**Annex**

**Conditions or restrictions with regard to the safe and effective use of the 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

The MAH shall agree the details of a controlled drug distribution system and educational material including a patient safety card with each National CompetentAuthority and must implement such programmes nationally to ensure that:

1. All healthcare practitioners who may prescribe eculizumab receive the appropriate educational material.

2. All patients being treated with eculizumab receive a patient safety card

3. Drug distribution will only be possible after written confirmation that the patient has effectively received meningococcal vaccination and/or antibiotic prophylaxis.

4. Vaccination reminders are sent to the prescribers.

The educational material should be agreed with the National Competent Authority and should contain the following:

- Summary of product characteristics
- Physician's guides to prescribing
- Patient's/carer's information brochures
- Patient safety card

The physician's guides to prescribing should be indication specific and contain the following key messages:

- Treatment with eculizumab increases the risk of severe infection and sepsis, especially of Neisseria meningitidis
- All patients must be monitored for signs of meningitidis
- The need for patients to be vaccinated against Neisseria meningitidis two weeks prior to receiving eculizumab and/or to receive antibiotic prophylaxis
- The requirement to vaccinate children against pneumococcus and haemophilus before eculizumab treatment
- The risk of infusion reactions including anaphylaxis and advice on post-infusion monitoring
- No clinical data on exposed pregnancies is available. Eculizumab should be given to a pregnant woman only if clearly needed. The need for effective contraception in women of childbearing potential during and up to five months after treatment. Breast-feeding should be discontinued during and up to five months after treatment.
- The risk of developing antibodies to eculizumab
- The safety concerns in children
- Risk of serious haemolysis following eculizumab discontinuation and postponement of administration, its criteria, the required post-treatment monitoring and its proposed management (PNH only)
- Risk of severe thrombotic microangiopathic complications following eculizumab discontinuation and postponement of administration, its signs, symptoms, monitoring and management (aHUS only)
- The need to explain to and ensure understanding of by patients/carers:
    - the risks of treatment with eculizumab

    - the signs and symptoms of sepsis/severe infection and what action to take
    - the patient's/carer's guides and their contents
    - the need to carry the patient safety card and to tell any healthcare practitioner that he/she is receiving treatment with eculizumab
    - the requirement for pre-treatment vaccinations/antibiotic prophylaxis
    - the enrolment in the registries
- Details of the PNH and aHUS registries and how to enter patients

The patient's/carer's guides should be indication specific and contain the following key messages:

- Treatment with eculizumab increases the risk of severe infection, especially Neisseria meningitidis
- Signs and symptoms of severe infection and the need to obtain urgent medical care
- The patient safety card and the need to carry it on their person and tell any treating healthcare professional that they are being treated with eculizumab
- The importance of meningococcal vaccination prior to treatment and/or to receive antibiotic prophylaxis
- The need for children to be vaccinated against pneumococcus and haemophilus before eculizumab treatment
- The risk of infusion reactions with eculizumab, including anaphylaxis, and the need for clinical monitoring post-infusion
- That eculizumab may be teratogenic and the need for effective contraception in women of childbearing potential during and up to five months after treatment, and that breast-feeding should be discontinued during and up to five months after treatment.
- Risk of severe thrombotic microangiopathic complications (in aHUS) following discontinuation/postponement of eculizumab administrations, their signs and symptoms and the recommendation to consult the prescriber before discontinuing/postponing eculizumab administrations
- Risk of severe haemolysis (in PNH) following discontinuation/postponement of eculizumab administrations, their signs and symptoms and the recommendation to consult the prescriber before discontinuing/postponing eculizumab administrations
- Enrolment in the PNH and aHUS registries
- The safety concerns in children

The patient safety card should contain:

- Signs and symptoms of infection and sepsis
- Warning to seek immediate medical care if above are present
- Statement that the patient is receiving eculizumab
- Contact details where a health care practitioner can receive further information

The MAH shall send annually to prescribers and pharmacists who prescribe/dispense eculizumab, a reminder about the need for (re)-vaccination against Neisseria meningitidis for patients on eculizumab.