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 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:

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 before launch of the medicinal product to ensure that:
    - Prior to prescribing all healthcare professionals who intend to prescribe (and in agreement with the National Competent Authority, dispense) Thalidomide LIPOMED are provided with an Educational Healthcare Professional's Kit containing the following:
        - Educational healthcare professional booklet with patient assessment algorithm and pregnancy testing and contraception requirements
        - Treatment initiation forms and/or equivalent tool for women of childbearing potential, women of non-childbearing potential, and male patients
        - Educational brochures for patients (female and male)
        - Patient cards and/or equivalent tools
        - Summary of product characteristics, package leaflet and labelling
        - Pregnancy reporting materials and information
        - Adverse reaction reporting forms.

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 (key elements of the Educational Healthcare professional's kit):

a) Educational healthcare professional booklet

- History of thalidomide, background on Thalidomide Lipomed and its licensed indication
- Posology
- Maximum duration of treatment prescribed according to the approved indication dosing regimens
    - 4 weeks of treatment for women with childbearing potential

- 12 weeks of treatment for men and for women without childbearing potential
- Teratogenicity and the need to avoid foetal exposure
- Guidance on handling the blisters or coated tablets of Thalidomide Lipomed for healthcare professionals and caregivers
- Obligations of healthcare professionals who intend to prescribe or dispense Thalidomide Lipomed 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 the MAH and the local health authority (if applicable to a Member State) using the provided forms
- Safety advice relevant to all patients
  - Guidance to prevent medication errors (potential confusion with the reference medicinal product)
  - Description and management of ischaemic heart disease (including myocardial infarction)
  - Disposal of unwanted medicinal product
  - Not to donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of thalidomide
- Algorithm for Pregnancy Prevention Programme implementation
  - This shall assist with patient categorisation and determination of required pregnancy prevention and testing measures
- Pregnancy Prevention Programme information
  - Definition of women of childbearing potential and actions the prescriber should take if unsure
  - Information on what is effective contraception
  - Safety advice for women of childbearing potential
    - 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
  - Safety advice for men
    - 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 of 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 treatment (including during dose interruptions) and for at least 7 days following discontinuation of thalidomide
- 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

b) Treatment initiation forms and/or equivalent tool

- There will be 3 types of treatment initiation forms and/or equivalent tool:
  - Women of childbearing potential
  - Women of non-childbearing potential
  - Male patients
- All treatment initiation forms and/or equivalent tool will 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 will 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 at least 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 her 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 any unused product to the pharmacist at the end of treatment
- Treatment initiation forms and/or equivalent tool for women with no childbearing potential will 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 treatment (including during dose interruptions) and for at least 7 days following discontinuation of thalidomide
    - That she should return any unused product to the pharmacist at the end of treatment
- Treatment initiation forms and/or equivalent tool for male patients will 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 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 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 any unused product to the pharmacist at the end of treatment

c) Educational brochures for patients:

- There will be 3 types of educational brochures for patients:
  - Brochure for women of childbearing potential
  - Brochure for women who are not of childbearing potential
  - Brochure for male patients
- All educational brochures for patients will 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 Lipomed 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
  - That the patients should tell their doctor about any adverse events

- That any unused product should be returned to the pharmacist at the end of the treatment
- In addition to the above information contained in all educational brochures, the educational brochures for women of childbearing potential will also include the following information:
  - 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 her doctor immediately upon suspicion of pregnancy
- In addition to the above information contained in all educational brochures, the educational brochures for male patients will also include the following information:
  - 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 treatment (including during dose interruptions) and for at least 7 days following discontinuation of thalidomide

d) Patient cards and/or equivalent tools:

- Verification that appropriate counselling has taken place
- Documentation of childbearing potential status
- Check box (or similar) which physician ticks to confirm that patient is using effective contraception (if woman of childbearing potential)
- Verification of initial negative pregnancy test prior to start of treatment (if woman of childbearing potential)
- Pregnancy test dates and results

e) Summary of product characteristics, package leaflet and labelling

f) Pregnancy initial and outcome reporting forms

g) Adverse reaction reporting forms

h) Post-marketing and compliance assessment (as applicable to a Member State)