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 should ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented:

Prior to launch of the product in each Member State, the Marketing Authorisation Holder shall agree the content and format of the educational material with the national competent authority.

The Marketing Authorisation Holder (MAH) should ensure that, at launch and thereafter, all Healthcare Professionals who are expected to use and/or prescribe Caprelsa are provided with an Educational pack.

The educational pack should contain the following:

- Summary of Product Characteristics and Package Leaflet
- Educational material for Healthcare Professionals
- Patient Alert Cards (text as agreed by the CHMP)

The educational material for Healthcare Professionals should contain the following key elements:

- Vandetanib prolongs the QTc interval and can cause Torsades de Pointes and sudden death
- Vandetanib treatment must not be started in patients:
    - Whose ECG QTc interval is greater than 480 msec
    - Who have congenital long QTc syndrome
    - Who have a history of Torsades de Pointes unless all risk factors that contributed to Torsades have been corrected.
- The need for an ECG, and serum levels of potassium, calcium and magnesium and thyroid stimulating hormone (TSH) and the times and situations when it should be performed
- Patients who develop a single value of corrected ECG QTc interval of at least 500 msec should stop taking vandetanib. Dosing can be resumed at a reduced dose after return of the ECG QTc interval to pretreatment status has been confirmed and correction of possible electrolyte imbalance has been made.
- If QTc increases markedly but stays below 500 msec, the advice of a cardiologist should be sought.
- Details of medicinal products where the co-administration of vandetanib is either contraindicated or not recommended.
- That vandetanib may cause Posterior reversible encephalopathy syndrome (PRES) also known as Reversible posterior leukoencephalopathy syndrome (RPLS)
- PRES should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Brain MRI should be performed in any patient presenting with seizures, confusion or altered mental status.

- The need to counsel patients about the risk of prolonged QTc and PRES and inform them of what symptoms and signs to be aware of and the actions to take

- The role and use of the Patient Alert Card