLADE* in patients with hepatic impairment, wait 3 weeks before increasing the dose.

Who is not suitable for *REVOLADE* therapy?[1]

REVOLADE is not recommended for use in children or adolescents aged less than 18 years. *REVOLADE* is also not recommended during pregnancy and in women of childbearing potential not using contraception. It is not known whether the active ingredient or metabolites of *REVOLADE* are excreted in human milk, although a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to abstain from *REVOLADE* therapy, taking into account the benefit of breast-feeding for the child and the benefit of *REVOLADE* therapy for the woman.

The diagnosis of ITP in adults and elderly patients should be confirmed by excluding other clinical entities with thrombocytopenia. Physicians should consider performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age and in those with systemic symptoms or abnormal signs such as increased peripheral blast cells.

REVOLADE should not be used for the treatment of conditions outside of the indicated patient population, including patients with MDS.

Is *REVOLADE* associated with any significant food or medicinal interactions?

Polyvalent cation-containing antacids, dairy products and other products containing polyvalent cations, such as mineral supplements, **must not be administered 4 hours before or after** taking *REVOLADE*. Polyvalent cations, including iron, calcium, magnesium, aluminium, selenium and zinc chelate with *REVOLADE* and significantly reduce absorption of the drug.[1] *REVOLADE* may be taken with food containing little (<50 mg) or preferably no calcium, such as fruit, lean beef or ham and unfortified soya milk.[17] Food with moderate or high levels of calcium has been shown to reduce exposure to *REVOLADE*.[1] For patients who require an antacid, you may be able to consider an alternative timing or non-heavy metal containing antacid, such as an H2 blocker or proton pump inhibitor.[17]

Patients should be informed about these potential food interactions, and it may be useful to assist your patients in developing an individualized plan to administer *REVOLADE* at a time each day that fits into their daily schedule.

When should the dose of *REVOLADE* be reduced or treatment interrupted?[1]

REVOLADE dosing should be adjusted to the minimum dose required to achieve and maintain a platelet count ≥50,000/μL as necessary to reduce the risk for bleeding. The *REVOLADE* dose should be reduced if the platelet count rises above 150,000/μL or discontinued if it rises above 250,000/μL. Additional information on dose adjustment with *REVOLADE* can be found in the 'Safety Management Essentials' on the next page.

Treatment with *REVOLADE* should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after four weeks of *REVOLADE* therapy at 75 mg once daily.

REVOLADE - SAFETY MANAGEMENT ESSENTIALS[1]

INDICATION: Adult chronic ITP in splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). *REVOLADE* may be considered as second-line treatment for adult non-splenectomised patients where surgery is contraindicated.

SAFETY INFORMATION

Hepatotoxicity	Increases in ALT, AST and bilirubin classified as 'common' (1-10 %). Discontinue *REVOLADE* if ALT levels ≥3x ULN and are progressive or persistent for ≥4 weeks or direct bilirubin ↑ or liver injury symptoms.
Thrombotic/ Thromboembolic complications	DVT and pulmonary embolism classified as 'uncommon' (0.1-1 %). Use with caution in patients with known risk factors for thromboembolism. Patients with chronic liver disease may have an increased risk of portal venous thrombosis
Haematological concerns	*REVOLADE* as a TPO-receptor agonist may increase the risk of reticulin fibers within the bone marrow. There is also a concern that TPO-receptor agonists may stimulate the progression of existing haematopoietic malignancies such as MDS.

DOSING

Start with: 50 mg/d for most patients
25 mg/d for East-Asian origin
25 mg/d for patients with hepatic impairment (Child–Pugh score ≥5)*

**REVOLADE* should not be used in ITP patients with hepatic impairment (Child–Pugh score ≥5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. After initiating the dose of *REVOLADE* in patients with hepatic impairment, wait 3 weeks before increasing the dose.

DOSE ADJUSTMENT

Goal: achieve and maintain a platelet count ≥50,000/µL

The lowest effective dosing regimen to maintain platelet counts should be used as clinically indicated.

Platelet count	Dose adjustment or response
<50,000/µL following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 75 mg/day.
≥50,000/µL to ≤150,000/µL	Use lowest dose of *REVOLADE* and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding.
>150,000/µL to ≤250,000/µL	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
>250,000/µL	Stop *REVOLADE*; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤100,000/µL, reinitiate therapy at a daily dose reduced by 25 mg.

REGULAR MONITORING:

Prior treatment Phase	*REVOLADE* initiated	Dose-adjustment Phase	Stable-dose Phase
		CBC (weekly)	CBC (monthly)
Liver Function Tests*		Liver Function Tests (every 2 weeks)	Liver Function Tests (monthly)
Peripheral blood smears		Peripheral blood smears (weekly)	Peripheral blood smears (monthly)

*Liver: Serum ALT, AST and bilirubin. CBC = complete blood count including platelets.

FOOD INTERACTIONS: Polyvalent cation-containing antacids, dairy products (or other calcium containing food products) and other products containing polyvalent cations, such as mineral supplements, must not be administered **4 hours before or after** taking *REVOLADE*.

OVERDOSE: Consider using metal cation preparation to limit absorption.

STOPPING: Platelets return to baseline within 2 weeks (consider bleeding risk); monitor platelet count weekly for 4 weeks after stopping.

THE LATEST, FULL PRESCRIBING INFORMATION FOR THIS PRODUCT IS IN ATTACHMENT.

In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Prescribing Information which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131) or alternatively, on the website of the European Medicines Agency http://www.ema.europa.eu.

REPORTING ADVERSE EVENTS (AEs):

Malta & Gibraltar: If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to: GSK (Malta) Limited, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131)

Malta: alternatively, any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system:

Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

Gibraltar: alternatively, any suspected AEs and medication errors can also be reported via the UK regulatory authority (MHRA): https://yellowcard.mhra.gov.uk/

References:

1 *REVOLADE* Summary of Product Characteristics. July 2012.

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