ANNEX 1

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DepoCyte 50 mg suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of suspension contains 10 mg cytarabine.
Each 5 ml vial contains 50 mg cytarabine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.
White to off-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Intrathecal treatment of lymphomatous meningitis. In the majority of patients such treatment will be part of symptomatic palliation of the disease.

4.2 Posology and method of administration

DepoCyte should be administered only under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

Posology

Paediatric population

Safety and efficacy in children aged under 18 years have not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made. DepoCyte is not recommended for use in children and adolescents until further data become available.

Adults and the elderly

For the treatment of lymphomatous meningitis, the dose for adults is 50 mg (one vial) administered intrathecally (lumbar puncture or intraventricularly via an Ommaya reservoir). The following regimen of induction, consolidation and maintenance therapy is recommended:

Induction therapy: 50 mg administered every 14 days for 2 doses (weeks 1 and 3).

Consolidation therapy: 50 mg administered every 14 days for 3 doses (weeks 5, 7 and 9) followed by an additional dose of 50 mg at week 13.

Maintenance therapy: 50 mg administered every 28 days for 4 doses (weeks 17, 21, 25 and 29).

Method of administration

DepoCyte is to be administered by slow injection over a period of 1-5 minutes directly into the cerebrospinal fluid (CSF) via either an intraventricular reservoir or by direct injection into the lumbar

sac. Following administration by lumbar puncture, it is recommended that the patient should be instructed to lie flat for one hour. All patients should be started on dexamethasone 4 mg twice daily either orally or intravenously for 5 days beginning on the day of injection of DepoCyte.

DepoCyte must not be administered by any other route of administration. DepoCyte must be used as supplied; it must not be diluted (see section 6.2). Patients should be observed by the physician for immediate toxic reactions.

If neurotoxicity develops, the dose should be reduced to 25 mg. If it persists, treatment with DepoCyte should be discontinued.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Patients with active meningeal infection.

4.4 Special warnings and precautions for use

Patients receiving DepoCyte should be concurrently treated with corticosteroids (e.g. dexamethasone) to mitigate the symptoms of arachnoiditis (see section 4.8), which is a very common adverse reaction.

Arachnoiditis is a syndrome manifested primarily by nausea, vomiting, headache and fever. If left untreated, chemical arachnoiditis may be fatal.

Patients should be informed about the expected adverse reactions of headache, nausea, vomiting and fever, and about the early signs and symptoms of neurotoxicity. The importance of concurrent dexamethasone administration should be emphasised at the initiation of each cycle of DepoCyte treatment. Patients should be instructed to seek medical attention if signs or symptoms of neurotoxicity develop, or if oral dexamethasone is not well tolerated.

Cytarabine, when administered intrathecally, has been associated with nausea, vomiting and serious central nervous system toxicity which can lead to a permanent deficit, this includes blindness, myelopathy and other neurological toxicity.

Administration of DepoCyte in combination with other neurotoxic chemotherapeutic agents or with cranial/spinal irradiation may increase the risk of neurotoxicity.

Infectious meningitis may be associated with intrathecal administration. Hydrocephalus has also been reported, possibly precipitated by arachnoiditis.

Blockage or reduction of CSF flow may result in increased free cytarabine concentrations in the CSF with increased risk of neurotoxicity. Therefore, as with any intrathecal cytotoxic therapy, consideration should be given to the need for assessment of CSF flow before treatment is started.

Although significant systemic exposure to free cytarabine is not expected following intrathecal treatment, some effects on bone marrow function cannot be excluded. Systemic toxicity due to intravenous administration of cytarabine consists primarily of bone marrow suppression with leucopenia, thrombocytopenia and anaemia. Therefore monitoring of the haemopoietic system is advised.

Anaphylactic reactions following intravenous administration of free cytarabine have been rarely reported.

Since DepoCyte's particles are similar in size and appearance to white blood cells, care must be taken in interpreting CSF examination following administration.

4.5 Interaction with other medicinal products and other forms of interaction

No definite interactions between DepoCyte delivered intrathecally and other medicinal products have been established.

Concomitant administration of DepoCyte with other antineoplastic agents administered by the intrathecal route has not been studied.

Intrathecal co-administration of cytarabine with other cytotoxic agents may increase the risk of neurotoxicity.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Despite the low apparent risk women of childbearing potential should not receive treatment until pregnancy is excluded and should be advised to use a reliable contraceptive method.

Given that cytarabine has a mutagenic potential which could induce chromosomal damage in the human spermatozoa, males undergoing DepoCyte treatment and their partner should be advised to use a reliable contraceptive method.

Pregnancy

Teratology studies in animals have not been conducted with DepoCyte and there are no adequate and well controlled studies in pregnant women.

Cytarabine, the active ingredient in DepoCyte, can cause foetal harm when administered systemically during pregnancy, mainly during the first trimester. Concern for foetal harm following intrathecal DepoCyte administration however, is low because systemic exposure to cytarabine is negligible. Despite the low apparent risk women of childbearing potential should not receive treatment until pregnancy is excluded and should be advised to use a reliable contraceptive method.

Breast-feeding

It is not known whether cytarabine is excreted in human milk following intrathecal administration. The systemic exposure to free cytarabine following intrathecal treatment with DepoCyte was negligible. Because of possible excretion in human milk and because of the potential for serious adverse reactions in nursing infants, the use of DepoCyte is not recommended in breast-feeding women.

Fertility

Fertility studies to assess the reproductive toxicity of DepoCyte have not been conducted. Because the systemic exposure to free cytarabine following intrathecal treatment with DepoCyte is negligible, the risk of impaired fertility is likely to be low (see section 5.3).

4.7 Effects on ability to drive and use machines

There have been no reports explicitly relating to effects of DepoCyte treatment on the ability to drive or use machines. However, on the basis of reported adverse reactions, patients should be advised against driving or using machines during treatment.

4.8 Undesirable effects

In Phase 1-4 studies the most commonly reported adverse reactions associated with DepoCyte were headache (23%), arachnoiditis (16%), pyrexia (14%), weakness (13%), nausea (13%), vomiting (12%), confusion (11%), diarrhoea (11%), thrombocytopenia (10%), and fatigue (6%).

For Phase 1-4 studies in patients with lymphomatous meningitis receiving either DepoCyte or cytarabine adverse reactions are listed by MedDRA body system organ class and by frequency (Very common (≥1/10); and Common (≥1/100 to < 1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000)) in Table 1 below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. Adverse reactions occurring in > 10% of cycles in either treatment group in Phase 1-4 study patients with lymphomatous meningitis receiving DepoCyte 50 mg (n = 151 cycles) or cytarabine (n = 99 cycles)

Blood and lymphatic system disorders	
DepoCyte	***Very common***: Thrombocytopenia
Cytarabine	***Very common***: Thrombocytopenia
Nervous system disorders	
DepoCyte	***Very common***: arachnoiditis, confusion, headache
Cytarabine	***Very common***: arachnoiditis, headache ***Common***: confusion
Gastrointestinal disorders	
DepoCyte	***Very common***: diarrhoea, vomiting, nausea
Cytarabine	***Very common***: diarrhoea, vomiting, nausea
General disorders and administration site conditions	
DepoCyte	***Very common***: weakness, pyrexia ***Common***: fatigue
Cytarabine	***Very common***: weakness, pyrexia, fatigue

*Induction and Maintenance cycle lengths were 2 and 4 weeks, respectively, during which the patient received either 1 dose of DepoCyte or 4 doses of cytarabine. Cytarabine patients not completing all 4 doses within a cycle are counted as a complete cycle.

Nervous system disorders

DepoCyte has the potential of producing serious neurological toxicity.

Intrathecal administration of cytarabine may cause myelopathy (3%) and other neurologic toxicities sometimes leading to a permanent neurological deficit. Following intrathecal administration of DepoCyte, serious central nervous system toxicity, including persistent convulsions (7%), extreme somnolence (3%), hemiplegia (1%), visual disturbances including blindness (1%), deafness (3%) and cranial nerve palsies (3%) have been reported. Symptoms and signs of peripheral neuropathy, such as pain (1%), numbness (3%), paresthesia (3%), hypoaesthesia (2%), weakness (13%), and impaired bowel (3%) and bladder control (incontinence) (1%), have also been observed and in some cases this combination of neurological signs and symptoms has been reported as Cauda equina syndrome (3%).

Adverse reactions possibly reflecting neurotoxicity are listed in Table 2 by MedDRA body system organ class and by frequency: Very common (≥1/10); Common (≥1/100 to < 1/10); and Uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2: Adverse reactions possibly reflecting neurotoxicities in Phase II, III, and IV patients receiving DepoCyte 50 mg (n = 99 cycles) or cytarabine (n = 84 cycles)	
Psychiatric disorders	
DepoCyte	***Common***: somnolence
Cytarabine	***Common***: somnolence
Nervous system disorders	
DepoCyte	***Common***: cauda equina syndrome, convulsions, cranial nerve palsies, hypoesthesia, myelopathy, paresthesia, hemiplegia, numbness
Cytarabine	***Common***: cauda equina syndrome, convulsions, cranial nerve palsies, hypoesthesia, myelopathy, paresthesia, hemiplegia, numbness
Eye disorders	
DepoCyte	***Common***: visual disturbances, blindness
Cytarabine	***Common***: visual disturbances, blindness
Ear and labyrinth disorders	
DepoCyte	***Common***: deafness
Cytarabine	***Common***: deafness
Gastrointestinal disorders	
DepoCyte	***Common***: impaired bowel control
Cytarabine	***Common***: impaired bowel control
Renal and urinary disorders	
DepoCyte	***Common***: urinary incontinence
Cytarabine	***Common***: urinary incontinence
General disorders and administration site conditions	
DepoCyte	***Very Common***: weakness ***Common***: pain
Cytarabine	***Very Common***: weakness ***Common***: pain

All patients receiving DepoCyte should be treated concurrently with dexamethasone to mitigate the symptoms of arachnoiditis. Toxic effects may be related to a single dose or to cumulative doses. Because toxic effects can occur at any time during therapy (although they are most likely within 5 days of administration), patients receiving DepoCyte therapy should be monitored continuously for the development of neurotoxicity. If patients develop neurotoxicity, subsequent doses of DepoCyte should be reduced, and treatment should be discontinued if toxicity persists.

Arachnoiditis, a very common adverse reaction associated with DepoCyte, is a syndrome manifested by several adverse reactions. The incidence of these adverse reactions, possibly reflecting meningeal irritation, are headache (24%), nausea (18%), vomiting (17%), pyrexia (12%), neck stiffness (3%), neck pain (4%), back pain (7%), meningism (<1%), convulsions (6%), hydrocephalus (2%), and CSF pleocytosis with or without altered state of consciousness (1%). Table 3 below lists these reactions for patients treated DepoCyte, and for patients treated with methotrexate and cytarabine as well.

Adverse reactions are listed by MedDRA body system organ class and by frequency: Very common (_≥1/10); Common (≥1/100 to < 1/10); and Uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3: Adverse reactions possibly reflecting meningeal irritation in Phase II, III, and IV patients	
Nervous system disorders	
DepoCyte (n = 929 cycles)	***Very common***: headache ***Common***: convulsions, hydrocephalus acquired, CSF pleocytosis ***Uncommon***: meningism
Methotrexate (n = 258 cycles)	***Very common***: headache ***Common***: convulsions, hydrocephalus acquired, meningism
Cytarabine (n = 99 cycles)	***Very common***: headache ***Common***: convulsions, meningism
Gastrointestinal disorders	
DepoCyte (n = 929 cycles)	***Very common***: vomiting, nausea
Methotrexate (n = 258 cycles)	***Very common***: vomiting, nausea
Cytarabine (n = 99 cycles)	***Very common***: vomiting, nausea
Musculoskeletal and connective tissue disorders	
DepoCyte (n = 929 cycles)	***Common***: back pain, neck pain, neck stiffness
Methotrexate (n = 258 cycles)	***Common***: back pain, neck pain ***Uncommon***: neck stiffness
Cytarabine (n = 99 cycles)	***Common***: back pain, neck pain, neck stiffness
General disorders and administration site conditions	
DepoCyte (n = 929 cycles)	***Very common***: pyrexia
Methotrexate (n = 258 cycles)	***Common***: pyrexia
Cytarabine (n = 99 cycles)	***Very common***: pyrexia

*Cycle length was 2 weeks during which the patient received either 1 dose of DepoCyte or 4 doses of cytarabine or methotrexate. Cytarabine and methotrexate patients not completing all 4 doses are counted as a fraction of a cycle.

Investigations

Transient elevations in CSF protein and white blood cells have been observed in patients following DepoCyte administration, and have also been noted after intrathecal treatment with methotrexate or cytarabine. These reactions have been reported mainly from post-marketing experience with DepoCyte as spontaneous case reports. Because these reactions are reported from a population of uncertain size, it is not possible to reliably estimate their frequency.

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

No overdoses with DepoCyte have been reported. An overdose with DepoCyte may be associated with severe arachnoiditis including encephalopathy.

In an early uncontrolled study without dexamethasone prophylaxis, single doses up to 125 mg were administered. One patient at the 125 mg dose level died of encephalopathy 36 hours after receiving DepoCyte intraventricularly. This patient, however, was also receiving concomitant whole brain irradiation and had previously received intraventricular methotrexate.

There is no antidote for intrathecal DepoCyte or unencapsulated cytarabine released from DepoCyte. Exchange of cerebrospinal fluid with isotonic sodium chloride solution has been carried out in a case of intrathecal overdose of free cytarabine and such a procedure may be considered in the case of DepoCyte overdose. Management of overdose should be directed at maintaining vital functions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimetabolites, pyrimidine analogues, ATC code: L01BC01

Mechanism of action

DepoCyte is a sustained-release formulation of cytarabine, designed for direct administration into the cerebrospinal fluid (CSF).

Cytarabine is a cell-cycle phase specific antineoplastic agent, affecting cells only during the S-phase of cell division. Intracellularly, cytarabine is converted into cytarabine-5'-triphosphate (ara-CTP), which is the active metabolite. The mechanism of action is not completely understood, but it appears that ara-CTP acts primarily through inhibition of DNA synthesis. Incorporation into DNA and RNA may also contribute to cytarabine cytotoxicity. Cytarabine is cytotoxic to a wide variety of proliferating mammalian cells in culture.

For cell-cycle phase specific antimetabolites the duration of exposure of neoplastic cells to cytotoxic concentrations is an important determination of efficacy.

Pharmacodynamic effects

In vitro studies, examining more than 60 cell lines, demonstrated that the median cytarabine concentration resulting in 50% growth inhibition (IC_{50}) was approximately 10 µM (2.4 µg/ml) for two days of exposure and 0.1 µM (0.024 µg/ml) for 6 days of exposure. The studies also demonstrated susceptibility of many solid tumour cell lines to cytarabine, particularly after longer periods of exposure to cytarabine.

Clinical efficacy and safety

In an open-label, active-controlled, multicentre clinical study, 35 patients with lymphomatous meningitis (with malignant cells found on CSF cytology) were randomised to intrathecal therapy with either DepoCyte (n=18) or unencapsulated cytarabine (n=17). During the 1 month Induction phase of treatment, DepoCyte was administered intrathecally as 50 mg every 2 weeks, and unencapsulated cytarabine as 50 mg twice a week. Patients who did not respond discontinued protocol treatment after 4 weeks. Patients who achieved a response (defined as clearing of the CSF of malignant cells in the absence of progression of neurological symptoms) went on to receive Consolidation and Maintenance therapy for up to 29 weeks.

Responses were observed in 13/18 (72%, 95% confidence intervals: 47, 90) of DepoCyte patients versus 3/17 (18% patients, 95% confidence intervals: 4, 43) in the unencapsulated cytarabine arm. A statistically significant association between treatment and response was observed (Fisher's exact test p-value = 0.002). The majority of DepoCyte patients went on beyond Induction to receive additional therapy. DepoCyte patients received a median of 5 cycles (doses) per patient (range 1 to 10 doses) with a median time on therapy of 90 days (range 1 to 207 days).

No statistically significant differences were noted in secondary endpoints such as duration of response, progression-free survival, neurological signs and symptoms, Karnofsky performance status, quality of life and overall survival. Median progression-free survival (defined as time to neurological progression or death) for all treated patients was 77 versus 48 days for DepoCyte versus

unencapsulated cytarabine, respectively. The proportion of patients alive at 12 months was 24% for DepoCyte versus 19% for unencapsulated cytarabine.

Paediatric population

In an open-label non-comparative dose escalation study in 18 paediatric patients (4 to 19 years) with leukaemic meningitis or neoplastic meningitis due to primary brain tumour, an intrathecal dose of 35 mg was identified as the maximum tolerated dose.

5.2 Pharmacokinetic properties

Absorption

Analysis of the available pharmacokinetic data shows that following intrathecal DepoCyte administration in patients, either via the lumbar sac or by intraventricular reservoir, peaks of free cytarabine were observed within 5 hours in both the ventricle and lumbar sac. These peaks were followed by a biphasic elimination profile consisting of an initial sharp decline and subsequent slow decline with a terminal phase half-life of 100 to 263 hours over a dose-range of 12.5 mg to 75 mg. In contrast, intrathecal administration of 30 mg free cytarabine has shown a biphasic CSF concentration profile with a terminal phase half-life of about 3.4 hours.

Pharmacokinetic parameters of DepoCyte (75 mg) in neoplastic meningitis patients in whom the medicinal product was administered either intraventricularly or by lumbar puncture suggest that exposure to the active substance in the ventricular or lumbar spaces is similar regardless of the route of administration. In addition, compared with free cytarabine, the formulation increases the biological half-life by a factor of 27 to 71 depending upon the route of administration and the compartment sampled. Encapsulated cytarabine concentrations and the counts of the lipid particles in which the cytarabine is encapsulated in followed a similar distribution pattern. AUCs of free and encapsulated cytarabine after ventricular injection of DepoCyte appeared to increase linearly with increasing dose, indicating that the release of cytarabine from DepoCyte and the pharmacokinetics of cytarabine are linear in human CSF.

Distribution

The transfer rate of cytarabine from CSF to plasma is slow and the conversion to uracil arabinoside (ara-U), the inactive metabolite, in the plasma is fast. Systemic exposure to cytarabine was determined to be negligible following intrathecal administration of 50 mg and 75 mg of DepoCyte.

Biotransformation

The primary route of elimination of cytarabine is metabolism to the inactive compound ara-U, (1-β-D-arabinofuranosyluracil or uracil arabinoside) followed by urinary excretion of ara-U. In contrast with systemically administered cytarabine which is rapidly metabolised to ara-U, conversion to ara-U in the CSF is negligible after intrathecal administration because of the significantly lower cytidine deaminase activity in the CNS tissues and CSF. The CSF clearance rate of cytarabine is similar to the CSF bulk flow rate of 0.24 ml/min.

Elimination

The distribution and clearance of cytarabine and of the predominant phospholipid component of the lipid particle (DOPC) following intrathecal administration of DepoCyte was evaluated in rodents. Radiolabels for cytarabine and DOPC were distributed rapidly throughout the neuraxis. More than 90% of cytarabine was excreted by day 4 and an additional 2.7% by 21 days. The results suggest that the lipid components undergo hydrolysis and are largely incorporated in the tissues following breakdown in the intrathecal space.

5.3 Preclinical safety data

A review of the toxicological data available for the constituent lipids (DOPC and DPPG) or similar phospholipids to those in DepoCyte indicates that such lipids are well tolerated in various animal species even when administered for prolonged periods at doses in the g/kg range.

The results of acute and subacute toxicity studies performed in monkeys suggested that intrathecal DepoCyte was tolerated up to a dose of 10 mg (comparable to a human dose of 100 mg). Slight to moderate inflammation of the meninges in the spinal cord and brain and/or astrocytic activation were observed in animals receiving intrathecal DepoCyte. These changes were believed to be consistent with the toxic effects of other intrathecal agents such as unencapsulated cytarabine. Similar changes (generally described as minimal to slight) were also observed in some animals receiving DepoFoam alone (DepoCyte vesicles without cytarabine) but not in sodium chloride solution control animals. Mouse, rat and dog studies have shown that free cytarabine is highly toxic for the haemopoietic system.

No carcinogenicity, mutagenicity or impairment of fertility studies have been conducted with DepoCyte. The active ingredient, cytarabine, was mutagenic in *in vitro* tests and was clastogenic *in vitro* (chromosome aberrations and sister chromatid exchange in human leukocytes) and *in vivo* (chromosome aberrations and sister chromatid exchange assay in rodent bone marrow, mouse micronucleus assay). Cytarabine caused the transformation of hamster embryo cells and rat H43 cells *in vitro*. Cytarabine was clastogenic to meiotic cells; a dose-dependent increase in sperm-head abnormalities and chromosomal aberrations occurred in mice given intraperitoneal (i.p.) cytarabine. No studies assessing the impact of cytarabine on fertility are available in the literature. Because the systemic exposure to free cytarabine following intrathecal treatment with DepoCyte was negligible, the risk of impaired fertility is likely to be low.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cholesterol
Triolein
Dioleoylphosphatidylcholine (DOPC)
Dipalmitoylphosphatidylglycerol (DPPG)
Sodium chloride
Water for injections

6.2 Incompatibilities

No formal assessments of pharmacokinetic drug-drug interactions between DepoCyte and other agents have been conducted. DepoCyte should not be diluted or mixed with any other medicinal products, as any change in concentration or pH may affect the stability of the microparticles.

6.3 Shelf life

18 months.

After first opening: from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 4 hours at 18 to 22°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.

6.5 Nature and contents of container

Type I glass vial closed with a fluororesin faced butyl rubber stopper and sealed with an aluminium flip-off seal containing 50 mg cytarabine in 5 ml suspension.

DepoCyte is supplied in individual cartons each containing one single-dose vial.

6.6 Special precautions for disposal and other handling

Preparation of DepoCyte

Given its toxic nature, special precautions should be taken in handling DepoCyte. See 'Precautions for the handling and disposal of DepoCyte' below.

Vials should be allowed to warm to room temperature (18°C -22°C) for a minimum of 30 minutes and be gently inverted to resuspend the particles immediately prior to withdrawal from the vial. Vigorous shaking should be avoided. No further reconstitution or dilution is required.

DepoCyte administration

DepoCyte must only be administered by the intrathecal route.

DepoCyte should be withdrawn from the vial immediately before administration. Since it is a single use vial and does not contain any preservative, the medicinal product should be used within 4 hours of withdrawal from the vial. Unused medicinal product must not be used subsequently. DepoCyte must not be mixed with any other medicinal products (see section 6.2). The suspension must not be diluted.

In-line filters must not be used when administering DepoCyte. DepoCyte is administered directly into the CSF via an intraventricular reservoir or by direct injection into the lumbar sac. DepoCyte should be injected slowly over a period of 1-5 minutes. Following administration by lumbar puncture, the patient should be instructed to lie flat for one hour. Patients should be observed by the physician for immediate toxic reactions.

All patients should be started on dexamethasone 4 mg twice daily either orally or intravenously for 5 days beginning on the day of DepoCyte injection.

Precautions for the handling and disposal of DepoCyte

The following protective recommendations are given due to the toxic nature of this substance:

- personnel should be trained in good technique for handling anticancer agents;
- male and female staff who are trying to conceive and female staff who are pregnant should be excluded from working with the substance;
- personnel must wear protective clothing: goggles, gowns, disposable gloves and masks;
- a designated area should be defined for preparation (preferably under a laminar flow system). The work surface should be protected by disposable, plastic backed, absorbent paper;
- all items used during administration or cleaning should be placed in high risk, waste-disposal bags for high temperature incineration;
- in the event of accidental contact with the skin, exposed areas should be washed immediately with soap and water;
- in the event of accidental contact with the mucous membranes, exposed areas should be treated immediately by copious lavage with water; medical attention should be sought.

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

7. MARKETING AUTHORISATION HOLDER

Pacira Limited
Wessex House
Marlow Road
Bourne End
Buckinghamshire
SL8 5SP
United Kingdom

8. MARKETING AUTHORISATION NUMBER

EU/1/01/187/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 July 2001
Date of latest renewal: 11 July 2011

10. DATE OF REVISION OF THE TEXT

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

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Almac Pharma Services Limited
20 Seagoe Industrial Estate
Craigavon, Co Armagh
BT63 5QD
United Kingdom

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)**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX

1. NAME OF THE MEDICINAL PRODUCT

DepoCyte 50 mg suspension for injection
Cytarabine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 50 mg cytarabine (10 mg/ml).

3. LIST OF EXCIPIENTS

Also contains: cholesterol, triolein, dioleoylphosphatidylcholine, dipalmitoylphosphatidylglycerol, sodium chloride, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection. One 5 ml vial.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intrathecal use.
Read the package leaflet before use.

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

Store in a refrigerator (2ºC - 8ºC).

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

Pacira Limited
Wessex House
Marlow Road
Bourne End
Buckinghamshire
SL8 5SP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/187/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

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

DepoCyte 50 mg suspension for injection
Cytarabine

Intrathecal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml.

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

DepoCyte 50 mg suspension for injection
Cytarabine

Read all of this leaflet carefully before you receive this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4..

What is in this leaflet:

1. What DepoCyte is and what it is given for

DepoCyte is used to treat lymphomatous meningitis.

Lymphomatous meningitis is a condition in which tumour cells have invaded the fluid or membranes that surround the brain and spinal cord.

DepoCyte is used in adults to kill lymphoma tumour cells.

2. What you need to know before you are given DepoCyte

DepoCyte should not be given
- if you are allergic to cytarabine or any of the other ingredients of this medicine (listed in section 6).
- if you have a meningeal infection.

Warnings and precautions
Severe neurological side effects have been reported with the use of DepoCyte. Symptoms have included effects on the nervous system (e.g. convulsions, pain, numbness or tingling, blindness or visual disturbances). Your doctor will check for these symptoms regularly.

Make sure you take as directed any dexamethasone tablets that you may have been prescribed, as they reduce the risk of unwanted effects caused by DepoCyte.

If your side effects get worse or you notice any new side effects, tell your doctor.

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

Pregnancy, breast-feeding and fertility
DepoCyte should not be given to pregnant women as it may harm an unborn child. Women of childbearing potential should use a reliable contraceptive method to avoid pregnancy whilst being treated with DepoCyte.

Male patients undergoing DepoCyte treatment should use a reliable contraceptive method.

Women should not breast-feed during treatment as DepoCyte may enter breast milk.

Driving and using machines
Do not drive during treatment.
Do not operate any tools or machines during treatment.

3. How DepoCyte is given

A qualified and experienced doctor or physician in the treatment of cancer will inject DepoCyte in the spinal fluid or lumber sac. DepoCyte must not be administered by any other way. Injections are given slowly over 1-5 minutes and you may be asked to lie flat for one hour afterwards.

You will also be given dexamethasone, usually as tablets but possibly by intravenous injection for 5 days after you receive each DepoCyte dose to help reduce any side effects which might occur.

Before DepoCyte is used the vial should be warmed to room temperature (18°C – 22°C) for at least 30 minutes. Just before withdrawing DepoCyte, the vial should be gently inverted to mix the particles evenly. It should not be shaken vigorously.

Proper precautions should be taken for the handling and administration of a cytotoxic drug (proper handling technique, use of a suitable designated area, protective clothing, procedures to address risk of contamination). Staff who are pregnant or trying to conceive (male and female) should not work with DepoCyte. In the event of accidental contact with the mucous membranes, treat immediately by copious washing with water; medical attention should be sought.

DepoCyte should be withdrawn from the vial immediately before administration; the medicinal product should be used within 4 hours of withdrawal from the vial. Unused medicinal product must be discarded and not used subsequently. DepoCyte must not be mixed with any other medicinal products. In-line filters must not be used when administering DepoCyte.

DepoCyte must be used as supplied without further dilution. The dose for adults is 50 mg (one vial of DepoCyte).

For the treatment of lymphomatous meningitis, DepoCyte is given according to the following schedules:

Start-up treatment: one vial of DepoCyte (50 mg) administered every 14 days for 2 doses (weeks 1 and 3).

Follow-up treatment: one vial of DepoCyte (50 mg) administered every 14 days for 3 doses (weeks 5, 7 and 9) followed by an additional dose at week 13.

Maintenance treatment: one vial of DepoCyte (50 mg) administered every 28 days for 4 doses (weeks 17, 21, 25 and 29).

If you are given more DepoCyte than you should
The recommended dose will be given to you by the doctor or physician as necessary. There is no antidote for DepoCyte. Management of overdose should be directed at maintaining vital functions.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Side effects may occur after each injection, usually within the first five days.

Your doctor will discuss these with you and will explain the potential risks and benefits of your treatment.

The frequency of possible side effects listed below is defined using the following convention: very common (affects more than 1 user in 10); common (affects 1 to 10 users in 100); uncommon (affects 1 to 10 users in 1,000); rare (affects 1 to 10 users in 10,000); very rare (affects less than 1 user in 10,000); not known (frequency cannot be estimated from the available data).

The severity of adverse events of DepoCyte may be increased when DepoCyte is given in combination with other chemotherapeutic agents.

Tell the medical staff monitoring you during this time, if you suffer from:

Very common (experienced in more than 1 in 10 patients)

- Nausea and/or vomiting
- Weakness
- Confusion
- Fever
- Headaches
- Dizziness
- Shaking

Common (experienced in less than 1 in 10 but more than 1 in 100 patients)

- Back pain
- Convulsion
- Neck pain
- A stiff or rigid neck
- Infection of the meninges
- Fatigue
- Pain, numbness or tingling (feeling of sensation of pins and needles)
- Blindness and other visual disturbances
- Hearing loss
- Persistent or extreme sleepiness
- Partial paralysis

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please inform the medical staff looking after you.

Reporting of side effects
If you get any side effects, talk to your doctor 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 DepoCyte

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

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

Store in a refrigerator (2°C – 8°C).

Do not freeze.

DepoCyte should be used as soon as possible after first opening, and should normally be used within 4 hours (stored at 18-22ºC).

DepoCyte is a sterile white to off-white-suspension. Do not use this medicine if you notice severe discolouration, a changed appearance or a defective container.

Do not throw away any medicines via wastewater. DepoCyte contains cytarabine, and should be disposed of in a manner consistent with local requirements.

6. Contents of the pack and other information

What DepoCyte contains

- The active substance is cytarabine. One ml of suspension contains 10 mg cytarabine. Each 5 ml vial contains 50 mg cytarabine
- The other ingredients are cholesterol, triolein, dioleoylphosphatidylcholine, dipalmitoylphosphatidylglycerol, sodium chloride, and water for injections.

What DepoCyte looks like and contents of the pack

DepoCyte is a white to off-white-suspension for injection supplied in a glass vial.
Each vial contains 5 ml of suspension for a single injection.
Each pack contains a single vial.

Marketing Authorisation Holder

Pacira Limited, Wessex House, Marlow Road, Bourne End, Buckinghamshire, SL8 5SP, United Kingdom.

Manufacturer

Almac Pharma Services Limited, 20 Seagoe Industrial Estate, Craigavon, Co Armagh, BT63 5QD, United Kingdom.

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

België/Belgique/Belgien
Mundipharma Comm VA.
Tél/Tel: +32 (0) 15 45 11 80
info@mundipharma.be

Lietuva
KBM Pharma OÜ
Tel. +372 733 8080
kbmpharma@kbmpharma.eu

България
ТП Мундифарма Медикъл ООД
Тел. +359 2 962 13 56/54
mundipharma@mundipharma.bg

Luxembourg/Luxemburg
Mundipharma Comm VA.
Tél: +32 (0) 15 45 11 80
info@mundipharma.be

Česká republika
Mundipharma Ges.m.b.H. Austria
Organizační složka ČR
Tel : +420 222 318 221
office@mundipharma.cz

Magyarország
Medis Hungary Kft
Információsvonal: +36 2 380 1028
info@medis.hu

Danmark
Mundipharma A/S
Tlf: +45 45 17 48 00
mundipharma@mundipharma.dk

Malta
Pacira Limited
Wessex House, Marlow Road
Bourne End, Buckinghamshire
SL8 5SP - Renju Unit
Tel: +44 (0) 1628 530554

Deutschland
Mundipharma GmbH
Tel: + 49 (0) 64 31 701-0
mundipharma@mundipharma.de

Nederland
Mundipharma Pharmaceuticals B.V.
Tel: +31 (0) 33 450 8270
info@mundipharma.nl

Eesti
KBM Pharma OÜ
Tel: +372 733 8080
kbmpharma@kbmpharma.eu

Norge
Mundipharma AS
Tlf: +47 67 51 89 00
post@mundipharma.no

Ελλάδα
Pacira Limited
Wessex House, Marlow Road
Bourne End, Buckinghamshire
SL8 5SP
Ηνωμένο Βασίλειο
Τηλ: +44 (0) 1628 530554

Österreich
Mundipharma Gesellschaft.m.b.H.
Tel: + 43 (0) 1 523 25 05
office@mundipharma.at

España
Mundipharma Pharmaceuticals, S.L.
Tel: +34 91 3821870
infomed@mundipharma.es

Polska
Mundipharma Polska Sp.z o.o.
Tel: +48(0) 22 866 87 12
office@mundipharma.pl

France
Mundipharma
Tel: +33 (0) 1 40 65 29 29
infomed@mundipharma.fr

Hrvatska
Medis Adria d.o.o.
Kolarova 7,
10000 Zagreb
Tel.: +385 1 2303 446

Ireland
Mundipharma Pharmaceuticals Limited
Tel: +353 1 2063800
oncologymedinfo@napp.co.uk

Ísland
Mundipharma A/S
Tel: +45 45 17 48 00
mundipharma@ mundipharma.dk

Italia
Mundipharma Pharmaceuticals Srl
Tel: + 39.02.318288216
Italy.InfoMedica@mundipharma.it

Κύπρος
Mundipharma Pharmaceuticals Ltd
Τηλ: +357 22 81 56 56
info@mundipharma.com.cy

Latvija
Institute of Innovative Biomedical Technology
Tel: +371 7 800810
info@ibti.lvoffice

Portugal
Companhia Portuguesa Higiene Pharma – Produtos Farmacêuticos, S.A.
Tel: +351 214 449 600
geral@ferrergrupo.com.pt

România
Mundipharma Gesellschaft m.b.H., Austria
Tel: +40 751 121 222
office@mundipharma.ro

Slovenija
Medis, d.o.o.
Tel: +386 158969 00
info@medis.si

Slovenská republika
Mundipharma Ges.m.b.H. - o.z
Tel: +421 2 63811611
mundipharma@mundipharma.sk

Suomi/Finland
Mundipharma Oy
Puh/Tel: +358 (0)9 8520 2065
info@mundipharma.fi

Sverige
Mundipharma AB
Tel: + 46 (0)31 773 75 30
info@mundipharma.se

United Kingdom
Napp Pharmaceuticals Limited
Tel: +44 (0) 1223 424444
oncologymedinfo@napp.co.uk

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.