ANNEX

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

- **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 shall ensure that in their Member State:

The MAH must ensure that, at launch, all physicians who are expected to prescribe Exjade are provided with a physician information pack containing the following:

Product information
Physician information about Exjade (brochure and pocket card)
Patient information pack

The physician information about Exjade should contain the following key elements:

- The need to monitor serum ferritin monthly

- That Exjade causes rises in serum creatinine in some patients
  - The need to monitor serum creatinine
    - On two occasions prior to initiation of treatment
    - Every week during the first month of initiation of treatment or after modification of therapy
    - Monthly thereafter
  - The need to reduce by 10 mg/kg the dose if serum creatinine rises:
    - Adults: >33% above baseline and creatinine clearance <LLN (90 ml/min)
    - Paediatrics: either > ULN or creatinine clearance falls to <LLN
  - The need to interrupt treatment if serum creatinine rises:
    - Adults and paediatrics: >33% above baseline or creatinine clearance <LLN (90 ml/min)
  - The need to consider renal biopsy:
    - When serum creatinine is elevated and if another abnormality has been detected (eg. proteinuria, signs of Fanconi's Syndrome).

- The importance of measuring creatinine clearance
- Brief overview of methods of measuring creatinine clearance
- That rises in serum transaminases occur in patients treated with Exjade
  - The need for liver function tests prior to prescription, then at monthly intervals or more often if clinically indicated
  - Not to prescribe to patients with pre-existing severe hepatic disease
  - The need to interrupt treatment if persistent or progressive increase in liver enzymes were noted.
- The need for annual auditory and ophthalmic testing
- The need for a guidance table highlighting pre-treatment measurements of serum creatinine, creatinine clearance, proteinuria, hepatic enzymes, ferritin, such as:

Before initiating treatment,	
Serum creatinine at Day - X	Value 1
Serum creatinine at Day - Y	Value 2

X and Y are the days (to be determined) when pre-treatment measurements should be performed.

- The educational programme should prompt doctors to report serious ADRs and certain selected ADRs as below:
  - All serious ADRs
  - Persistent and progressive increase in hepatic enzymes
  - Increase in serum creatinine levels (>33% above baseline) or decrease of creatinine clearance (<90 ml/min).

- Significant changes found in auditory or ophthalmological testing
- Gallstones
- Unexpected ADRs according to the SPC.

The Patient information pack should include the following information:

- Patient information leaflet
- Information on the need for regular monitoring, and when it should be carried out, of serum creatinine, creatinine clearance, proteinuria, hepatic enzymes, ferritin
- Information that renal biopsy may be considered if significant renal abnormalities occur.
- Patient booklet where the physician can record the results of the above along with the dose of Exjade
- Reminder card for dates of tests