資料３－③　ヒスタミン 二塩酸塩
(histamine dihydrochloride)

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ceplene 0.5 mg/0.5 ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

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

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

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 1 and 2.

Table 1: 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 2: For treatment cycles 4-6 with Ceplene and IL-2, same as for Table 1 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.1 9 to w.2 1	**w.2 8 to w.3 0**	**w.3 7 to w.3 9**	**w.4 6 to w.4 8**	**w.55 - to w.57**	**w.6 4 to w.6 6**	**w.7 3 to w.7 5**	IL-2 16 400 IU/kg followed by 0.5 ml Ceplene. Twice daily
w.2 2 to w.2 7	**w.3 1 to w.3 6**	**w.4 0 to w.4 5**	**w.4 9 to w.5 4**	**w.58 to w.63**	**w.6 7 to w.7 2**	**w.7 6 to w.8 1**	Treatment-free (6 weeks)

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

Dose modification

Patients should be monitored for the expected symptomatic adverse reactions and laboratory changes associated with this treatment. Doses of Ceplene and IL-2 should be modified as necessary based on individual patient tolerance to treatment. It is recommended that dose modifications be addressed early in treatment. The dose reductions can be temporary or permanent.
Should Ceplene related toxicities occur (such as hypotension, headache), the injection time can be increased from 5 minutes to a maximum of duration of 15 minutes.

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

For patients experiencing grade 1-4 neurologic toxicity

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

For patients experiencing grade 1-4 generalised toxic dermatitis

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

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

- treatment should be discontinued until the event has returned to grade 1
- the time of injection of the dose of Ceplene should be extended to a maximum of 15 minutes.
- for cardiac, hepatic or renal toxicities the dose should be reduced by 20% for both Ceplene and IL-2.

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

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

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

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

Fever

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

Abnormal WBC counts

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

Localised toxic dermatitis

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

Special populations

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

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

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

Method of administration

For subcutaneous use only.

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

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

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

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

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Patients with significantly compromised cardiac function, e.g., NYHA Class III/IV.
- Patients receiving systemic steroid therapy, clonidine and 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 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 Pregnancy and lactation

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

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Acute Myeloid Leukaemia

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

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

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

Blood and lymphatic system disorders
Very common: eosinophilia, thrombocytopenia

Metabolism and nutrition disorders
Common: anorexia

Psychiatric disorders
Common: insomnia

Nervous system disorders
Very common: headache, dizziness, dysgeusia

Cardiac disorders
Very common: tachycardia
Common: palpitations

Vascular disorders
Very common: flushing, hypotension

Respiratory, thoracic, and mediastinal disorders
Very common: cough, dyspnoea
Common: nasal congestion

Gastrointestinal disorders
Very common: nausea, dyspepsia, diarrhoea.
Common: vomiting, upper abdominal pain, dry mouth

Skin and subcutaneous tissue disorders
Very common: rash
Common: erythema, increased sweating, night sweats, pruritus

Musculoskeletal and connective tissue disorders
Very common: arthralgia, myalgia
Common: limb pain, back pain

General disorders and administration site conditions
Very common: injection site granuloma, fatigue, pyrexia, injection site erythema, feeling hot, injection site reaction, injection site pruritus, influenza like illness, rigors, injection site inflammation, injection site pain
Common: injection site urticaria, injection site bruising, injection site rash, injection site swelling, weakness, chest pain

Other oncology (advanced tumour) studies

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

Blood and lymphatic system disorders
Common: anaemia

Skin and subcutaneous tissue disorders
Very common: dry skin

Ear and labyrinth disorders
Common: vertigo

Endocrine disorders
Common: acquired hypothyroidism

Metabolism and nutrition disorders
Very common: decreased appetite
Common: dehydration

Psychiatric disorders
Very common: anxiety
Common: depression

Nervous system disorders
Common: paraesthesia

Vascular disorders
Common: hot flushes

Respiratory, thoracic, and mediastinal disorders
Common: wheezing

Gastrointestinal disorders
Common: constipation, abdominal distention, stomatitis

General disorders and administration site conditions
Very common: malaise, oedema peripheral, weight decreased

Common: injection site fibrosis, pain

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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 (EMEA) will review any new information which may become available every year and this SPC will be updated as necessary.

5.2 Pharmacokinetic properties

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

Histamine is eliminated by metabolism in kidney, liver and other tissues. The main enzymes involved in the metabolism of histamine are HNMT (histamine-N-methyltransferase) and DAO (diamine

oxidase). The metabolites are mainly excreted in urine. The mean half-life was 0.75 to 1.5 hours in patients.

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

It is not known whether histamine crosses the placenta.

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

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

5.3 Preclinical safety data

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vials: 3 years

6.4 Special precautions for storage

Do not freeze.

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

The vials contain 0.5 ml of solution (0.70 ml including overfill) to facilitate the dose extraction of a single 0.5 ml dose.
Patients are provided with capped polypropylene syringes and instructed to extract 0.5 ml of solution into the syringe.

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

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

7. MARKETING AUTHORISATION HOLDER

EpiCept GmbH
Goethestrasse 4
D-80336 München
Germany

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OF THE MARKETING AUTHORISATION

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

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

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

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 3.0 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 3.0 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

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

In addition, an updated RMP should be submitted

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

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

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

Clinical aspects:

Clinical Study to evaluate the Biomarkers and Pharmacologic Endpoints of Ceplene plus low dose Interleukin-2 in approximately 100 Adult Patients stratified by age greater or less than 60 years with Acute Myeloid Leukemia in First Complete Remission (CR), with well characterized Morphologic, Cytogenetic and Molecular profiles (First Patient In Q2, 2009 Final Study Results Q4, 2011)

Clinical study to evaluate Minimal Residual Disease (MRD) for the assessment of the anti-leukaemic activity of Ceplene plus low dose Interleukin-2 in approximately 150 Adult Patients stratified by age greater or less than 60 years with Acute Myeloid Leukemia in First Complete Remission. (First Patient In Q3, 2009 Final Study Results Q2, 2012)

Determine the feasibility of conducting, in conjunction with collaborative groups in Europe and/or the United States, a Multicenter Randomized Open-Label Study to Evaluate the Safety and Efficacy of Ceplene plus Interleukin-2 to be determined in approximately 350 adult Patients (stratified by age greater or less than 60 years) with Acute Myeloid Leukemia in First Complete Remission by Q3, 2009.

If this study design is feasible and agreed to by the CHMP, EpiCept commits to conduct the study and to aim for a start of recruitment within 1 year of agreement on protocol synopsis and recruitment of 10 patients/month.

ANNEX III

LABELLING AND PACKAGE LEAFLET