USER GUIDE
for healthcare
professionals

Ceplene®

Histamine dichlorhydrate

▼ 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 at the back of the document for how to report adverse reactions.

This guide has been produced to promote the use and proper use injections of **Ceplene®** in combination with interleukin-2 (**IL-2**).

LABORATOIRES DELBERT

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ANNEXES

Ceplene® Histamine dihydrochloride use concomitant **IL-2** Interleukin-2
By subcutaneous injection[1]

1 complete treatment

10 cycles of treatment
(About 18 months)

1 cycle of treatment

3 weeks of treatment (21 days)	+	**3 weeks** treatment-free (21 days)	Cycles 1 to 3
3 weeks of treatment (21 days)	+	**6 weeks** treatment-free (42 days)	Cycles 4 to 10

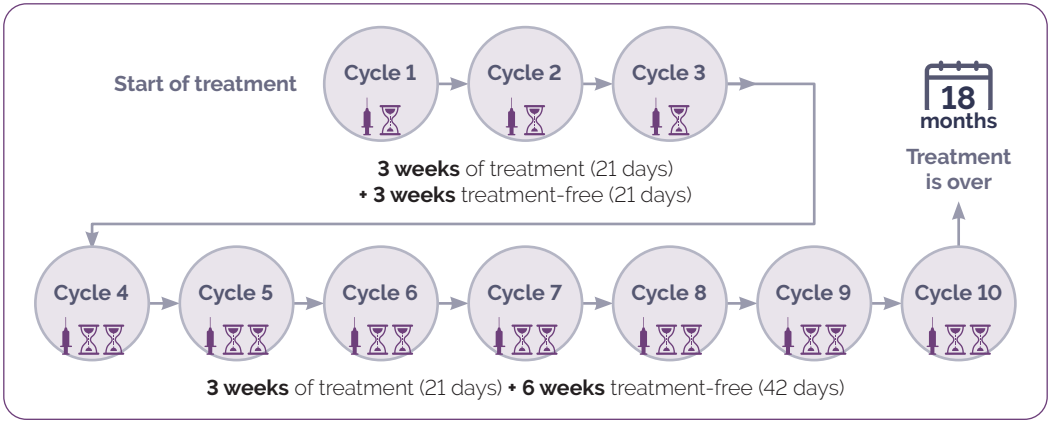
1 day of treatment

1 Injection of **IL-2** + 1 Injection of **Ceplene®**
2 times a day, every 6 hours

IL-2 is administered twice daily as a subcutaneous injection 1 to 3 minutes prior to the administration of **Ceplene®**.

1. CYCLES OF TREATMENT[1]

This treatment is not permanent and will end after the 10th cycle of treatment.



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2. DOSAGE[1]

1 Injection of **Ceplene®**
Histamine dihydrochloride

0.5 ml
=
1 vial of **Ceplene®**

A vial of **Ceplene®** contains 0.70 ml of solution (including overfill) to facilitate the dose extraction of a single 0.5 ml dose.

1 Injection of **IL-2**
Interleukin-2

16 400 IU/kg
=
prefilled seringe of **IL-2**,
to be prepared

3. **IL-2** INFORMATION[1]

To be prepared by the pharmacy in a controlled aseptic environment from **aldesleukin** vials (1 vial = 22×10^6 IU).

Prescribed and dispensed to the patient in capped polypropylene tuberculin prefilled sterile syringes[1].

For more information, see Annex I: **IL-2** preparation based on the patients' weight, page 9.

4. DOSE MODIFICATION IN CASE OF INTOLERANCE OR ADVERSE EVENTS[1]

Patient should be monitored for the expected symptomatic adverse reactions and laboratory changes associated with this treatment.

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**.

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.

For more information, see Annex II: Dose modification in case of intolerance or adverse event, page 10-11, and Annex III: Modified doses of **IL-2** and **Ceplene®**, page 12.

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5. PRESCRIPTION AND DISPENSATION[1]

Prescription
of **Ceplene®**
in association with **IL-2**

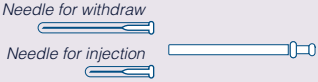
Preparation of the syringes prefilled with IL-2 in the pharmacy

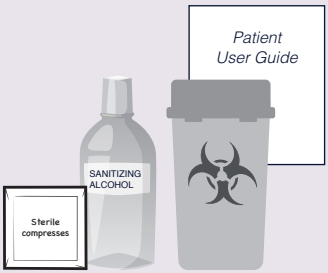
Dispensing
to the patient

For more information about **Ceplene®** and **IL-2** administrations, see page 6.

PRESCRIPTION CONTENT

- **Ceplene®** vials
- Injection material for **Ceplene®**
- Syringes prefilled with **IL-2**





For more information, see Annex IV: Prescription content, page 13.

SPECIAL PRECAUTIONS FOR STORAGE

Ceplene®
Keep at ambiant temperature
(15 °C–25 °C)

IL-2 reconstituted and diluted syringes
Store in a refrigerator
(2 °C–8 °C)

Studies have shown chemical stability and sterility of diluted aldesleukin (**IL-2**) 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.

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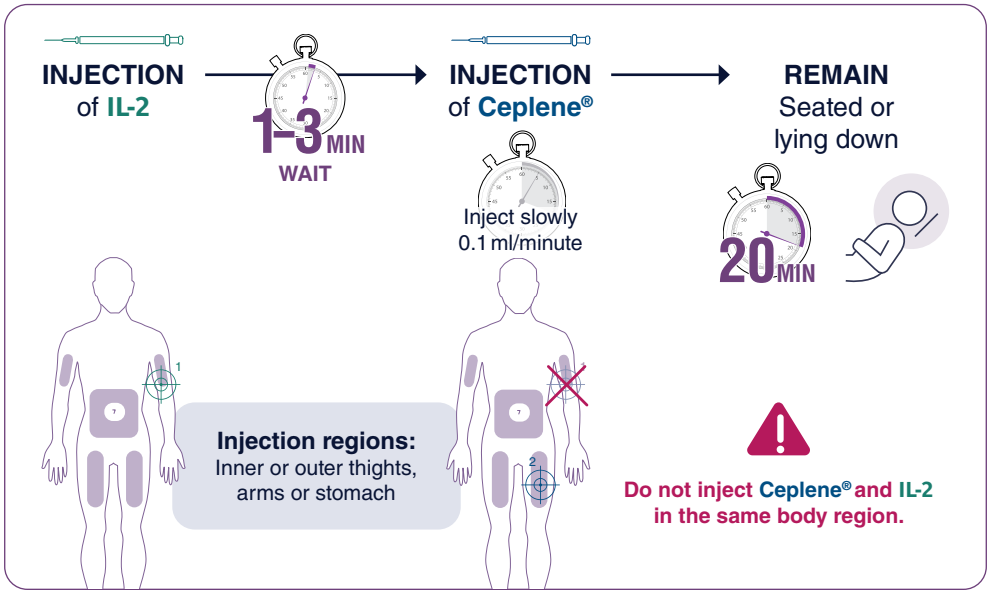
6. METHOD OF ADMINISTRATION[1]

The first dose of **Ceplene®** and **IL-2** will be administered at the hospital, under direct supervision by a physician.

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 can respond appropriately should signs or symptoms of hypotension occur.



The patient needs to be monitored during the injection.

For more information, see Annex V: Injection preparation Protocol, page 14.
For more information, see Annex VI: Instruction for injection, page 15.

7. CONTRAINDICATIONS[1]

- Hypersensitivity to the active substance or to any of the excipients of **Ceplene®**.
- 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 breastfeeding.

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8. SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE[1]

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.

Day 1 of first cycle: **Ceplene®** must be administered at the clinic, under direct supervision by a physician

- 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®**.

Patients must not take any additional dose to make up for the forgotten doses and continue with the treatment as prescribed.

Patients should not drive or operate machines for at least 1 hour after receiving **Ceplene®**.

Ceplene® in conjunction with **IL-2** should be used with caution in patients with:

- **Poorly compensated cardiac function.**
- **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 (unless the use of antibiotics and antivirals were for prophylaxis purposes).
- 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.
- A prior **history of autoimmune disease** (including systemic lupus, inflammatory bowel disease, psoriasis and rheumatoid arthritis).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:
  - 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.

For further information please refer to the **Ceplene®** SmPC.

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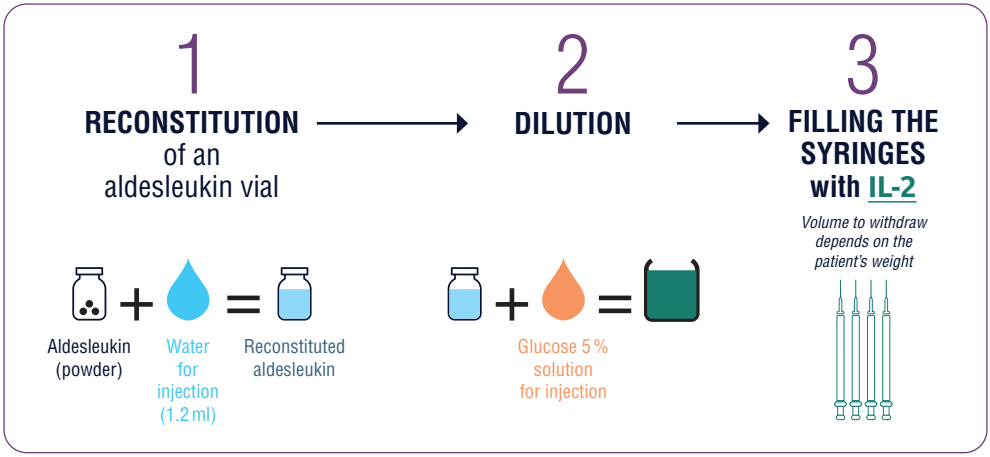
ANNEXES

IL-2 preparation based on the patient's weight

In a controlled aseptic environment
/ By the pharmacy



IL-2 posology based on the patient's weight

Patient's weight (kg)	Standard posology (µg)	Standard posology (UI)	Injection volume (ml)	Number of aldesleukin vials needed for 1 cycle (21 days)	Number of aldesleukin vials needed for 1 week (7 days)
≤50	50	820 000	0.25	2	1
>50 to ≤60	60	984 000	0.30	2	1
>60 to ≤70	70	1 148 000	0.35	3	1
>70 to ≤80	80	1 312 000	0.40	3	1
>80 to ≤90	90	1 476 000	0.45	3	1
>90 to ≤100	100	1 640 000	0.50	4	2
>100	100	1 640 000	0.50	4	2

Table modified from ***Ceplene®*** *SmPC, 03/2023*

For more information, see Annex III: Modified doses of **IL-2** and **Ceplene®**, page 12.

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Dose modification in case of intolerance or adverse event

If you notice any adverse event after taking the drug, please contact pharmacovigilance@delbert.fr.

Adverse event		Recommandation
Grade 1 toxicity event		No recommendations Exception of: • **Grade 1 neurologic toxicity** • **Grade 1 generalised toxic dermatitis** *(Refer to the relevant sections below)*
Grade 1 to 4 neurologic toxicity	Grade 1 to 3	1. Treatment should be **discontinued** until grade 0 toxicity event has been achieved. 2. Treatment should then be resumed at a **20 % dose reduction** for both **Ceplene®** and **IL-2**.
	Grade 4	**Discontinuation** of treatment should be considered.
Grade 1 to 4 generalised toxic dermatitis	Grade 1	1. Treatment should be **delayed for 48 hours** or until all symptoms have been resolved. 2. Resuming treatment using: • Full dose of **Ceplene®** • Reduced **IL-2** dose by 20 %
	Grade 2	1. **IL-2** dose should be reduced by 50 %. Only increased to full dose if the symptoms do not reappear. 2. **IL-2** and **Ceplene®** doses should be seperated by **60 minutes**, which should be maintained throughout treatment.
	Grade 3 to 4	1. Treatment should be **discontinued** and not resumed until events have been resolved. 2. Treatment should **only be resumed after consideration** of risk-benefit to the patient.
Grade 2 (including cardiac function, renal, hepatic) toxicity	1. Treatment should be **discontinued** until the event has returned to grade 1. 2. The time of injection of **Ceplene®** should be extended to a maximum of **15 minutes**.	
	Cardiac, Hepatic or Renal toxicity	The dose should be reduced by **20 %** for both **Ceplene®** and **IL-2**.
Grade 3 and 4 (including **hypotension and 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.

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Adverse event		Recommandation
For **persistent hypotension, headache, arrythmia, 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. If abnormal WBC counts re-occur during the following cycle a **permanent IL-2 reduction** is recommended.
Localised toxic dermatitis		1. Treatment should be discontinued until symptoms resolved. 2. Treatment can be resumed by administering: • **Ceplene®** at full dose • **IL-2** at **50%**
Special populations	**Elderly patients**	The efficacy of **Ceplene®** has not been fully demonstrated in patients older than 60.
	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 of **Ceplene®** SmPC). 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.**

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Modified doses of IL-2 and Ceplene®

Dose reduction of IL-2 by 20 % in the event of adverse reactions

Dose reduction of IL-2 by 20 %	
Patient's weight (kg)	Injection volume (ml)
≤ 50	0.20
> 50 to ≤ 60	0.25
> 60 to ≤ 70	0.30
> 70 to ≤ 80	0.30
> 80 to ≤ 90	0.35
> 90 to ≤ 100	0.40
> 100	0.40

Table modified from ***Ceplene®*** *SmPC, 03/2023*

Dose reduction of Ceplene® by 20 % in the event of adverse reactions

When reducing the dose of **Ceplene®** by 20 %, a 90 kg patient must **withdraw 0.4 ml** of **Ceplene®** solution from their graduated syringe, instead of the usual 0.5 ml.

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Prescription content

Material needed for the injection of Ceplene®

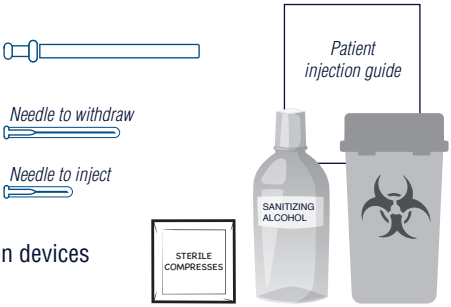
For **1 injection of Ceplene®:**

- 1 ml graduated capped polypropylene syringe
- 1 hypodermic needle to withdraw **Ceplene®** from the vial
- 1 hypodermic needle to inject **Ceplene®**

Sanitizing alcohol, sterile compresses

Puncture-proof container for disposal of injection devices

Patient Injection Guide



For the injection of **Ceplene®**, use hypodermic needles 25G (or up).

Summary of the quantities of Ceplene® and IL-2 to be prescribed

	Quantity for **1 cycle** (21 days)	Quantity for **1 week** (7 days)
Ceplene®		
Ceplene® vials	**42**	**14**
1 ml capped polypropylene syringes (graduated) (for the injection of **Ceplene®**)	**42**	**14**
Needles to **withdraw Ceplene®**	**42**	**14**
Needles to **inject Ceplene®**	**42**	**14**
IL-2		
Capped polypropylene tuberculin syringes prefilled with IL-2 *Dosage based on the patient's weight*	**42**	**14**
Others		
Sterile compresses	**As needed**	**As needed**
Sanitizing alcohol	**As needed**	**As needed**

Do not forget to add a few more syringes and needles in case of breakage.

Table modified from **Ceplene®** *SmPC, 03/2023*

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Injection preparation protocol

Preparation for injection of **IL-2**

IL-2 is to be dispensed to the patient as pre-filled capped tuberculin syringes, ready for use.

Preparation for injection of **Ceplene®**

01. To prepare a dose of **Ceplene®**, you will need the following:
    - 1 vial **Ceplene®** solution (0.5 ml)
    - 1 sterile graduated syringe with needle
    - 1 alcohol wipe.

02. Take 1 vial out of the carton.

03. Check the expiry date (EXP) on the vial label. Do not use if the date has passed the last day of the month shown.

04. Wash your hands thoroughly with soap and water.

05. 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.

06. Remove the plastic cap from the vial, exposing the stopper with the inner rubber circle. Use an alcohol wipe to clean the rubber part of the stopper. Do not touch the stopper with your hands.

07. 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.

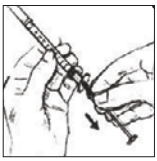
Fig. 1

08. 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.

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


Fig. 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.

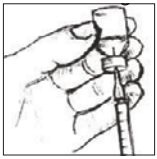
Fig. 3

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 “Instruction for injection” information below.

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Instruction for injection

For the injection you will need the following:

- 1 prepared syringe for your **IL-2** (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.

01. 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.

02. Inject **IL-2** as you have been instructed.

03. **Wait 1 to 3 minutes.**

04. 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 possible injection sites, see Figure 4.

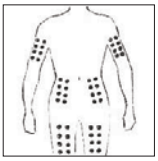
Fig. 4

05. 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.

06. Pinch up a section of the cleaned skin between your thumb and forefinger, without squeezing it. See Figure 5.


Fig. 5

07. Hold the 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.

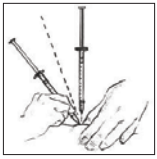
Fig. 6

08. 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 **IL-2**.

09. 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.

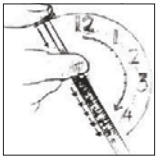
Fig. 7

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.

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▼ 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.

Ceplene® (histamine dihydrochloride) 0.5 mg/0.5 ml solution for injection. Rx. ATC code: L03AX14. **Indication*:** Ceplene maintenance therapy is indicated for adult patients with acute myeloid leukaemia (AML) in first remission concomitantly treated with interleukin-2 (IL-2). **Dosage and method of administration*:** Ceplene maintenance therapy should be administered following completion of consolidation therapy in patients concomitantly treated with IL-2. IL-2 is administered twice daily as a subcutaneous injection and Ceplene is administered 1 to 3 minutes after each injection of IL-2, not concomitantly and not into the same anatomic region. Each 0.5 ml Ceplene dose is injected slowly subcutaneously, over 5–15 minutes. 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 recommended dosing regimen, dose modifications and method of administration please see section 4.2 of the SmPC. **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 or patients who have received an allogenic stem cell transplant. **Pregnancy and breastfeeding:** Ceplene is contraindicated during pregnancy and breast feeding. **Special warnings and precautions for use*:** The efficacy of Ceplene has not been fully demonstrated in patients older than age 60. 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. 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, renal disease, stroke within the last 12 months, clinically significant infection within last 14 days before starting treatment and in patients with history of autoimmune disease. For information regarding interaction with other medicinal products and other forms of interaction, please see section 4.5 of the SmPC. Patients should not drive or operate machines for at least 1 hour after receiving Ceplene. **Undesirable effects*:** Very common (≥ 1/10): upper respiratory tract infections, eosinophilia, thrombocytopenia, headache, dizziness, dysgeusia, tachycardia, flushing, hypotension, cough, dyspnoea, nausea, dyspepsia, diarrhea, rash, arthralgia, myalgia, decreased appetite, anxiety, dry skin, malaise, oedema peripheral, decreased weight, fatigue, pyrexia, feeling hot, influenza like illness, chills and injection site complication as granuloma, erythema, pruritus, inflammation and pain).

Country	Packages	Reimbursement	Dispensing group	Price (retail price)
Denmark	14 x 0.5 ml	No	BEGR	10.500 (DKK)
Norway	14 x 0.5 ml	H-prescription	C	11 943.50 (NOK)
Sweden	14 x 0.5 ml	Yes	N/A	Please see www.fass.se

The sections marked with * have been abbreviated in connection to the approved SmPC. For more information about Ceplene, please see the full SmPC on EMA's webpage. Latest revision of the SmPC: 03/2023. **Marketing authorization holder:** Laboratoires Delbert, 49 Rue Rouelle, 75015 Paris, France. **Contact:** pharmacovigilance@delbert.fr.

Suspected adverse reactions can be reported to Laboratoires Delbert: delbertpvmi.nordics@biomapas.com, or +46 8 124 000 29.

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