**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 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 the 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 (AML) 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.

Posology

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 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°C – 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°C – 8°C.

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

*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 µg/kg dose, with a minimum standard dosage volume of 0.25 mL (50 µg) and a maximum dose of 0.5 mL (100 µg). 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 (µg)** | **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 0.05 mL
** 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 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 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*

The safety and efficacy of Ceplene in children below 18 years of age have not yet been established. No data are available.

Method of administration

Ceplene is 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.

For instructions on reconstitution and dilution of Interleukin-2 (aldesleukin) before administration, see section 6.6.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients with significantly compromised cardiac function, e.g., NYHA Class III/IV.
- Patients receiving systemic steroid therapy, clonidine and $H_2$ 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.
- $H_1$ blocking agents and neuroleptics (anti-psychotics) with $H_1$ receptor blocking properties.
- Tricyclic anti-depressants that may have $H_1$ and $H_2$ 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 Summary of Product Characteristics (SmPC) for IL-2 and observe the respective medical product interactions.

$H_2$ 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.

$H_1$ receptor blocking antihistamines or neuroleptics (anti-psychotics) with $H_1$ receptor blocking properties that might decrease efficacy of Ceplene should be avoided.

Tricyclic anti-depressants may have $H_1$ and $H_2$ 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

<u>Contraception in males and females</u>

Women of childbearing potential and sexually active men must use effective methods of contraception during treatment with Ceplene and IL-2.

Pregnancy

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.

Breast-feeding

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.

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

Fertility

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).

## 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 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 considered at least possibly related to the treatment of low-dose IL-2 with Ceplene in AML studies (n=280 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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000). The ADRs identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under “not known”.

| System Organ Class | very common | common |
|---|---|---|
| Blood and lymphatic system disorders | eosinophilia, thrombocytopenia | leucopenia, neutropenia |
| Infections and infestations | upper respiratory tract infections | pneumonia |

| | | |
|---|---|---|
| Metabolism and nutrition disorders | | anorexia |
| Psychiatric disorders | | insomnia |
| Nervous system disorders | headache, dizziness, dysgeusia | |
| Cardiac disorders | tachycardia | palpitations |
| Vascular disorders | flushing, hypotension | |
| Respiratory, thoracic, and mediastinal disorders | cough, dyspnoea | nasal congestion |
| Gastrointestinal disorders | nausea, dyspepsia, diarrhoea | vomiting, abdominal pain upper, dry mouth, gastritis, abdominal distention |
| Skin and subcutaneous tissue disorders | rash | erythema, hyperhidrosis, night sweats, pruritus |
| Musculoskeletal and connective tissue disorders | arthralgia, myalgia | pain in extremity, back pain |
| General disorders and administration site conditions | injection site granuloma, fatigue, pyrexia, injection site erythema, feeling hot, injection site reaction, injection site pruritus, influenza like illness, chills, injection site inflammation, injection site pain | injection site urticaria, injection site bruising, injection site rash, injection site swelling, asthenia, 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 reactions, not listed above, were at least possibly related to the study medicine:

| System Organ Class | very common (≥ 1/10) | common (≥ 1/100 to < 1/10) |
|---|---|---|
| Blood and lymphatic system disorders | | anaemia |
| Endocrine disorders | | hypothyroidism |
| Metabolism and nutrition disorders | decreased appetite | dehydration |
| Psychiatric disorders | anxiety | depression |
| Nervous system disorders | | paraesthesia |
| Ear and labyrinth disorders | | vertigo |

| | | |
|---|---|---|
| Vascular disorders | | hot flush |
| Respiratory, thoracic, and mediastinal disorders | | wheezing |
| Gastrointestinal disorders | | constipation, abdominal distention, stomatitis |
| Skin and subcutaneous tissue disorders | dry skin | |
| General disorders and administration site conditions | malaise, oedema peripheral | injection site fibrosis, pain |
| Investigations | weight decreased | |

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 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: Immunostimulants, other immunostimulants, ATC code: L03AX14.

Mechanism of action

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.

Pharmacodynamic effects

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 NAPDH 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.

Clinical efficacy and safety

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 SmPC will be updated as necessary.

Paediatric population

Ceplene is indicated for use in adults. There are no data available on pharmacodynamic properties in children below 18 years of age.

## 5.2 Pharmacokinetic properties

Absorption

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.

Distribution

Patients showed a higher degree of variability with respect to systemic exposure as compared to healthy subjects. Overall systemic exposure of Ceplene was greater in patients versus healthy subjects. However, this difference was not statistically significant.
It is not known whether histamine crosses the placenta.

Biotransformation/Elimination

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.

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 (2°C – 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 0.70 mL of solution (including overfill) to facilitate the dose extraction of a single 0.5 mL dose.
Patients should be 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°C – 8°C.

*Initial reconstitution*

Each vial of aldesleukin (1.3 mg / vial) is reconstituted aseptically with 1.2 mL water for injections (see commercially available aldesleukin SmPC). 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 x $10^6$ IU (1,300 µg) of aldesleukin per 1.2 mL.

*Subsequent dilution to 200 µg/mL*

The entire contents of the reconstituted vial (1.2 mL) is then further diluted aseptically with 5.3 mL dextrose 5%w/v solution for injection to a total volume of 6.5 mL providing a final concentration of 200 µg/mL (3.3 x $10^6$ IU/mL) of IL-2 (aldesleukin).

When reconstituted and diluted, 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°C – 8°C).

Please see section 4.2 for IL-2 dispensing instructions.

## 7. MARKETING AUTHORISATION HOLDER

Meda AB
Box 906
SE 170 09 Solna
Sweden

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/477/001

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

Date of first authorisation: 07/10/2008
Date of latest renewal: 26/08/2013

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europe.eu.

**ANNEX II**

**A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

**E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES**

## A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Labiana Pharmaceuticals, S.L.U.
C/ Casanova, 27-31
08757 Corbera de Llobregat (Barcelona)
Spain

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) ) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

## E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

| Description | Due date |
|---|---|

| Description | Due date |
|---|---|
| Evaluate Minimal Residual Disease (MRD) at baseline and follow-up in a clinical study or registry, as appropriate, for the assessment of the anti-leukaemic activity of Ceplene plus low dose Interleukin-2 in a sufficient number of adult patients stratified by age greater or less than 60 years with Acute Myeloid Leukemia in First Complete Remission | Annual reports within the annual re-assessment |

**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)

One vial of 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 vials

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach 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

Meda AB
Box 906
SE 170 09 Solna
Sweden

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/477/001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

Inspect each vial visually for particulate matter and discolouration prior to administration. Use only clear and colourless solution.

## 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

0.5 mL

## 6. OTHER

**B. PACKAGE LEAFLET**

**Package leaflet: Information for the user**

**Ceplene 0.5 mg/0.5 mL solution for injection**
Histamine dihydrochloride

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Ceplene is and what is used for

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.

Ceplene is used, together with IL-2, to treat a particular type of leukaemia called acute myeloid leukaemia (AML) which is a cancer of blood forming cells in the bone marrow. It is used to maintain the remission (the period during which the disease is less severe or not detectable). 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. What you need to know before you use Ceplene

### Do not use Ceplene

- If you are allergic (hypersensitive) to histamine or any of the other ingredients of this medicine (listed in section 6).
- 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.
    - $H_2$ 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.

### Warnings and precautions

Talk to your doctor or pharmacist before using 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 “Other medicines and Ceplene” 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.

**Other medicines and Ceplene**

Tell your doctor or pharmacist if you are taking or have recently taken or might take 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").
- **$H_2$ blockers** such as cimetidine, ranitidine, famotidine or nizatidine. They 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, thoridazine, clozapine and risperidone. They are used to treat mental conditions.
- **Tricyclic antidepressant medicines** such as amitryptiline, imipramine, or **monoamine oxidase inhibitors**, such as phenelzine, isocarboxazide, tranylcypromine or moclobemide. They are used to treat depression.
- **Anti-malarial or medicines used to treat infections responsible for sleeping sickness**.
- **Beta-blockers**, such as propranolol, metoprolol, atenolol. They are used for angina and heart beat disorders.
- Any treatment for **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.

**Ceplene with food, drink and alcohol**

There is no information available about interactions of Ceplene with food, drink and alcohol. Ceplene is injected subcutaneously so that absorption from the gastrointestinal tract is not influenced by food and drink.

**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.

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

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

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. This can affect your ability to drive and operate machines.

## 3. How to take Ceplene

Always use Ceplene exactly as your doctor has instructed. You should check with your doctor, pharmacist or nurse 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. Your doctor will let you know how much it is and how to inject it.

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 or nurse.

**If you use 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 to take 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 stop taking Ceplene**

If you want to stop taking Ceplene you should try to consult your doctor in advance. Please inform your doctor immediately if you have stopped taking Ceplene by your own decision.

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

## 4. Possible side effects

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

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

Hypotension (low blood pressure) may occur very commonly and may lead to light-headedness and fainting. If you notice a severe drop in blood pressure after use of Ceplene please contact your physician immediately or at least prior to administration of further Ceplene injections.

**Very common side effects** (may affect more than 1 in 10 people)

- 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 and dizziness
- Altered taste (dysgeusia)
- Rapid heart beat (tachycardia)
- Flushing
- Cough, difficulty in breathing (dyspnoea)
- Infections of the upper breathing (respiratory) tract
- 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, injection site reaction, itching at the injection site, flu-like symptoms, shivering (chills), injection site inflammation and pain.

**Common side effects** (may affect up to 1 in 10 people)

- Decrease in the number of white blood cells (leucopenia)
- Decrease in the number of a certain type of white blood cells (neutropenia)
- Inflammation of the lung (pneumonia)

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

**Additional side effects observed when Ceplene was used in other types of treatment:**

**Very common side effects** (may affect more than 1 in 10 people)

- Dry skin
- Anxiety
- Feeling of general discomfort or unease
- Accumulation of fluid in the body especially in the legs (oedema)
- Loss of weight

**Common side effects** (may affect up to 1 in 10 people)

- 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)
- Drying-out of the body (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

**Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Ceplene

Keep this medicine out of the sight and reach of children.

**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.

Do not freeze.

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

**Interleukin-2 (IL-2, aldesleukin)**

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

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.

## 6. Content of the pack and other 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 vials.

**Marketing Authorisation Holder**

Meda AB
Box 906
SE 170 09 Solna
Sweden

**Manufacturer**

Labiana Pharmaceuticals, S.L.U.
C/ Casanova, 27-31
08757 Corbera de Llobregat (Barcelona)
Spain

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
Terhulpsesteenweg 166
B-1170 Brussels
Tél/Tel: +32 (0)2 5 04 08 11

**Lietuva**
Meda Pharma SIA
Ukmergės g. 369A
LT-12142 Vilnius
Tel.: +370 52059367

**България**
ТП Меда Фармасойтикалс

**Luxembourg/Luxemburg**
Meda Pharma S.A./N.V.

Ул. Одрин 71-75, ет.2, ап 7
1303 София
Тел.: +359 2 4177977

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

**Danmark**
Meda AS
Solvang 8
DK-3450 Allerød
Tlf: +45 44 52 88 88

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

**Eesti**
Meda Pharma SIA
Parda tn 4
EE-10151 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.L.
Avenida de Castilla, 2
Parque Empresarial San Fernando
Edificio Berlín
E-28830 San Fernando de Henares (Madrid)
Tel: +34 91 669 93 00

**France**
MEDA Pharma
40-44 rue Washington
F-75008 Paris
Tél: +33 (0)1 56 64 10 70

**Hrvatska**
Medical Intertrade d.o.o.
Dr. Franje Tuđmana 3
10431 Sveta Nedelja
Tel: +385 1 3374 010

Chaussée de la Hulpe 166
Terhulpsesteenweg 166
B-1170 Brussels
Belgique / Belgien
Tél/Tel: +32 (0)2 5 04 08 11

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

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

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

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

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

**Polska**
Meda Pharmaceuticals Sp.z.o.o.
ul. Domaniewska 39A
PL-02-672 Warszawa
Tel: +48 22 697 7100

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

**România**
Meda Pharmaceuticals Switzerland GmbH,
Reprezentatei
Calea Floreasca, Primul District 141-143 – RO
Bucureşti

Tel.: +40212309030

**Ireland**
Meda Health Sales Ireland Ltd.
34/35 Block A
Dunboyne Business Park
Dunboyne
IRL-Co Meath
Tel: +353 1 802 66 24

**Ísland**
Meda AB
Box 906
S-170 09 Solna
Svíþjóð
Sími: +46 8 630 1900

**Italia**
Meda Pharma S.p.A.
Via Felice Casati, 20
I-20124 Milano
Tel: + 39 039 73901

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

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

**Slovenija**
MEDA Pharmaceuticals Switzerland GmbH,
Podružnica Ljubljana
Cesta 24. junija 23
SI-1231 Ljubljana
Tel: +386 (0)59 096 951

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

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

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

**United Kingdom**
Meda Pharmaceuticals Ltd.
Skyway House
Parsonage Road
Takeley
Bishop´s Stortford
CM22 6PU – UK
Tel.: + 44 845 460 0000

**This leaflet was last revised in**

This medicine 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 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. There 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 graduated 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.**

**Figure 1**

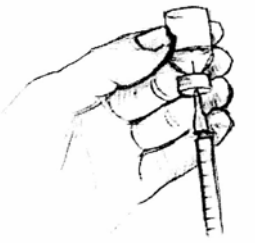
8. Pull the needle cover straight off. With the vial standing on a flat surface, insert the needle straight through the rubber stopper into the vial.

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

**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.**

**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.
    NOTE: The vial of Ceplene contains an overfill to facilitate the dose extraction of a single 0.5 mL dose.
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.

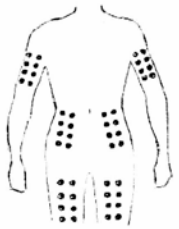
For the injection you will need the following:

- 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.**

**Figure 4**

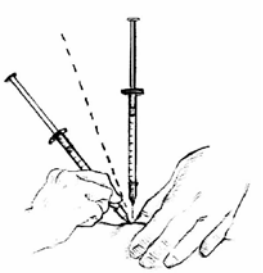


5. Make sure that the area of the skin you select is exposed. Use an alcohol wipe to clean it. Allow the area to dry for 10 seconds.
6. Pinch up a section of the cleaned skin between your thumb and forefinger, without squeezing it. **See Figure 5.**

**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.**

**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.**

**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.