

**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.
  - **H<sub>2</sub> 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”).
- **H<sub>2</sub> 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 your 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 CEPLENE

Keep out of the reach and sight of children.

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.

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. 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

**This leaflet was last approved in {MM/YYYY}**

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 (EMA) 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 (EMA) 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.

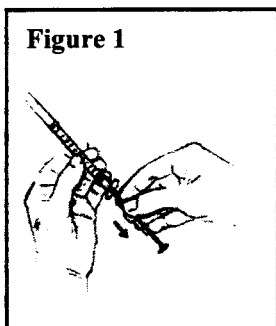
### **PREPARATION FOR INJECTION OF CEPLENE**

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

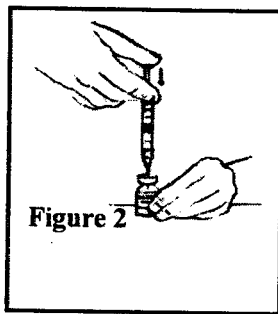
#### **Method**

- 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.**

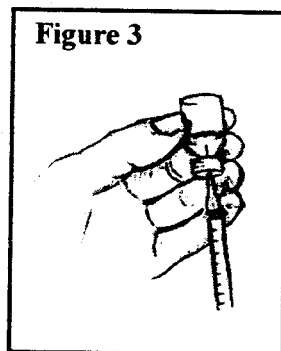


- 8 Pull the needle cover straight off. With the vial standing on a flat surface, insert the needle straight through the rubber stopper into the vial.

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:

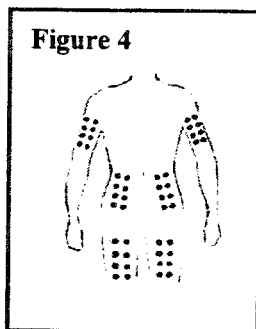
- 1 prepared syringe for your IL-2 injection (refer to the IL-2 package leaflet and your doctor's dose instructions).
- 1 prepared syringe containing Ceplene.
- Alcohol wipe(s).
- A timer, clock or watch with a second hand.
- A puncture-proof container so you can dispose of used syringes safely.

### **Method**

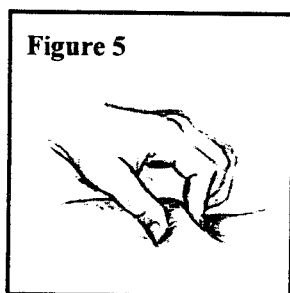
1. Find a comfortable, well-lit place to sit and where you can lie back. Place the pre-prepared syringes containing IL-2, Ceplene and an opened alcohol wipe where you can reach them. For

your safety it is very important that you are sitting where you can lean back or lie flat when you perform the injections.

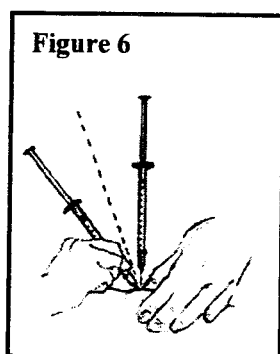
2. Inject IL-2 as you have been instructed.
3. Wait 1 to 3 minutes.
4. Decide where you will inject Ceplene. You may choose the inner or outer thighs, arms or stomach. **Ceplene and IL-2 must not be injected into the same region.** For example, if you inject IL-2 in the left arm, you could inject Ceplene 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**.

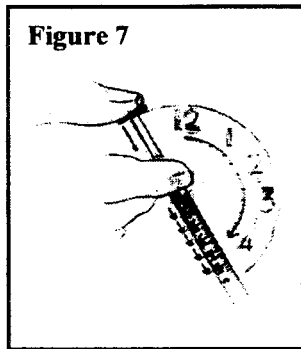


7. Hold needle either vertically (90°) or at a 45° angle to the skin and insert it under the skin as far as it will go in one quick motion. The needle must be inserted under the skin, but not into any blood vessels below the skin. See **Figure 6**.



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.