Annex related to the Art. 127a

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Conditions or restriction with regard to the safe and effective use of the medicinal product to be implemented by the Member States

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

1. The Member States shall agree the details of a controlled distribution system with the MAH according to national regulations and healthcare systems and must implement such programme nationally to ensure that:
    - Prior to launch, all doctors and pharmacists who intend to prescribe or dispense Thalidomide Celgene receive a Dear Healthcare Professional letter as described below.
    - Prior to prescribing all healthcare professionals who intend to prescribe (and in agreement with the National Competent Authority, dispense) Thalidomide Celgene are provided with an Educational Healthcare Professional's Kit containing the following:
        - Healthcare professional booklet
        - Patient booklets
        - Patient cards
        - Summary of Product Characteristics, Package Leaflet and Labelling

2. The Member States shall put into place measures to ensure that:
    - The maximum treatment duration for one prescription shall be
        - 4 weeks for women with childbearing potential
        - 12 weeks for men and women without childbearing potential
    - Prescriptions can only be dispensed within 7 days of the date of the prescription

3. The Member States shall ensure that the MAH implements a pregnancy prevention programme (PPP) within their territory. Details of how the PPP will be implemented should be agreed with the Marketing Authorisation Holder and put in place prior to the marketing of the product.

4. The Member States should agree the local implementation of the patient card system

5. The Member States should ensure that the MAH provides the educational materials to the national patients' organisations for review or if such an organisation does not exist or can not be involved, to a relevant patients group. Patients involved should be preferably naïve to the history of thalidomide. Results of the user testing will have to be provided to the national competent authority and final materials validated at a national level.

6. The Member State should agree with the Marketing Authorisation Holder prior to the launch of the product:
    - The most appropriate strategies to monitor the off label use within national territory
    - The collection of detailed data to understand demographics of target population, indication and number of women of childbearing potential in order to monitor closely the off-label use within national territory
    - The set-up of national measures to assess the effectiveness of and compliance with the PPP.

7. The Member States shall ensure that the following key elements are included in the appropriate material:

Dear Healthcare Professional letter

The Dear Healthcare Professional letter will consist of two parts:

- Core text as agreed by the CHMP
- National specific requirements agreed with the National Competent Authority regarding:
    - Distribution of the product
    - Procedures to ensure that all appropriate measures have been performed prior to thalidomide being dispensed

Educational healthcare professional's kit

The Educational healthcare professional's kit shall contain the following elements:

- Healthcare professional booklet
    - History of thalidomide, background on Thalidomide Celgene and its licensed indication
    - Posology
    - Maximum duration of treatment prescribed
        - 4 weeks for women with childbearing potential
        - 12 weeks for men and women without childbearing potential
    - Teratogenicity and the need to avoid foetal exposure
    - Obligations of healthcare professionals who intend to prescribe or dispense Thalidomide Celgene including
        - The need to provide comprehensive advice and counselling to patients
        - That patients should be capable of complying with the requirements for the safe use of thalidomide
        - Need to provide patients with the appropriate patient educational material
        - Report any pregnancy or adverse events to Celgene and the local health authority using the forms provided in the "Educational Healthcare Professional's Kit" (if applicable to a Member State)

    - Safety Advice relevant to all patients
        - Description and management of ischaemic heart disease (including myocardial infarction)
        - Disposal of unwanted medicine
        - Not to donate blood during treatment (including dose interruptions) and for at least 7 days following discontinuation of thalidomide

    - Algorithm for Pregnancy Prevention Plan implementation
        - This shall assist with patient categorisation, and determination of required pregnancy prevention and testing measures.

    - Pregnancy Prevention Programme information
        - Definition of women with childbearing potential (WCBP) and actions the prescriber should take if unsure
        - Information on what is effective contraception
        - Safety advice for WCBP
            - Need to avoid foetal exposure
            - Pregnancy prevention requirement, definition and need for adequate contraceptive methods
            - That if she needs to change or stop using her method of contraception she should inform:
              - the physician prescribing her contraception that she is on thalidomide
              - the physician prescribing thalidomide that she has stopped or changed her method of contraception

- Pregnancy testing requirements
    - Advice on suitable tests
    - Frequency (before commencing, monthly during treatment and after finishing treatment)
- Need to stop thalidomide immediately upon suspicion of pregnancy
- Need to tell treating doctor immediately upon suspicion of pregnancy

▪ <u>Safety advice for men</u>

- The need to avoid foetal exposure
- That thalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a women with childbearing potential not using effective contraception
- That if his partner becomes pregnant he should inform his treating doctor immediately and always use a condom during intercourse
- That he should not donate semen during therapy (including during dose interruptions) and for at least 7 days following discontinuation of thalidomide

o Pregnancy reporting requirements

▪ Instruction to stop thalidomide immediately upon suspicion of pregnancy, if female patient
▪ Need to refer patient to physician specialised or experienced in dealing with teratology for advice and evaluation
▪ Complete pregnancy reporting form as provided in the "Educational Healthcare Professional's Kit"
▪ Local contact details for reporting of any suspected pregnancy

- Pregnancy initial and outcome reporting forms
- Post-marketing and compliance assessment (as applicable to a Member State)
- Adverse reaction reporting forms

- Treatment initiation forms and/or equivalent tool
    - There should be 3 types of treatment initiation forms: and/or equivalent tool
        - Women of childbearing potential
        - Women of non-childbearing potential
        - Male patient

    - All treatment initiation forms and/or equivalent tool should contain the following elements:
        - Teratogenicity warning
        - Patients receive appropriate counselling prior to treatment initiation
        - Date of counselling
        - Affirmation of patient understanding regarding the risk of thalidomide and the PPP measures.
        - Patient details, signature and date
        - Prescriber name, signature and date
        - Aim of this document i.e. as stated in the PPP: "The aim of the treatment initiation form is to protect patients and any possible foetuses by ensuring that patients are fully informed of and understand the risk of teratogenicity and other adverse reactions associated with the use of thalidomide. It is not a contract and does not absolve anybody from his/her responsibilities with regard to the safe use of the product and prevention of foetal exposure."

    - Treatment initiation forms and/or equivalent tool for women of childbearing potential should also include:
        - Confirmation that the physician has discussed the following:

- The need to avoid foetal exposure
- That if she is pregnant or plans to be, she must not take thalidomide
- The need for effective contraception, without interruption, at least 4 weeks before starting treatment, throughout the entire duration of treatment, and 4 weeks after the end of treatment
- That if she needs to change or stop using her method of contraception she should inform:
  - the physician prescribing her contraception that she is on thalidomide
  - the physician prescribing thalidomide that she has stopped or changed her method of contraception
- The need for pregnancy tests i.e. before treatment, at least every 4 weeks during treatment and after treatment
- The need to stop thalidomide immediately upon suspicion of pregnancy
- The need to contact their doctor immediately upon suspicion of pregnancy
- That she should not share the treatment with any other person
- That she should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of thalidomide
- That she should return the capsules to the pharmacist at the end of treatment

- Treatment initiation forms and or equivalent tool for women with no childbearing potential should also include:
  - Confirmation that the physician has discussed the following:
    - That she should not share the treatment with any other person
    - That she should not donate blood during therapy (including during dose interruptions) and for at least 7 days following discontinuation of thalidomide
    - That she should return the capsules to the pharmacist at the end of treatment

- Treatment initiation forms and or equivalent tool for male patients should also include:
  - Confirmation that the physician has discussed the following:
    - The need to avoid foetal exposure
    - That thalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a women with childbearing potential not on effective contraception
    - That if his partner becomes pregnant he should inform his treating doctor immediately and always use a condom
    - That he should not donate blood or semen during treatment (including during dose interruptions) and for at least 7 days following discontinuation of thalidomide
    - That he should not share the treatment with any other person
    - That he should return the capsules to the pharmacist at the end of treatment

- Patient cards and/or equivalent tools:
  - verification that appropriate counselling has taken place
  - documentation of childbearing status potential
  - check box (or similar) which physician ticks to confirm that patient is using effective contraception (if female with childbearing potential)

- verification of initial negative pregnancy test prior to start of treatment (if female with childbearing potential)
- pregnancy test dates and results

- Education brochure for patients:
  - The educational brochures for patient should be of 3 types:
    - Brochure for women of childbearing potential
    - Brochure for women patients who are not of childbearing potential
    - Brochure for male patients

  - All educational brochures for patients should contain the following information
    - That thalidomide is teratogenic
    - That thalidomide may cause ischaemic heart disease, (including myocardial infarction)
    - Description of the patient card and its use in the individual Member State
    - Guidance on handling Thalidomide Celgene for patients, caregivers and family members
    - National or other applicable specific arrangements for a prescription for thalidomide to be dispensed
    - That thalidomide must not be given to any other person
    - That the patient should not donate blood during therapy and for at least 7 days (including dose interruptions) following discontinuation of thalidomide
    - That the patient should tell their doctor about any adverse events
    - That any unused capsules should be returned to the pharmacist at the end of the treatment

  - The following information should also be provided in the appropriate educational brochures
    - Women of childbearing potential
      - The need to avoid foetal exposure
      - The need for effective contraception
      - That if she needs to change or stop using her method of contraception she should inform:
        - the physician prescribing her contraception that she is on thalidomide
        - the physician prescribing thalidomide that she has stopped or changed her method of contraception
      - The need for pregnancy tests i.e. before treatment, at least every 4 weeks during treatment and at least 4 weeks after treatment
      - The need to stop thalidomide immediately upon suspicion of pregnancy
      - The need to contact their doctor immediately upon suspicion of pregnancy

    - Male patients
      - The need to avoid foetal exposure
      - That thalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a woman with childbearing potential not on effective contraception
      - That if his partner becomes pregnant he should inform his treating doctor immediately and always use a condom
      - That he should not donate semen during therapy (including during dose interruptions) and for at least 7 days following discontinuation of thalidomide.