

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ceplene 0.5 mg/0.5 ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of 0.5 ml of solution contains 0.5 mg of histamine dihydrochloride.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ceplene maintenance therapy is indicated for adult patients with acute myeloid leukaemia in first remission concomitantly treated with interleukin-2 (IL-2). The efficacy of Ceplene has not been fully demonstrated in patients older than age 60.

4.2 Posology and method of administration

Ceplene maintenance therapy should be administered following completion of consolidation therapy in patients concomitantly treated with IL-2 under the supervision of a physician experienced in the management of acute myeloid leukaemia.

For dosing instructions for Ceplene in combination with IL-2, see posology below.

Interleukin-2 (IL-2)

IL-2 is administered twice daily as a subcutaneous injection 1 to 3 minutes prior to the administration of Ceplene; each dose of IL-2 is 16 400 IU/kg (1 µg/kg).

Interleukin-2 (IL-2) is commercially available as a recombinant IL-2; aldesleukin. The reconstitution, dilution, dispensing and storage directions below are specific to aldesleukin.

Dispensing Instructions for IL-2 (aldesleukin)

IL-2 (aldesleukin) should be aseptically reconstituted, diluted and dispensed in capped polypropylene tuberculin syringes by the pharmacy based on the individual patient's weight (see administration chart for aldesleukin below) at the recommended dose of 16 400 IU/kg (1 µg/kg). Up to two weeks supply of pre-filled capped tuberculin syringes may be provided to patients for home administration, with instructions that the syringes be stored under refrigeration at 2°– 8°C prior to administration.

Studies have shown chemical stability and sterility of diluted aldesleukin (dispensed in capped polypropylene tuberculin syringes) for up to three weeks when prepared in a controlled aseptic environment and stored under refrigeration at 2°– 8°C.

NOTE: Dispensing of aldesleukin must be carried out under controlled aseptic conditions.

Initial Reconstitution: Each vial of aldesleukin (1.3 mg / vial) is reconstituted aseptically with 1.2 mL Water for Injections (see commercially available aldesleukin Summary of Product

Characteristics). Direct the diluent against the side of the vial to avoid excessive foaming. Gently swirl to facilitate complete dissolution of the powder. Do NOT shake the vial during the entire reconstitution process. The resulting solution contains 22×10^6 IU (1,300 μ g) of aldesleukin per 1.2 ml.

Subsequent Dilution to 200 μ g/ml: The entire contents of the reconstituted vial (1.2ml) is then further diluted aseptically with 5.3ml Dextrose 5%w/v Solution for Injection to a total volume of 6.5 ml providing a final concentration of 200 μ g/ml (3.3×10^6 IU/ml) of IL-2 (aldesleukin).

Dispensing of dilute IL-2 (Aldesleukin) for each patient: The diluted IL-2 (aldesleukin) is aseptically drawn up into sterile polypropylene tuberculin syringes and capped for each patient at 1 μ g/kg dose, with a minimum standard dosage volume of 0.25 ml (50 μ g) and a maximum dose of 0.5 ml (100 μ g). Dosing volumes based on patient weight are provided in Table 1 below. This table also provides the volume required if a 20% dose reduction is prescribed.

Table 1: Administration Chart for IL-2 (aldesleukin)

Patient Weight (kg)	Standard Dosage (μ g)	Injection Volume* (ml)	20% Dose Reduction Injection Volume (ml)**
≤ 50	50	0.25	0.20
>50 to ≤ 60	60	0.30	0.25
>60 to ≤ 70	70	0.35	0.30
>70 to ≤ 80	80	0.40	0.30
>80 to ≤ 90	90	0.45	0.35
>90 to ≤ 100	100	0.50	0.40
>100	100	0.50	0.40

*Injection volume rounded up to the nearest 0.05ml

** Injection volumes based on 20% reductions are rounded thus actual dose reductions vary from 15%-25%

Ceplene

0.5 ml solution is sufficient for a single dose (see section 6.6).

Ceplene is administered 1 to 3 minutes after each injection of IL-2. Each 0.5 ml Ceplene dose is injected slowly, over 5-15 minutes.

Treatment cycles

Ceplene and IL-2 are administered for 10 treatment cycles: each cycle consists of a treatment period of 21 days (3 weeks) followed by a three-week or six-week treatment-free period.

For cycles 1-3, each cycle consists of 3 weeks of treatment, followed by a 3-week treatment free period. For cycles 4-10, each cycle consists of 3 weeks of treatment, followed by a 6-week treatment-free period.

The recommended dosing regimen is presented in Tables 2 and 3.

Table 2 : For treatment cycles 1-3 with Ceplene and IL-2

Week number (w)*			Treatment*
Cycle 1	Cycle 2	Cycle 3	
w.1 to w.3 (Days 1-21)	w.7 to w.9 (Days 1-21)	w.13 to w.15 (Days 1-21)	IL-2 16 400 IU/kg followed by 0.5 ml Ceplene. Twice daily.
w.4 to w.6	w.10 to w.12	w.16 to w.18	Treatment-free (3 weeks)

*see dose modification for provisions for the modification to dose and dosage schedule

Table 3: For treatment cycles 4-10 with Ceplene and IL-2, same as for Table 2 above, with the exception of number of cycles and duration of rest periods

Week number (w)*							Treatment*
Cycles							
4	5	6	7	8	9	10	
w.19 to w.21	w.28 to w.30	w.37 to w.39	w.46 to w.48	w.55- to w.57	w.64 to w.66	w.73 to w.75	IL-2 16 400 IU/kg followed by 0.5 ml Ceplene. Twice daily
w.22 to w.27	w.31 to w.36	w.40 to w.45	w.49 to w.54	w.58 to w.63	w.67 to w.72	w.76 to w.81	Treatment-free (6 weeks)

*see dose modification for provisions for the modification to dose and dosage schedule

Dose modification

Patients should be monitored for the expected symptomatic adverse reactions and laboratory changes associated with this treatment. Doses of Ceplene and IL-2 should be modified as necessary based on individual patient tolerance to treatment. It is recommended that dose modifications be addressed early in treatment. The dose reductions can be temporary or permanent.

Should Ceplene related toxicities occur (such as hypotension, headache), the injection time can be increased from 5 minutes to a maximum of duration of 15 minutes.

For patients experiencing grade 1 toxicity events:

No altered dose recommendations with the exception of grade 1 neurologic toxicity and grade 1 generalised toxic dermatitis. For the dose recommendations for these grade 1 toxicity events refer to the relevant sections below:

For patients experiencing grade 1-4 neurologic toxicity

- for grade 1 to 3 toxicity, treatment should be discontinued until grade 0 toxicity event has been achieved. Treatment should then be resumed at a 20% dose reduction for both Ceplene and IL-2.
- for grade 4 toxicity, discontinuation of treatment should be considered.

For patients experiencing grade 1-4 generalised toxic dermatitis

- for grade 1 toxicity, the treatment should be delayed for 48 hours or until all symptoms have been resolved. Treatment should then be resumed using the full dose of Ceplene, but reducing the IL-2 dose by 20%.
- for grade 2 toxicity, the IL-2 dose should be reduced 50% and only increased to full dose if the symptoms do not reappear. Ceplene and IL-2 doses should be separated by 60 minutes, which should be maintained throughout treatment.
- for grade 3 and 4 toxicity, treatment should be discontinued and not resumed until events have been resolved. Treatment should only be resumed after consideration of risk – benefit to the patient.

For patients experiencing grade 2 (including cardiac function, renal, hepatic) toxicity:

- treatment should be discontinued until the event has returned to grade 1
- the time of injection of the dose of Ceplene should be extended to a maximum of 15

minutes.

- for cardiac, hepatic or renal toxicities the dose should be reduced by 20% for both Ceplene and IL-2.

For patients experiencing grade 3 and 4 (including hypotension, arrhythmia) toxicities:

- treatment should be discontinued until the event is resolved. A maximum delay of one treatment cycle can be considered for the resolution of grade 3 and 4 events.

For persistent hypotension, headache, arrhythmia, cardiac, hepatic and renal toxicities:

- the time of injection of the dose of Ceplene should be extended to a maximum of 15 minutes.
- the dose amount of both Ceplene and IL-2 should be reduced by 20%.

Fever

- IL-2 can be discontinued for 24 hours and then restarted at a 20% dose reduction level.

Abnormal WBC counts

- the dose of IL-2 can be reduced by 20% for the remaining duration of the treatment course and if abnormal WBC counts re-occur during the following cycle a permanent IL-2 reduction is recommended.

Localised toxic dermatitis

- treatment should be discontinued until symptoms resolved. Treatment can be resumed by administering Ceplene at the full dose and IL-2 at 50%.

Special populations

Renal impairment:

Patients with renal impairment may be more sensitive to the blood pressure lowering effects of Ceplene. Although the degree of renal impairment has no demonstrable effect on the pharmacokinetic disposition of Ceplene, caution is warranted when Ceplene is administered to patients with severe renal impairment. However, no Ceplene dose reduction is normally required in renally impaired patients.

Hepatic impairment:

Ceplene should be used with caution in patients with moderate to severe hepatic impairment (see section 5.2). Plasma Ceplene levels are higher in patients with moderate and severe liver impairment, and these patient groups tend to experience more tachycardia and lower blood pressure after Ceplene dosing than do patients with normal or mildly affected liver function. Plasma drug levels were not predictive of adverse effects, however, and effects did not correlate closely with drug exposure. Dose reduction of Ceplene is normally not required in hepatically impaired patients, but caution should be used in these patients.

Paediatric Population:

Ceplene is not recommended for use in children below 18 years of age due to a lack of data on safety and efficacy in this age group (see section 5.1 and 5.2).

Method of administration

For subcutaneous use only.

One to 3 minutes after the subcutaneous administration of IL-2 has been completed, Ceplene should be administered by slow subcutaneous injection at a rate not to exceed 0.1 ml (0.1 mg histamine dihydrochloride) per minute. The usual time for administering a 0.5 ml Ceplene dose is 5 minutes. To reduce potential adverse reactions, the administration time may be lengthened to a maximum of 15 minutes, see below. Ceplene can be administered via an *ambulatory infusion* syringe pump or by *controlled* manual subcutaneous injection *by syringe with a timer*.

The first dose of Ceplene and IL-2 on day 1 of the initiation of the first cycle of treatment should be administered in the clinic under direct supervision by a physician. Patient monitoring on day 1 should include vital signs, including pulse, blood pressure and respiratory rate. If the patient experiences a significant change in vital signs, the physician should evaluate the status of the patient and continue to monitor vital signs; these patients should be monitored during subsequent treatments.

Subsequent injections of Ceplene may be self-administered at home by a patient who demonstrates a good understanding of necessary precautions and who has demonstrated adequate injection skills. Injections should be preferably administered in a supervised setting in the presence of an adult family member, friend, or other care provider who is capable of responding appropriately should signs or symptoms of hypotension occur.

The preferred injection areas are the thighs and the abdomen. Ceplene should not be injected into the same anatomic region as IL-2.

The twice daily dosing of IL-2 and Ceplene should be separated by a minimum of 6 hours. Patients should remain at rest for 20 minutes after injection of Ceplene.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Patients with significantly compromised cardiac function, e.g., NYHA Class III/IV.
- Patients receiving systemic steroid therapy, clonidine and H₂ blocking agents.
- Patients who have received an allogenic stem cell transplant.
- During pregnancy.
- During breast feeding.

4.4 Special warnings and special precautions for use

Ceplene should be administered 1 to 3 minutes after IL-2 administration, and not concomitantly.

- Rapid subcutaneous injection or injection into a vascular space may result in *severe* hypotension, tachycardia, or syncope.

Treatment with Ceplene in conjunction with IL-2 should be used with caution in patients with poorly compensated cardiac function. Patients with cardiac disease should be evaluated for ventricular ejection fraction and wall function by echocardiography or nuclear medicine stress test and then treated with caution.

- Patients should be monitored during treatment for possible clinical complications due to hypotension or hypovolaemia. Ceplene should be administered in the clinic under supervision of the physician on day 1 of the initial treatment cycle. Patient monitoring on day 1 should include vital signs, including pulse, blood pressure and respiratory rate.
- Patient monitoring during subsequent treatment days or cycles should be performed as long as the patient continues to experience significant changes in vital signs during administration of Ceplene. If significant hypotension or related symptoms are observed in subsequent treatment cycles, dose reduction should be initiated and if required, administered in hospital until responses to treatment allow for home administration.

- Caution should be used for patients with any of the following: symptomatic peripheral arterial disease, past or present peptic or oesophageal ulcer disease with a history of bleeding, clinically significant renal disease and stroke within the last 12 months. Where appropriate, consideration should be made to providing concomitant treatment with a proton pump inhibitor.
- Patients with clinically significant infection requiring the use of antibiotics, antifungals, or antivirals, or who have completed prior anti-infectious therapy within 14 days of starting treatment should be treated with caution unless the use of antibiotics and antivirals were for prophylaxis purposes.
- Patients with a prior history of autoimmune disease (including systemic lupus, inflammatory bowel disease, psoriasis and rheumatoid arthritis) should be treated with caution.
- Monitoring of laboratory test results is recommended including standard haematological and blood chemistry tests.
- Patients receiving the following medicinal products should be treated with caution (see section 4.5)
 - Beta-blockers or other anti-hypertensive agents.
 - H₁ blocking agents and neuroleptics (anti-psychotics) with H₁ receptor blocking properties.
 - Tricyclic anti-depressants that may have H₁ and H₂ receptor blocking properties.
 - Monoamine oxidase inhibitors and anti-malarial and anti-trypanosomal agents.
 - Neuromuscular blocking agents, narcotic analgesics, and various contrast media.

4.5 Interaction with other medicinal products and other forms of interaction

While posology differs, when Ceplene is used in conjunction with IL-2, physicians should also refer to the SmPC for IL-2 and observe the respective medical product interactions.

H₂ receptor antagonists with imidazole structures similar to histamine, e.g., cimetidine, systemic steroids and clonidine, must not be used during treatment with Ceplene (see section 4.3).

Beta-blockers and other anti-hypertensive agents should be used with caution during treatment with Ceplene. Concurrent administration of medicinal products with cardiotoxicity or blood pressure lowering effects may increase the toxicity of Ceplene.

H₁ receptor blocking antihistamines or neuroleptics (anti-psychotics) with H₁ receptor blocking properties that might decrease efficacy of Ceplene should be avoided.

Tricyclic anti-depressants may have H₁ and H₂ receptor blocking properties and should be avoided.

Monoamine oxidase inhibitors, anti-malarial, and anti-trypanosomal active substances may alter the metabolism of Ceplene and should be avoided (see section 4.4).

It has been noted that neuromuscular blocking agents, narcotic analgesics, and various contrast media can induce the release of endogenous histamine; therefore in patients undergoing diagnostic or surgical procedures, the additive effect of Ceplene treatment should be considered prior to the procedure (see section 4.4).

4.6 Fertility, pregnancy and lactation

For Ceplene, no clinical data on exposed pregnancies are available. Animal studies showed reproductive toxicity but only at maternotoxic doses, and did not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see Section 5.3). Ceplene in conjunction with IL-2 must not be used during pregnancy.

It is unknown whether histamine is excreted in human breast milk. The excretion of histamine in milk has not been studied in animals, but at maternotoxic doses in rats, offspring showed slight toxicity during early lactation (see Section 5.3). Ceplene in conjunction with IL-2 must not be used during breast-feeding.

No clinical data are available on the effects of Ceplene on fertility. Animal studies revealed no adverse effects on fertility apart from a slight reduction in implantations and viable foetuses (see section 5.3). Women of childbearing potential and sexually active men must use effective methods of contraception during treatment with Ceplene and IL-2.

Refer to the IL-2 SmPC for information on pregnancy and lactation with IL-2.

4.7 Effects on ability to drive and use machines

Ceplene has minor or moderate influence on the ability to drive and use machines. Administration of Ceplene can cause hypotension and may result in dizziness, light-headedness and blurred vision. Patients should not drive or operate machines for at least 1 hour after receiving Ceplene.

4.8 Undesirable effects

Acute Myeloid Leukaemia

Adverse reactions were reported to be at least possibly related to IL-2 and Ceplene treatment in almost all patients in studies in acute myeloid leukaemia (AML).

The most common adverse reactions experienced by 30% or more of patients receiving IL-2 and Ceplene (listed in descending order of frequency) were: flushing, headache, fatigue, injection site granuloma, pyrexia and injection site erythema.

The adverse reactions occurring in at least 5% of patients considered at least possibly related to the treatment of low-dose IL-2 with Ceplene in AML studies (n=196 for the IL-2 and Ceplene treatment arm) are listed below by body system organ, class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common ($\geq 1/10$) and common ($\geq 1/100$ to $< 1/10$).

Blood and lymphatic system disorders

Very common: eosinophilia, thrombocytopenia

Metabolism and nutrition disorders

Common: anorexia

Psychiatric disorders

Common: insomnia

Nervous system disorders

Very common: headache, dizziness, dysgeusia

Cardiac disorders

Very common: tachycardia

Common: palpitations

Vascular disorders

Very common: flushing, hypotension

Respiratory, thoracic, and mediastinal disorders

Very common: cough, dyspnoea

Common: nasal congestion

Gastrointestinal disorders

Very common: nausea, dyspepsia, diarrhoea.

Common: vomiting, upper abdominal pain, dry mouth

Skin and subcutaneous tissue disorders

Very common: rash

Common: erythema, increased sweating, night sweats, pruritus

Musculoskeletal and connective tissue disorders

Very common: arthralgia, myalgia

Common: limb pain, back pain

General disorders and administration site conditions

Very common: injection site granuloma, fatigue, pyrexia, injection site erythema, feeling hot, injection site reaction, injection site pruritus, influenza like illness, rigors, injection site inflammation, injection site pain

Common: injection site urticaria, injection site bruising, injection site rash, injection site swelling, weakness, chest pain

Other oncology (advanced tumour) studies

Ceplene and low dose IL-2 have been investigated in other clinical studies at different doses (1.0 mg histamine dihydrochloride twice a day) and with different dose regimens of low-dose IL-2 and interferon-alfa. The following adverse events, not listed above, were reported in at least 5% of patients and as at least possibly related to the study medicine:

Blood and lymphatic system disorders

Common: anaemia

Skin and subcutaneous tissue disorders

Very common: dry skin

Ear and labyrinth disorders

Common: vertigo

Endocrine disorders

Common: acquired hypothyroidism

Metabolism and nutrition disorders

Very common: decreased appetite

Common: dehydration

Psychiatric disorders

Very common: anxiety

Common: depression

Nervous system disorders

Common: paraesthesia

Vascular disorders

Common: hot flushes

Respiratory, thoracic, and mediastinal disorders

Common: wheezing

Gastrointestinal disorders

Common: constipation, abdominal distention, stomatitis

General disorders and administration site conditions

Very common: malaise, oedema peripheral, weight decreased

Common: injection site fibrosis, pain

4.9 Overdose

Administration of Ceplene or IL-2 by rapid infusion or into vascular spaces, at higher doses than the approved ones, may exaggerate the adverse reactions associated with Ceplene.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other cytokines and immunomodulators; ATC code: L03AX14.

Ceplene/IL-2 is an immunotherapy which aims to induce immune-mediated destruction of residual myeloid leukaemic cells and thereby to prevent relapse of leukaemia. The role of Ceplene is to protect lymphocytes, in particular NK cells and T cells, which are responsible for the immune-mediated destruction of residual leukaemic cells. The role of IL-2 is to promote the functions of NK cells and T cells by activating the anti-leukaemic properties of these cells and by expanding these cell populations by inducing cell cycle proliferation. The mechanism by which Ceplene improves the anti-leukaemic function of lymphocytes in AML is not completely established; it is considered to be by inhibition of reactive oxygen species (ROS or “oxygen free radicals”), which are synthesised by monocytes/macrophages and granulocytes. ROS are known to limit the anti-leukaemic effects of lymphocyte activators such as IL-2, by triggering dysfunction and death by apoptosis in NK cells and T cells. Ceplene inhibits NADPH oxidase which initiates the formation and release of ROS from phagocytes. By inhibiting oxidase function and reducing ROS production, Ceplene protects IL-2-activated NK cells and T cells from oxygen free radical-induced inhibition and apoptosis. The concomitant administration of Ceplene and IL-2 therefore aims to optimise the anti-leukaemic functions of NK cells and T cells.

There have been 2 clinical studies to evaluate the use of Ceplene in the maintenance of remission in adult AML patients. Study AML-1 was exploratory, enrolling 39 AML patients in remission to determine the dose and feasibility of Ceplene administered together with IL-2. Results of this pilot study were used to design and implement a multi-national phase 3 trial. The randomised phase 3 trial (0201) compared Ceplene+IL-2 treatment to no treatment in 261 patients in first remission (CR1) and in another 59 patients in subsequent remission after relapse (CR>1). For CR1 patients, the median duration of leukaemia-free survival increased from 291 days (9.7 months) to 450 days (15 months) after Ceplene/IL-2 versus no maintenance treatment (ITT, $p=0.01$, $n=261$). The number of CR1 patients remaining leukaemia-free for 3 years was 40% after Ceplene+IL-2 versus 26% in patients not receiving this treatment ($p=0.01$).

This medicinal product has been authorised under “Exceptional circumstances”. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information which may become available every year and this SPC will be updated as necessary.

5.2 Pharmacokinetic properties

Histamine is rapidly absorbed after subcutaneous injection. Maximum plasma concentration is reached approximately 10 minutes after end of subcutaneous infusion. Histamine concentrations and PK were highly variable across studies, as well as within the normal volunteer and patient groups. Patients showed a higher degree of variability with respect to systemic exposure as compared to healthy subjects.

Histamine is eliminated by metabolism in kidney, liver and other tissues. The main enzymes involved in the metabolism of histamine are HNMT (histamine-N-methyltransferase) and DAO (diamine oxidase). The metabolites are mainly excreted in urine. The mean half-life was 0.75 to 1.5 hours in patients.

There are no significant effects of age or weight on the pharmacokinetic properties of histamine. Clearance of Ceplene is almost twice as high in females resulting in considerably lower systemic exposure than in males.

It is not known whether histamine crosses the placenta.

Renal impairment

The pharmacokinetics of histamine are similar in healthy volunteers with normal renal function compared to volunteers with mild, moderate, or severe renal impairment. In subjects with severe renal impairment, there were decreases in systolic and diastolic blood pressure at plasma histamine concentrations which caused no appreciable decrease in blood pressure in other subjects. Thus, subjects with severe renal impairment may be more sensitive to the blood pressure lowering effects of exogenously administered histamine than subjects with normal renal function or subjects with mild or moderate renal impairment. Although the degree of renal impairment has little effect on the PK disposition of histamine, caution should be used in the administration of histamine to patients with severe renal impairment.

Hepatic impairment

A study was performed to measure the PK of histamine in normal volunteers compared to patients with mild, moderate, and severe hepatic impairment. There were no clinically significant differences in safety parameters or in pharmacodynamics. Plasma histamine concentrations were highly variable and were considerably higher in the groups of patients with moderate or severe hepatic impairment (medians 10 and 5 times the normal volunteers respectively). Patients with all degrees of hepatic impairment may have tachycardia or hypotension for 30-60 minutes after Ceplene+IL-2 administration.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated-dose toxicity, local tolerance and genotoxicity. Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to clinical use. No carcinogenicity studies have been performed on Ceplene.

Histamine dihydrochloride was not teratogenic in rats or rabbits at doses resulting in several hundred-fold greater systemic exposures than the clinical exposure. In female rats dosed before mating to gestation day 7, slightly reduced numbers of implantations and viable foetuses were found, but without any dose-response and within the range of historical control data. In the peri-post natal development study, high doses of histamine dihydrochloride caused maternal toxicity, and the offspring showed toxicity during lactation (fewer live pups at day 21 compared to lactation at day 4) but not after weaning.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies this medicinal product should not be mixed with other medicinal products, diluents or infusion solutions.

6.3 Shelf life

Unopened vials: 3 years

6.4 Special precautions for storage

Ceplene

Do not freeze.

Interleukin-2 (IL-2; aldesleukin)

Diluted IL-2 (aldesleukin) dispensed in capped polypropylene tuberculin syringes is to be stored in the refrigerator at 2– 8°C.

6.5 Nature and contents of container

2 ml type I glass vial, with bromobutyl rubber stopper and flip-off aluminium over seal, containing 0.5 ml of solution (0.70 ml including overfill).

Each carton contains 14 vials.

6.6 Special precaution for disposal and other handling

Ceplene

The vials contain 0.5 ml of solution (0.70 ml including overfill) to facilitate the dose extraction of a single 0.5 ml dose.

Patients are provided with capped polypropylene syringes and instructed to extract 0.5 ml of solution into the syringe.

The solution should be visually inspected for particulate matter and discolouration prior to administration. The solution must be clear and colourless.

Any unused product or waste material should be disposed of in accordance with local requirements.

Interleukin-2 (IL-2; aldesleukin)

Dilute IL-2 dispensed in capped polypropylene tuberculin syringes is to be prepared by the Pharmacy in a controlled aseptic environment and stored in a refrigerator at 2° – 8° C.

When reconstituted and diluted according to the directions in Section 4.2, stability of dilute IL-2 (aldesleukin) in capped polypropylene tuberculin syringes has been demonstrated for up to 21 days when stored at refrigerated temperatures (2° -8°C).

Please see Section 4.2 for IL-2 dispensing instructions.

7. MARKETING AUTHORISATION HOLDER

EpiCept GmbH
Goethestrasse 4
D-80336 München
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/477/001

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

07/10/2008

10. DATE OF REVISION OF THE TEXT

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**
- C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER**

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Catalent UK Packaging Ltd
Lancaster Way, Wingates Industrial Park
Westhoughton, Bolton
Lancashire, BL5 3XX
United Kingdom

B. CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

• CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

• OTHER CONDITIONS

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 4.0 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the annual reassessment of the benefit/risk profile.

Clinical aspects:

Clinical Study to evaluate the Biomarkers and Pharmacologic Endpoints of Ceplene plus low dose Interleukin-2 in approximately 100 Adult Patients stratified by age greater or less than 60 years with Acute Myeloid Leukemia in First Complete Remission (CR), with well characterized Morphologic, Cytogenetic and Molecular profiles (Final Study Results Q4, 2011)

Clinical study to evaluate Minimal Residual Disease (MRD) for the assessment of the anti-leukaemic activity of Ceplene plus low dose Interleukin-2 in approximately 150 Adult Patients stratified by age greater or less than 60 years with Acute Myeloid Leukemia in First Complete Remission. (Final Study Results Q2, 2012)

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

Ceplene 0.5 mg/0.5 ml solution for injection
Histamine dihydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

0.5 ml of solution contains 0.5 mg histamine dihydrochloride.

3. LIST OF EXCIPIENTS

Sodium chloride, water for injections, and sodium hydroxide and/or hydrochloric acid to adjust the pH.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
14 x 2 ml glass vials
Each vial contains one 0.5 ml dose.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use only.
Inject slowly over 5-15 minutes.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

EpiCept GmbH
Goethestrasse 4
D-80336 München
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ceplene

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ceplene 0.5 mg/0.5 ml solution for injection
Histamine dihydrochloride
Subcutaneous use only.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Each vial contains one 0.5 ml dose

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ceplene 0.5 mg/0.5 ml solution for injection Histamine dihydrochloride

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Ceplene is and what it is used for
2. Before you use Ceplene
3. How to use Ceplene
4. Possible side effects
5. How to store Ceplene
6. Further information, instructions for self-injection of Ceplene

1. WHAT CEPLENE IS AND WHAT IT IS USED FOR

What Ceplene is

Ceplene belongs to a group of medicines called immunomodulatory medicines. These medicines help the body's immune system fight diseases like cancer by improving the immune system's natural role in fighting disease. The active substance in Ceplene is histamine dihydrochloride; it is identical to a naturally occurring substance in the body. It is used together with low doses of interleukin-2 (IL-2), another medicine which helps the immune system to fight diseases like cancer.

What Ceplene is used for

Ceplene is used, together with IL-2, to treat a particular type of leukaemia called acute myeloid leukaemia (AML). It is used to maintain the remission (the period during which the disease is less severe or not detectable). As your doctor has discussed with you, acute myeloid leukaemia is a cancer of blood forming cells in the bone marrow. Ceplene with IL-2 will help your immune system attack any remaining cancer cells after a previous cancer treatment.

During your treatment, you will always use **IL-2 AND Ceplene**. Ask your doctor if you have any questions about Ceplene or IL-2.

2. BEFORE YOU USE CEPLENE

Do NOT use Ceplene

- If you are **allergic** (hypersensitive) to histamine or any of the other ingredients of Ceplene.
- If you have severe **heart problems**.
- If you are receiving one of the following medicines:
 - **Steroids** such as prednisone and dexamethasone. They are used to inhibit activity of the immune system (immunosuppressant) and to reduce inflammation.
 - **Clonidine**, a medicine used to reduce high blood pressure.
 - **H₂ blockers** such as cimetidine, ranitidine, famotidine or nizatidine which are used to treat stomach ulcers, indigestion (dyspepsia) or heartburn.
- If you have received a stem cell transplant (a kind of **bone marrow transplant**) from a donor.
- If you are **pregnant**.
- If you are **breast-feeding**.

Take special care with Ceplene

- Ceplene and IL-2 are not to be injected at the same time. IL-2 has to be injected first. Ceplene must be injected **1 to 3 minutes later**.
- Ceplene must be **injected slowly** in the layer of tissue just under the skin (**subcutaneously**), over a period of approximately 5 to 15 minutes. Rapid injection can cause a drop in your blood pressure and make you feel faint or even pass out.
- You will start your treatment with Ceplene in the clinic under supervision of a doctor. You must be monitored to check how you respond to treatment. Your doctor will check your blood pressure, pulse rate and lung function. Your doctor will also carry out some blood tests during treatment.
- If you have had one of the following conditions you will be monitored in the hospital during the next treatment days or the next cycles of treatment:
 - **bleeding ulcers**,
 - **stroke**,
 - **narrowing of the arteries** (systemic peripheral arterial disease),
 - **heart disease** (for severe heart problems see above “Do NOT use Ceplene”),
 - a history of **auto-immune disease** (a disease where the immune system attacks the body’s own cells or tissues, such as systemic lupus, rheumatoid arthritis, inflammatory bowel disease or psoriasis).
- If you are taking any **other medicines** mentioned under “**Taking other medicines**” or if you are to have an **operation** or special **X-ray investigation requiring an injection**, talk to your doctor.
- If you **have an infection** your doctor will closely monitor you. If you **have had an infection** within 14 days of starting this treatment which required you to take medicines to treat infections (antibiotics, antifungals or antivirals), your doctor will closely monitor you.
- If you have **kidney problems**, talk to your doctor before using this medicine. A decrease of blood pressure may occur.
- If you have **liver problems**, talk to your doctor before using this medicine. Your doctor may change your dose.

Children and adolescents

Ceplene use is not recommended in children and adolescents, as there is no information available about using this medicine in this age group.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

If you are taking any of the following medicines, please be sure to **discuss this with your doctor** or pharmacist before using Ceplene. Some of them must not be taken during treatment with Ceplene or may need special precautions:

- **Steroids** such as prednisone and dexamethasone. They are used to inhibit activity of the immune system (immunosuppressant) and to reduce inflammation (see above “Do NOT use Ceplene”).
- **H₂ blockers** such as cimetidine, ranitidine, famotidine or nizatidine which are used to treat stomach ulcers, indigestion (dyspepsia) or heartburn (see above “Do NOT use Ceplene”).
- **Antihistamines** used to treat allergy.
- Certain **anti-psychotics** such as chlorpromazine, flupenthixol, thioridazine, clozapine and risperidone. They are used to treat mental conditions.
- **Tricyclic antidepressant medicines** such as amitriptyline, imipramine, or **monoamine oxidase inhibitors**, such as phenelzine, isocarboxazide, tranylcypromine or moclobemide. They are used to treat depression.
- **Malaria or medicines used to treat infections responsible for sleeping sickness.**
- **Beta-blockers**, such as propranolol, metoprolol, atenolol for angina and heart beat disorders or any treatment of **high blood pressure** (for example thiazide diuretics (bendrofluazide), ACE inhibitors (captopril), calcium antagonists (nifedipine) and alpha-blockers (prazosin).

Also, if you are to have an **operation** or special **X-ray investigation** requiring an injection, first make sure that your doctor knows that you are receiving Ceplene. Certain medicines used for an operation (for example neuromuscular blocking medicines and narcotic pain-killers) or dyes used for certain X-rays may interfere with this medicine.

Pregnancy and breast-feeding

There is no information about the use of Ceplene in pregnant women.

Therefore, the treatment with Ceplene and IL-2 must not be used during pregnancy.

It is not known whether Ceplene appears in breast milk. Therefore Ceplene and IL-2 must not be used during breast-feeding.

For both men and women using this treatment, contraception must be used as it is important not to conceive a child while being treated with Ceplene and IL-2.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Do not drive or use machines within one hour after receiving a Ceplene injection as it may reduce blood pressure causing dizziness, light-headedness and blurred vision which can affect your ability to drive and operate machines.

3. HOW TO USE CEPLENE

Always use Ceplene exactly as your doctor has instructed. You should check with your doctor or pharmacist if you are not sure about this.

This treatment must be prescribed and supervised by a physician with knowledge of acute myeloid leukaemia.

Dosage

Since you will be using both IL-2 and Ceplene in a combined treatment, information about both dosages is provided:

Interleukin-2 (IL-2)

IL-2 is injected twice daily as a subcutaneous injection (in the layer of tissue just under the skin) 1 to 3 minutes before the injection of Ceplene. Each dose is calculated from your body weight. **You should use 16400 IU* per kg bodyweight.** Your doctor will let you know how much it is and how to inject it.

*IU=international units, a measurement specifying the amount of IL-2

Ceplene

The **usual dose** of Ceplene is **0.5 ml** of solution **twice a day** given as a slow subcutaneous injection (in the layer of tissue just under the skin).

Ceplene must be injected **1 to 3 minutes after IL-2**.

The two medicines, IL-2 and Ceplene, are both injected twice a day, with a minimum of 6 hours between injections.

Treatment periods and treatment breaks

The treatment with IL-2 and Ceplene lasts for 81 weeks and is cyclic.

- For the first 18 weeks: you will use IL-2 and Ceplene **daily for 3 weeks**, followed by a **3 week break** (no treatment at all).
- For the following 63 weeks: you will use IL-2 and Ceplene **daily for 3 weeks**, followed by a **6 week break** (no treatment at all).

Injecting Ceplene yourself

Your doctor may decide that it would be more convenient for you to inject IL-2 and Ceplene yourself. Your doctor or nurse will show you how to inject yourself. **Do not try to inject yourself unless a qualified professional has trained you.**

It is recommended that you **always have someone with you when injecting this medicine**, such as an adult family member, friend or other care provider who could help you if you feel light-headed or faint.

For further instructions on how to inject this medicine yourself, please read the section “INSTRUCTIONS FOR SELF-INJECTION OF CEPLENE” at the end of this leaflet.

Your doctor may advise you that it is appropriate to use a syringe pump to regulate the injection of Ceplene. If you are using a syringe pump you must refer to the instructions provided by the pump manufacturer and the training provided by your doctor, nurse and/or pharmacist.

If you have used more Ceplene than you should

You must use this medicine exactly as it has been prescribed for you. If you accidentally inject more than you were told to, contact your doctor or pharmacist immediately.

If you forget a dose of Ceplene

Do not take any additional dose to make up for the forgotten doses. Continue with the treatment as prescribed. If you have missed one of your doses in a day, contact your doctor or pharmacist.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ceplene can cause side effects, although not everybody gets them.

If you experience any side effects during or soon after the injection, tell you doctor.

Side effects observed when Ceplene is used as described in this package leaflet

Very common side effects (occurs in more than 1 in 10 people who use the medicine)

- Increase in the number of a certain type of white blood cells in the blood (eosinophilia) and decrease in the number of blood platelets (thrombocytopenia)
- Headache, dizziness and tiredness
- Altered taste (dysgeusia)
- Rapid heart beat (tachycardia)
- Flushing and low blood pressure (hypotension) leading to light-headedness and fainting
- Cough, difficulty in breathing (dyspnoea)
- Nausea, indigestion (dyspepsia) and diarrhoea
- Rash
- Joint and muscle pain (arthralgia and myalgia)
- Inflamed granulated skin at the injection site, fatigue, fever (pyrexia), injection site redness, feeling hot, itching at the injection site, flu-like symptoms, shivering (rigors), injection site inflammation and pain.

Common side effects (occurs in less than 1 in 10 people but more than 1 in 100 people who use the medicine)

- Loss of appetite
- Difficulty in sleeping (insomnia)
- Feeling your own heart beat (palpitations)
- Nasal congestion
- Vomiting, upper abdominal pain and dry mouth
- Abnormal redness of the skin (erythema), increased sweating, night sweats and itching (pruritus)
- Pain in limbs and back pain
- Hives, bruising, rash and swelling at the injection site, weakness and chest pain

Side effects observed when Ceplene was used in other types of treatment

Very common side effects (occurs in more than 1 in 10 people who use the medicine)

- Dry skin
- Anxiety
- Feeling of general discomfort or unease
- Accumulation of fluid in the body especially in the legs and loss of weight

Common side effects (occurs in less than 1 in 10 people but more than 1 in 100 people who use the medicine)

- Sensation of spinning (vertigo)
- Your body does not make enough thyroxine, a body chemical called a hormone (hypothyroidism)
- Decrease in the number of red blood cells (anaemia)
- Dehydration
- Depression
- Tingling, prickling or numbness of the skin (paraesthesia)
- Hot flushes
- Wheezing
- Constipation, swollen stomach, inflamed mouth
- Pain and formation of extra tissue in the skin around the injection site

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE

Keep out of the reach and sight of children.

Do not freeze.

Medicines must not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Interleukin-2 (IL-2, aldesleukin)

Store pre-filled, capped syringes of diluted IL-2 dispensed by the Pharmacist in the refrigerator (at 2° – 8° C) until use.

Ceplene

Do not use Ceplene after the expiry date which is stated on the carton and vial label . The expiry date refers to the last day of that month.

6. FURTHER INFORMATION

What Ceplene contains

- The active substance is histamine dihydrochloride. One vial contains 0.5 mg histamine dihydrochloride in 0.5 ml solution.
- The other ingredients are water for injections and sodium chloride, and it may also contain sodium hydroxide and/or hydrochloric acid for pH adjustment.

What Ceplene looks like and contents of the pack

Ceplene is a clear, colourless liquid. It is provided in a glass vial with a grey rubber stopper and a blue peel flip off aluminium tamper evident over seal.

Ceplene is available in pack sizes of 14 single-use vials.

Marketing Authorisation Holder

EpiCept GmbH, Goethestrasse 4, D-80336 München, Germany.

Manufacturer

Catalent UK Packaging Ltd, Lancaster Way, Wingates Industrial Park, Westhoughton, Bolton, Lancashire, BL5 3XX, United Kingdom

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien

Meda Pharma S.A./N.V.
Chaussée de la Hulpe 166
Terhulpesteenweg 166
1170 Brussels
Tél/Tel: +32 (0)2 5 04 08 11

Luxembourg/Luxemburg

Meda Pharma S.A./N.V.
Chaussée de la Hulpe 166
Terhulpesteenweg 166
B-1170 Brussels
Belgique / Belgien
Tél/Tel: +32 (0)2 5 04 08 11

България

Екофарм ЕООД
Бул. Черни връх 14; бл.3.
1421 София
Тел.: + 359 2 950 44 10

Magyarország

MEDA Pharma Hungary Kereskedelmi Kft.
1139 Budapest
Váci ut 91
Tel: +36 1 236 3410

Česká republika

Malta

MEDA Pharma s.r.o.
Kodaňská 1441 / 46
100 10 Praha 10
Tel: +420 234 064 201

Danmark

Meda AS
Solvang 8
3450 Allerød
Tlf: +45 44 52 88 88

Deutschland

MEDA Pharma GmbH & Co. KG
Benzstraße 1
61352 Bad Homburg
Tel: +49 (0) 6172 888 01

Eesti

Meda Pharma SIA
Narva mnt. 11D
EE10151 Tallinn
Tel: +372 62 61 025

Ελλάδα

MEDA Pharmaceuticals A.E.
Ευρυτανίας, 3
GR-15231 Χαλάνδρι-Αττική
Τηλ: +30 210 6 77 5690

España

Meda Pharma S.A.U.
Avenida de Castilla, 2
Parque Empresarial San Fernando
Edificio Berlín
28830 San Fernando de Henares (Madrid)
Tel: +34 91 669 93 00

France

MEDA Pharma SAS
25 Boulevard de l'Amiral Bruix
F-75016 Paris
Tél: +33 (0)1 56 64 10 70

Ireland

Meda Health Sales Ireland Ltd.
Office 10
Dunboyne Business Park
Dunboyne
Co Meath
Tel: +353 1 802 66 24

Ísland

Meda AB
Box 906
170 09 Solna
Svíþjóð

Alfred Gera & Sons Ltd.
10 Triq Il Masgar
Qormi
Qrm 3217
Tel: +356 21 446205

Nederland

MEDA Pharma B.V.
Krijgsman 20
1186 DM Amstelveen
Tel: +31 (0)20 751 65 00

Norge

Meda A/S
Askerveien 61
1384 Asker
Tlf: +47 66 75 33 00

Österreich

MEDA Pharma GmbH
Guglgasse 15
1110 Wien
Tel: + 43 (0)1 86 390 0

Polska

Meda Pharmaceuticals Sp.z.o.o.
Al. Jana Pawla II 15
00-828 Warszawa
Tel: +48 22 697 7100

Portugal

MEDA Pharma - Produtos Farmacêuticos, S.A.
Rua do Centro Cultural, 13
1749-066 Lisboa
Tel: +351 21 842 0300

România

SODIMED SRL
B-dul Timișoara, nr. 100G, sector 6
București
Tel.: + 40 (0) 21 408 63 34

Slovenija

Medical Intertrade d.o.o.
Karlovska cesta 1
1000 Ljubljana
Tel: +386 1 2529 113

Slovenská republika

MEDA Pharma spol. s. r.o.
Trnavská cesta 50
821 02 Bratislava
Tel: +421 2 4914 0172

Sími: +46 8 630 1900

Italia

Meda Pharma S.p.A.
Viale Brenta, 18
20139 Milano
Tel: +39 02 57 416 1

Suomi/Finland

Meda Oy
Vaisalantie 4/Vaisalavägen 4
FI-02130 Espoo/Esbo
Puh/Tel: +358 20 720 9550

Κύπρος

MEDA Pharmaceuticals A.E.
Ευρυτανίας, 3
GR-15231 Χαλάνδρι-Αττική
Τηλ: +30 210 6 77 5690
Ελλάδα

Sverige

Meda AB
Box 906
170 09 Solna
Tel: +46 (0)8 630 1900

Latvija

Meda Pharma SIA
Ojāra Vācieša iela 13
LV-1004 Rīga
Tāl: +371 7 805 140

United Kingdom

Meda Pharmaceuticals Ltd.
Skyway House
Parsonage Road
Takeley
Bishop's Stortford
CM22 6PU
Tel.: + 44 845 460 0000

Lietuva

Meda Pharma SIA
Veiverių g. 134
LT-46352 Kaunas
Tel. + 370 37330509

This leaflet was last approved in

This medicine has been authorised “Exceptional circumstances”. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicine. The European Medicines Agency will review any new information on this medicine every year and this package leaflet will be updated as necessary. Detailed information on this medicine is available on the European Medicine Agency website: <http://www.ema.europa.eu> They are also links to other websites about rare diseases and treatments.

INSTRUCTIONS FOR SELF-INJECTION OF CEPLENE

This section contains information on how to give yourself an injection of Ceplene.

For general information about the dosage and how to use Ceplene and IL-2, please see Section 3, “HOW TO USE CEPLENE”.

Read the following instructions carefully. It is important that you do not try to give yourself the injection unless you have received special training from your doctor or nurse. If you are not sure about how to give yourself the injection or you have any questions, please ask your doctor or nurse for help.

If you feel faint or dizzy during or after the injections, tell your doctor before injecting your next dose. Your doctor may want to increase the time you take to complete your injection, or change your dose.

You will have to inject Ceplene and IL-2 twice a day by subcutaneous injection (in the layer of tissue just under the skin), according to the directions provided by your doctor.

Always inject IL-2 first. Ceplene must be injected **1 to 3 minutes later**.

Ceplene must not be mixed with any other products and must not be diluted.

Your doctor will explain to you how to prepare and inject IL-2.

It is recommended that you always have **someone with you when injecting Ceplene**, such as an adult family member, friend, or other care provider to help you if you feel light-headed or faint.

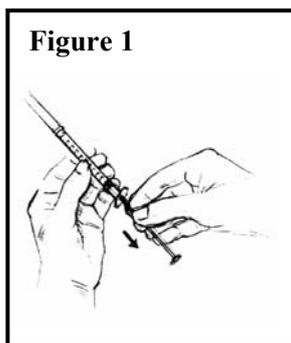
PREPARATION FOR INJECTION OF CEPLENE

To prepare a dose of Ceplene you will need the following:

- 1 vial of Ceplene solution (0.5 ml)
- 1 sterile syringe with needle
- 1 alcohol wipe

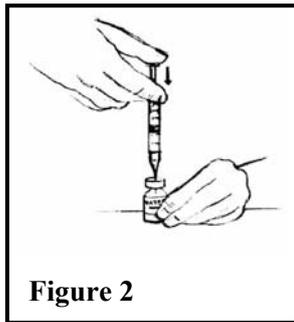
Method

1. Take 1 vial out of the carton. Check the expiry date (EXP) on the vial label.
2. Do not use if the date has passed the last day of the month shown.
3. Wash your hands thoroughly with soap and water.
4. Double check the vial label to make sure you are using the correct medicine. The solution must be clear and colourless. If not, use another vial and inform your doctor or pharmacist.
5. Remove the plastic cap from the vial, exposing the stopper with the inner rubber circle.
6. Use an alcohol wipe to clean the rubber part of the stopper. Do not touch the stopper with your hands.
7. Pick up the sterile syringe. Notice the numbered marks on it. Each mark (0.1, 0.2, 0.3, etc) represents one-tenth of a millilitre (0.1 ml). With the needle cover on, pull back the plunger and draw air into the syringe to the level (number of millilitres) instructed by your doctor. **See Figure 1.**

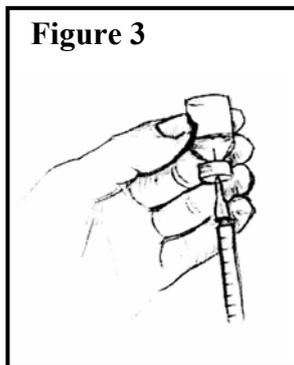


8. Pull the needle cover straight off. With the vial standing on a flat surface, insert the needle straight through the rubber stopper into the vial.

9. Push the plunger of the syringe down to inject air into the vial. **See Figure 2.**



10. Holding both the vial and the syringe, turn the vial upside down. Adjust the syringe so that the tip of the needle is slightly above the rubber stopper but still within the solution. **See Figure 3.**



11. Slowly pull back the plunger to draw the solution into the syringe, filling it to the level (number of millilitres) instructed by your doctor. If bubbles appear in the syringe, push the solution slowly back into the vial and withdraw the solution again.
12. Take the needle out of the vial. Do not lay the syringe down or let the needle touch anything.
13. Replace the cover on the needle. Place the syringe on a clean flat surface.
14. There may be a small amount of solution left in the vial. This is to be returned to the pharmacist for disposal.
15. Double check the syringe to make sure that you have withdrawn the correct amount.
16. Take the syringe and follow the “INSTRUCTIONS FOR INJECTION” information below.

INSTRUCTIONS FOR INJECTION

You will usually inject two doses of 0.5 ml in a day, unless your doctor has prescribed a lower dose for you.

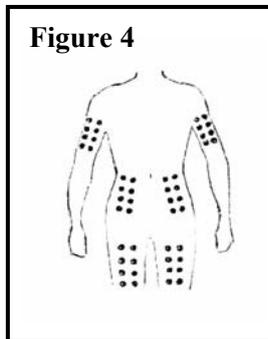
For the injection you will need the following:

- 1 prepared syringe for your IL-2 injection (refer to the IL-2 package leaflet and your doctor’s dose instructions).
- 1 prepared syringe containing Ceplene.
- Alcohol wipe(s).
- A timer, clock or watch with a second hand.
- A puncture-proof container so you can dispose of used syringes safely.

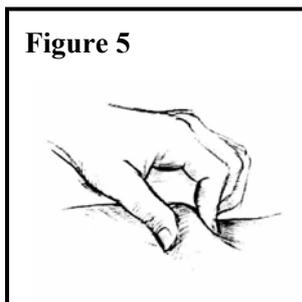
Method

1. Find a comfortable, well-lit place to sit and where you can lie back. Place the pre-prepared syringes containing IL-2, Ceplene and an opened alcohol wipe where you can reach them. For your safety it is very important that you are sitting where you can lean back or lie flat when you perform the injections.
2. Inject IL-2 as you have been instructed.

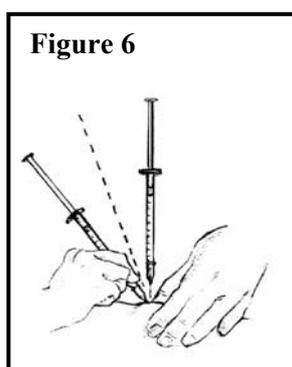
3. Wait 1 to 3 minutes.
4. Decide where you will inject Ceplene. You may choose the inner or outer thighs, arms or stomach. **Ceplene and IL-2 must not be injected into the same region.** For example, if you inject IL-2 in the left arm, you could inject Ceplene into the left or right thigh, the stomach, or the right arm. Always vary the site that you inject. For possible injection sites, see **Figure 4**.



5. Make sure that the area of the skin you selected is exposed. Use an alcohol wipe to clean it. Allow the area to dry for 10 seconds.
6. Pinch up a section of the cleaned skin between your thumb and forefinger, without squeezing it. See **Figure 5**.

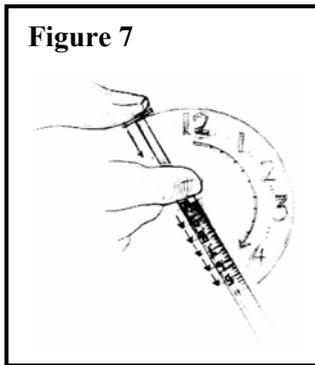


7. Hold needle either vertically (90°) or at a 45° angle to the skin and insert it under the skin as far as it will go in one quick motion. The needle must be inserted under the skin, but not into any blood vessels below the skin. See **Figure 6**.



8. Slightly pull back the plunger. **If blood appears, do not inject Ceplene because the needle has entered a blood vessel.** Withdraw and discard the syringe as instructed. Obtain new supplies and start the procedure over again, even if 3 minutes have passed after injection of IL-2.
9. Notice the numbered marks on each syringe. Each mark (0.1, 0.2, 0.3, etc.) represents one-tenth of a millilitre (0.1 ml).

10. Push down the syringe plunger and inject one-tenth of a millilitre (0.1 ml) every minute, or more slowly if instructed to do so by your doctor. **See Figure 7.**



- 11 **Never inject Ceplene any faster or all at once.**
12 When the syringe is empty, remove the needle from your skin.
13 Apply gentle pressure with the alcohol wipe over the injection site without rubbing it.
14 **Remain seated or lying down for 20 minutes** after injecting Ceplene.
15 Dispose of the syringe in the puncture-proof container as instructed.