ANNEX

CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT TO BE IMPLEMENTED BY THE MEMBER STATES

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The Member States must ensure that all conditions with regard to the safe and effective use of the medicinal products described below are implemented:

The MAH shall agree the details of an educational programme with the National Competent Authorities and must implement such programme nationally to ensure that, prior to prescribing, all physicians are provided with a healthcare professional information pack containing the following:

- Educational material
- Summary of Product Characteristics (SmPC) and Package Leaflet and Labelling

Key elements to be included in the educational material

Hepatotoxicity

• Educate patients about the potential for hepatic enzyme elevations, importance of monthly laboratory monitoring of ALT and AST, as well as the signs and symptoms associated with liver injury (e.g. jaundice).
• Measure serum ALT, AST and bilirubin prior to initiation of Revolade, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose.
• Discontinue Revolade if ALT levels increase (≥ 3X the upper limit of normal [ULN]) 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.
• Exercise caution when administering eltrombopag to patients with hepatic disease. Use a lower starting dose of eltrombopag and monitor closely when administering eltrombopag to patients with hepatic impairment..

Thromboembolic events

• Eltrombopag should not be used in patients with hepatic impairment (Child Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. If use of eltrombopag is deemed necessary, the starting dose must be 25mg once daily.
• Educate patients about the potential for thromboembolic events (TEE) in patients with chronic ITP and those known risk factors for thromboembolic events (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome).
• Educate patients about chronic liver disease and the risk of thromboembolic events.
• In patients with chronic liver disease treated with eltrombopag there was an association between TEE and platelet counts ≥ 200,000/µl.
• A dose reduction is recommended for ITP patients with platelet counts between 150,000-250,000/µl.
• Revolade should be interrupted if platelet counts increase to > 250,000/µl. Once the platelet count is < 100,000/µl, reinitiate therapy at a reduced daily dose.

Posology

• Educate patients on the appropriate administration of Revolade (e.g. titration of Revolade, food-drug interaction, dose recommendations for special populations [e.g. east Asians]).
• Awareness to prescribers of the labelled indication and warnings associated with non-indicated populations (e.g. not recommended for use in children, pregnant or lactating females, other off label uses).

Food Interactions

• Educate patients about the potential food-drug interaction (i.e. chelation with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc). Antacids, dairy products and other products containing polyvalent cations, such as mineral supplements, must be administered at least four hours apart from Revolade dosing to avoid significant reduction in Revolade absorption due to chelation.
• Assist patient in developing a plan to administer Revolade at a time each day that fits into the patient's own daily schedule.

Reoccurrence of Thrombocytopenia

• Educate patients about the potential risk of bleeding after treatment has stopped (include incidence in clinical trials and likelihood of reoccurrence of thrombocytopenia after cessation of treatment).
• Following discontinuation of Revolade, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increase the bleeding risk and in some cases may lead to bleeding.
• Monitor platelet count weekly for 4 weeks following discontinuation of Revolade.

Increased Bone Marrow Reticulin Fibres

• Educate patients about the potential for bone marrow reticulin fibre formation.
• Background information on reticulin in the bone marrow (i.e. background rates of reticulin in bone marrow in ITP patients and the observed incidence and potential mechanism of action of reticulin deposition in response to Revolade).
• Prior to initiation of Revolade, examine the peripheral blood smear closely to establish a baseline level of cellular morphologic abnormalities.
• Following identification of a stable dose of Revolade, perform complete blood count (CBC) with white blood cell count (WBC) differential monthly.
• If immature or dysplastic cells are observed, examine peripheral blood smears for new or worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s).
• If the patient develops new or worsening morphological abnormalities or cytopenia(s), discontinue treatment with Revolade and consider a bone marrow biopsy, including staining for fibrosis.

Haematological malignancies

• The diagnosis of ITP in adults and elderly patients should have been confirmed by excluding other clinical entities with thrombocytopenia. Consideration should be given to performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age, those with systemic symptoms or abnormal signs.
• Educate patients about the theoretical risk of haematological malignancies with thrombopoietin receptor agonists.
• Importance of not using Revolade outside the context of its license unless in a clinical trial setting.

Potential for Off-label Use

• The risk-benefit for the treatment of thrombocytopenia in non ITP patient populations has not been established.
• The risk-benefit of Revolade in paediatric ITP has not been established.