ANNEX

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

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 (SPC) and Package Leaflet and Labelling

<u>Key elements to be included in the educational material</u>

- Posology
- Obligations of the health care professional in relation to the prescribing of romiplostim and the need to provide comprehensive advice on risk-benefit to patients.
- The documents will discuss the following identified and potential risks:
    - The incidence in clinical trials and likelihood of reoccurrence of thrombocytopenia after cessation of treatment. Advice on management of patients upon cessation of romiplostim.
    - Background information on reticulin in the bone marrow. Background rates of reticulin in the bone marrow in ITP patients and the observed incidence and potential mechanism of action of reticulin deposition in response to romiplostim. Warning that, whilst no data exists, an outcome of reticulin deposition in response to romiplostim may be bone marrow fibrosis. Advice on when further investigations and a bone marrow biopsy might be appropriate.
    - The incidence in clinical trials of thrombotic/thromboembolic complications. Advice to follow dose adjustment guidelines to avoid platelet counts above the normal range.
    - Romiplostim should not be used in patients with moderate to severe hepatic impairment unless the expected benefit outweighs the identified risk of portal venous thrombosis. If use of romiplostim is deemed necessary, platelet count should be closely monitored to minimise the risk of thromboembolic complications.
    - The potential for thromboembolic events in patients with chronic ITP and those known risk factors for thromboembolic events (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome).
    - The incidence of neutralising antibodies to romiplostim in clinical trials. The implications of romiplostim-neutralising antibodies cross-reacting with endogenous thrombopoietin (TPO). Antibody testing available upon request of physician, contact details for this antibody testing.
    - Romiplostim may induce the progression of existing haematological malignancies and myelodysplastic syndrome (MDS). Therefore, it should not be used in these indications outside the context of a clinical trial. Data from clinical trials in MDS on the incidence of blast cell increases and progression to AML.
    - Reiteration that the risk-benefit for the treatment of thrombocytopenia in non ITP patient populations has not been established. Clarification that risk-benefit for the treatment of paediatric ITP has not been established.
    - The incidence of medication errors in clinical trials. Provision of dosing calculator to simplify the calculation of the correct dose and guide in correct reconstitution and administration.