ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lysodren 500 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg of mitotane.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White, biconvex, round, scored tablets.
They are bisected on one side and impressed "BL" over "L1" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenocortical carcinoma (ACC).

The effect of Lysodren on non functional adrenocortical carcinoma is not established.

4.2 Posology and method of administration

Treatment should be initiated and followed by a suitably experienced specialist.

Posology
Treatment in adults should be started with 2 - 3 g mitotane per day and increased progressively (e.g. at two-week intervals) until mitotane plasma levels reach the therapeutic window 14 – 20 mg/L.

If it is urgent to control Cushing's symptoms in highly symptomatic patients, higher starting doses between 4 - 6 g per day could be necessary and daily dose increased more rapidly (e.g. every week). A starting dose higher than 6 g/day is generally not recommended.

Dose adjustments, monitoring and discontinuation
Dose adjustment is aimed to reach a therapeutic window (mitotane plasma levels 14 - 20 mg/L) which ensures optimal use of Lysodren with acceptable safety. There are some data suggesting that a mitotane plasma level above 14 mg/L may result in enhanced efficacy (see section 5.1). Mitotane plasma levels higher than 20 mg/L may be associated with severe undesirable effects, including neurological toxicity, and offer no further benefit in terms of efficacy, therefore this threshold should not be exceeded. Mitotane plasma levels should therefore be monitored in order to adjust the Lysodren dose and to avoid reaching toxic levels. For further information on the sample testing please contact the Marketing Authorisation Holder or its local representative (see section 7).

Dosing should be individually adjusted based on mitotane plasma levels monitoring and clinical tolerance until mitotane plasma levels reach the therapeutic window 14 - 20 mg/L. The target plasma concentration is usually reached within a period of 3 to 5 months.

Mitotane plasma levels should be assessed after each dose adjustment and at frequent intervals (e.g. every two weeks), until the optimal maintenance dose is reached. Monitoring should be more frequent

(e.g. every week) when a high starting dose has been used. It should be taken into account that dose adjustments do not produce immediate changes in plasma levels of mitotane (see section 4.4). In addition, because of tissue accumulation, mitotane plasma levels should be monitored regularly (e.g. monthly) once the maintenance dose has been reached.

Regular monitoring (e.g. every two months) of mitotane plasma levels is also necessary after interruption of treatment. Treatment can be resumed when mitotane plasma levels range between 14 - 20 mg/L. Due to the prolonged half-life, significant serum concentrations may persist for weeks after cessation of therapy.

If serious adverse reactions occur, such as neurotoxicity, treatment with mitotane may need to be temporarily interrupted. In case of mild toxicity, the dose should be reduced until the maximum tolerated dose is attained.

Treatment with Lysodren should be continued as long as clinical benefits are observed. If no clinical benefits are observed after 3 months at optimal dose, treatment should be permanently discontinued.

Special populations

Paediatric population
The experience in children is limited.

The paediatric posology of mitotane has not been well characterised but appears equivalent to that of adults after correction for body surface area.

Treatment should be initiated at 1.5 to 3.5 g/m^2/day in children and adolescents with the objective of reaching 4 g/m^2/day. Mitotane plasma levels should be monitored as for adults, with particular attention when plasma levels reach 10 mg/L as a quick increase in plasma levels may be observed. Dose may be reduced after 2 or 3 months according to the mitotane plasma levels or in case of serious toxicity.

Hepatic impairment
There is no experience in the use of mitotane in patients with hepatic impairment, so data are insufficient to give a dose recommendation in this group. Since mitotane is mainly metabolised through the liver, mitotane plasma levels are expected to increase if liver function is impaired. The use of mitotane in patients with severe hepatic impairment is not recommended. In patients with mild to moderate hepatic impairment, caution should be exercised and monitoring of liver function should be performed. Monitoring of mitotane plasma levels is specially recommended in these patients (see section 4.4).

Renal impairment
There is no experience in the use of mitotane in patients with renal impairment, so data are insufficient to give a dose recommendation in this group. The use of mitotane in patients with severe renal impairment is not recommended and, in cases of mild to moderate renal impairment, caution should be exercised. Monitoring of mitotane plasma levels is specially recommended in these patients (see section 4.4).

Elderly patients (≥ 65 years old)
There is no experience on the use of mitotane in elderly patients, so data are insufficient to give a dose recommendation in this group. Caution should be exercised and frequent monitoring of mitotane plasma levels is especially recommended in these patients.

Method of administration
The total daily dose may be divided in two or three doses according to patient's convenience. Tablets should be taken with a glass of water during meals containing fat-rich food (see section 4.5). Patients should be advised not to use any tablets showing signs of deterioration, and caregivers to wear disposable gloves when handling the tablets.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Lactation (see section 4.6).
Concomitant use with spironolactone (see section 4.5).

4.4 Special warnings and precautions for use

Before the initiation of the treatment: Large metastatic masses should be surgically removed as far as possible before starting mitotane treatment, in order to minimise the risk of infarction and haemorrhage in the tumour due to a rapid cytotoxic effect of mitotane.

Risk of adrenal insufficiency: All patients with non functional tumour and 75% of patients with functional tumour show signs of adrenal insufficiency. Therefore, steroid replacement may be necessary in these patients. Since mitotane increases plasma levels of steroid binding proteins, free cortisol and corticotropin (ACTH) determinations are necessary for optimal dosing of steroid substitution (see section 4.8). Glucocorticoid insufficiency is more frequent, but mineralocorticoid insufficiency may also be associated and the steroid substitution may need to be adapted accordingly.

Shock, severe trauma or infection: Mitotane should be temporarily discontinued immediately following shock, severe trauma or infection, since adrenal suppression is its prime action. Exogenous steroids should be administered in such circumstances, since the depressed adrenal gland may not immediately start to secrete steroids. Because of an increased risk of acute adrenocortical insufficiency, patients should be instructed to contact their physician immediately if injury, infection, or any other concomitant illness occurs.

Monitoring of plasma levels: Mitotane plasma levels should be monitored in order to adjust the mitotane dose, particularly if high starting doses are considered necessary. Dose adjustments may be necessary to achieve the desired therapeutic levels in the window between 14 - 20 mg/L and avoid specific adverse reactions (see section 4.2). For further information on the sample testing please contact the Marketing Authorisation Holder or its local representative (see section 7).

Hepatic or renal impairment: There are insufficient data to support the use of mitotane in patients with severe hepatic or renal impairment. In patients with mild or moderate hepatic or renal impairment, caution should be exercised and monitoring of mitotane plasma levels is particularly recommended (see section 4.2).

Hepatotoxicity has been observed in patients treated with mitotane. Cases of liver damage (hepatocellular, cholestatic and mixed) and autoimmune hepatitis were observed. Liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin, and alkaline phosphatase [ALP] levels) should be periodically monitored, especially during the first months of treatment or when it is necessary to increase the dose. If AST and/or ALT are increased > 5 ULN, or ALP or bilirubin > 2 ULN, there is risk of liver injury/failure. In this case, Lysodren treatment should be interrupted. Treatment can be resumed at physician’s discretion depending on the severity of the event as well as the patient's clinical condition.

Metabolism and nutrition disorders: Regardless of Lysodren dosage, triglycerides should be monitored regularly especially in patients with or at risk of dyslipidemia (such as metabolic syndrome, alcohol abuse, high fat diet…). Triglyceride-lowering therapy and discontinuation of Lysodren may be considered in case of severe hypertriglyceridemia as it is a potential cause of acute pancreatitis.

Mitotane tissue accumulation: Fat tissue can act as a reservoir for mitotane, resulting in a prolonged half-life and potential accumulation of mitotane. Consequently, despite a constant dose, mitotane levels may increase. Therefore, monitoring of mitotane plasma levels (e.g. every two months) is also necessary after interruption of treatment, as prolonged release of mitotane can occur. Caution and close monitoring of mitotane plasma levels are highly recommended when treating overweight

patients and patients with recent weight loss.

Central nervous system disorders: Long-term continuous administration of high doses of mitotane may lead to reversible brain damage and impairment of function. Behavioural and neurological assessments should be made at regular intervals, especially when mitotane plasma levels exceed 20 mg/L (see section 4.8).

Blood and lymphatic system disorders: All blood cells can be affected with mitotane treatment. Leukopenia (including neutropenia), anemia and thrombocytopenia have been reported frequently during mitotane treatment (see section 4.8). Red blood cell, white blood cell and platelet counts should be monitored during mitotane treatment.

Bleeding time: Prolonged bleeding time has been reported in patients treated with mitotane. In some patients, in vitro bleeding time may be normal but with pathologic adenosine diphosphate (ADP)-induced platelet aggregation. This should be taken into account when surgery is considered (see section 4.8).

Warfarin and coumarin-like anticoagulants: When administering mitotane to patients on coumarin-like anticoagulants, patients should be closely monitored for a change in anticoagulant dose requirements (see section 4.5).

Substances metabolised through cytochrome P450 and particularly cytochrome 3A4: Mitotane is a hepatic enzyme inducer and it should be used with caution in case of concomitant use of medicinal products influenced by hepatic metabolism (see section 4.5).

Premenopausal women: Non-malignant ovarian macrocysts, often bilateral and multiple, have been observed with higher incidence in this population. The ovarian macrocysts may be symptomatic (e.g., pelvic pain or discomfort, vaginal bleeding or menstrual disorders) or asymptomatic. Isolated cases of complicated cysts have been reported (adnexal torsion and haemorrhagic cyst rupture). Improvement after mitotane discontinuation has been observed. Women should be urged to seek medical advice if they experience gynaecological symptoms such as bleeding and/or pelvic pain. Periodic ovarian ultrasound monitoring is recommended in premenopausal women treated with mitotane.

Paediatric population: In children and adolescents, neuro-psychological retardation can be observed during mitotane treatment. In such cases, thyroid function should be investigated in order to identify a possible thyroid impairment linked to mitotane treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Spironolactone: Mitotane must not be given in combination with spironolactone, since this active substance may block the action of mitotane (see section 4.3).

Warfarin and coumarin-like anticoagulants: Mitotane has been reported to accelerate the metabolism of warfarin through hepatic microsomal enzyme induction, leading to an increase in dose requirements for warfarin. Therefore, patients should be closely monitored for a change in anticoagulant dose requirements when mitotane is administered to patients on coumarin-like anticoagulants.

Substances metabolised through cytochrome P450: Mitotane has been shown to have an inductive effect on cytochrome P450 enzymes. Therefore, the plasma concentrations of the substances metabolised via cytochrome P450 may be modified. In the absence of information on the specific P450 isoenzymes involved, caution should be taken when co-prescribing active substances metabolised by this route such as, among others, anticonvulsants, rifabutin, rifampicin, griseofulvin and St. John's wort (*Hypericum perforatum*). Particularly, mitotane has been shown to have an inductive effect on cytochrome 3A4. Therefore, the plasma concentrations of the substances metabolised via cytochrome 3A4 may be modified. Caution should be taken when co-prescribing active substances metabolised by this pathway such as, among others, sunitinib, etoposide and midazolam and dose should be adjusted as appropriate when coadministered with mitotane.

Enzyme induction is likely to persist after discontinuation of mitotane treatment.

Medicinal products active on central nervous system: Mitotane can cause central nervous system undesirable effects at high concentrations (see section 4.8). Although no specific information on pharmacodynamic interactions in the central nervous system is available, this should be borne in mind when co-prescribing medicinal products with central nervous system depressant action.

Fat-rich food: Data with various mitotane formulations suggest that administration with fat-rich food enhances absorption of mitotane.

Hormone binding protein: Mitotane has been shown to increase plasma levels of hormone binding proteins (e.g. sex hormone-binding globulin (SHBG) and corticosteroid-binding globulin (CBG)). This should be taken into account when interpreting the results of hormonal assays and may result in gynaecomastia.

4.6 Fertility, pregnancy and lactation

Pregnancy
Data, based on a limited number of exposed pregnancies, indicate abnormalities on the adrenals of the foetus after exposure to mitotane. Mitotane has been detected in foetal cord blood. Pregnant women should be advised of a potential risk to the foetus. Animal reproduction studies have not been conducted with mitotane. Animal studies with similar substances have shown reproductive toxicity (see section 5.3). Lysodren is not recommended during pregnancy and in women of childbearing potential not using contraception.

Women of childbearing potential
Women of childbearing potential must use an effective contraception during treatment and after discontinuation of treatment as long as mitotane plasma levels are detectable, which may require several months. The prolonged elimination of mitotane from the body after discontinuation of Lysodren should be considered (see section 5.2).

Breast-feeding
Due to the lipophilic nature of mitotane, it is likely to be excreted in breast milk. Because of the potential for serious adverse reactions in the breastfed infant, breast-feeding is contraindicated while taking mitotane (see section 4.3) and after treatment discontinuation as long as mitotane plasma levels are detectable.

4.7 Effects on ability to drive and use machines

Lysodren has a major influence on the ability to drive and use machines. Ambulatory patients should be warned not to drive or use machines.

4.8 Undesirable effects

Safety data are based on literature (mainly retrospective studies). More than 80 % of patients treated with mitotane have shown at least one type of undesirable effect. Adverse reactions listed below are classified according to frequency and system organ class. Frequency groupings are defined according to the following convention: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Frequency of adverse reactions

System Organ Class	Adverse reaction		
	Very common	**Common**	**Not Known**
Infections and infestations			Opportunistic infection
Blood and lymphatic system disorders	Leukopenia Bleeding time prolonged	Anaemia Thrombocytopenia	
Immune system disorders			Hypersensitivity reactions
Endocrine disorders	Adrenal insufficiency		Thyroid disorder Hypogonadism (in males)
Metabolism and nutrition disorders	Decreased appetite Hypercholesterolemia Hypertriglyceridaemia		Hypouricaemia
Psychiatric disorders	Confusional state		
Nervous system disorders	Ataxia Paraesthesia Vertigo Somnolence	Mental impairment Polyneuropathy Movement disorder Dizziness Headache	Balance disorder
Eye disorders			Maculopathy Retinal toxicity Diplopia Lenticular opacities Visual impairment Vision blurred
Vascular disorders			Hypertension Orthostatic hypotension Flushing
Gastrointestinal disorders	Mucosal inflammation Vomiting Diarrhoea Nausea Epigastric discomfort		Salivary hypersecretion Dysgeusia Dyspepsia
Hepatobiliary disorders	Elevated liver enzymes	Autoimmune hepatitis	Liver injury (hepatocellular/cholestatic /mixed)
Skin and subcutaneous tissue disorders	Skin rash		Pruritus
Muscoloskeletal and connective tissue disorders	Muscular weakness		
Renal and urinary disorders			Cystitis haemorrhagic Haematuria Proteinuria
Reproductive system and breast disorders	Gynaecomastia		Ovarian macrocysts
General disorders and administration site conditions	Asthenia		Hyperpyrexia Generalised aching
Investigations	Blood cholesterol increased Blood triglycerides		Blood uric acid decreased Blood androstenedione decreased (in females)

	increased		Blood testosterone decreased (in females) Sex hormone binding globulin increased Blood testosterone free decreased (in males) Corticosteroid binding globulin increased Thyroxin binding globulin increased

Description of selected adverse reactions

Gastrointestinal disorders are the most frequently reported (10 to 100 % of patients) and are reversible when the dose is reduced. Some of these effects (anorexia) may constitute the hallmark of initial central nervous system impairment.

Nervous system undesirable effects occur in approximately 40 % of patients. Other undesirable central nervous effects have been reported in literature such as memory defects, aggressiveness, central vestibular syndrome, dysarthria, or Parkinson syndrome. Serious undesirable effects appear linked to the cumulative exposure to mitotane and are most likely to occur when mitotane plasma levels are at 20 mg/L or above. At high doses and after prolonged utilization, brain function impairment can occur. Nervous system undesirable effects appear reversible after cessation of mitotane treatment and decrease in plasma levels (see section 4.4).

Skin rashes which have been reported in 5 to 25 % of patients do not seem to be dose related.

Leukopoenia has been reported in 8 to 12 % of patients. Prolonged bleeding time appears a frequent finding (90 %): although the exact mechanism of such an effect is unknown and its relation with mitotane or with the underlying disease is uncertain, it should be taken into account when surgery is considered.

The activity of liver enzymes (gamma-GT, aminotransferase, alkaline phosphatase) is commonly increased. Liver enzymes levels usually normalize when the mitotane dose is decreased or temporarily interrupted or discontinued. However, autoimmune hepatitis has been reported in 7 % of patients with no other information on mechanism. Very rare serious cases of liver injury (acute hepatic failure and hepatic encephalopathy) have been observed.

Hypogonadism: Hypogonadism in males (with symptoms such as gynaecomastia, libido decreased, erectile dysfunction, fertility disorders) has been described.

Premenopausal women
Non-malignant ovarian macrocysts (with symptoms such as pelvic pain, vaginal bleeding, menstrual disorders or asymptomatic) have been described.

Paediatric population
Neuro-psychological retardation may be observed during mitotane treatment. In such cases, thyroid function should be investigated in order to identify a possible thyroid impairment linked to mitotane treatment. Hypothyroidism and growth retardation may be also observed. One case of encephalopathy has been observed in a paediatric patient five months after initiation of the treatment; this case was considered to be related to an increased mitotane plasma level of 34.5 mg/L. After six months mitotane plasma levels were undetectable and the patient recovered clinically.
Oestrogenic-like effects (such as gynaecomastia in male patients and breast development and/or vaginal bleeding in female patients) have been observed.

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

Mitotane overdose may lead to central nervous system impairment especially if mitotane plasma levels are above 20 mg/L. No proven antidotes have been established for mitotane overdose. Temporary interruption of Lysodren should be considered. The patient should be followed closely, taking into account that impairment is reversible, but given the long half-life and the lipophilic nature of mitotane, it may take weeks to return to normal. Other effects should be treated symptomatically. Because of its lipophilic nature, mitotane is not likely to be dialysable.

It is recommended to increase frequency of mitotane plasma level monitoring (e.g. every two weeks) in patients at risk of overdose (e.g. in case of renal or hepatic impairment, obese patients or patients with a recent weight loss).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: L01XX23.

Mechanism of action
Mitotane is an adrenal cytotoxic active substance, although it can apparently also cause adrenal inhibition without cellular destruction. Its biochemical mechanism of action is unknown. Available data suggest that mitotane modifies the peripheral metabolism of steroids and that it also directly suppresses the adrenal cortex. The administration of mitotane alters the extra-adrenal metabolism of cortisol in humans, leading to a reduction in measurable 17-hydroxy corticosteroids, even though plasma levels of corticosteroids do not fall. Mitotane apparently causes increased formation of 6-beta-hydroxy cholesterol.

Clinical efficacy and safety
Mitotane has not been studied in a comprehensive clinical development program. Available clinical information comes mainly from published data in patients with inoperable or metastatic adrenal carcinoma. In terms of overall survival, four studies conclude that mitotane treatment does not increase the survival rate whereas five find an increase in the survival rate. Among the latter, three studies find such an increase only in patients in whom mitotane plasma is above 14 mg/L.

Mitotane plasma levels and the possible relationship with its efficacy were studied in the FIRM ACT trial, a randomized, prospective, controlled, open–label, multicenter, parallel-group study to compare the efficacy of etoposide, doxorubicin and cisplatin plus mitotane (EDP/M) to that of streptozotocin plus mitotane (Sz/M) as first-line treatment in 304 patients. The analysis of patients who achieved mitotane levels ≥ 14 mg/L at least once in 6 six months versus patients who mitotane levels were < 14 mg/L could suggest that patients with mitotane plasma levels ≥ 14 mg/L could have an improvement in disease control rate (62.9% versus 33.5%; p< 0. 0001). However, this result should be cautiously taken since the examination of the mitotane effects was not the primary endpoint of the study.

In addition, mitotane induces a state of adrenal insufficiency which leads to the disappearance of Cushing syndrome in patients with secreting adrenal carcinoma and necessitates substitution hormonotherapy.

Paediatric population
Clinical information comes mainly from a prospective trial (n= 24 patients) in children and adolescents aged at diagnosis from 5 months to 16 years (median age: 4 years) who had an unresectable primary tumour or who presented a tumour recurrence or a metastasic disease; most of the children (75%) presented with endocrine symptoms. Mitotane was given alone or combined with chemotherapy with various agents. Overall, the disease-free interval was 7 months (2 to 16 months). There were recurrences in 40% of children; the survival rate at 5 years was 49%.

5.2 Pharmacokinetic properties

Absorption
In a study performed in 8 patients with adrenal carcinoma treated with 2 to 3 g daily of mitotane, a highly significant correlation was found between plasma mitotane concentration and the total mitotane dose. The target plasma mitotane concentration (14 mg/L) was reached in all patients within 3 to 5 months and the total mitotane dose ranged between 283 and 387 g (median value: 363 g). The threshold of 20 mg/L was reached for cumulative amounts of mitotane of approximately 500 g. In another study, 3 patients with adrenal carcinoma received Lysodren according to a precise protocol allowing fast introduction of a high dose if the product was well tolerated: 3 g (as 3 intakes) on day 1, 4.5 g on day 2, 6 g on day 3, 7.5 g on day 4 and 9 g on day 5. This dose of Lysodren was continued or decreased in function of side effects and plasma mitotane levels. There was a positive linear correlation between the cumulative dose of Lysodren and the plasma levels of mitotane. In two of the 3 patients, plasma levels of more than 14 mg/L were achieved within 15 days and in one of them levels above 20 mg/L were achieved within approximately 30 days. In addition, in both studies, in some patients, the plasma mitotane levels continued to rise despite maintenance or a decrease of the daily dose of mitotane.

Distribution
Autopsy data from patients show that mitotane is found in most tissues of the body, with fat as the primary site of storage.

Biotransformation
Metabolism studies in man have identified the corresponding acid, 1,1-(o,p'-dichlorodiphenyl) acetic acid (o,p'-DDA), as the major circulating metabolite, together with smaller quantities of the 1,1-(o,p'-dichlorodiphenyl)-2,2 dichloroethene (o,p'-DDE) analogue of mitotane. No unchanged mitotane has been found in bile or in urine, where o,p'-DDA predominates, together with several of its hydroxylated metabolites. For induction with cytochrome P450, see section 4.5.

Elimination
After intravenous administration, 25% of the dose was excreted as metabolites within 24 hours. Following discontinuation of mitotane treatment, it is slowly released from storage sites in fat, leading to reported terminal plasma half-lives ranging from 18 to 159 days.

5.3 Preclinical safety data

Non-clinical data on the general toxicity of mitotane is limited.

Reproductive toxicity studies have not been performed with mitotane. However, dichlorodiphenyltrichlorethane (DDT) and other polychlorinated biphenyl analogues are known to have deleterious effects on fertility, pregnancy and development, and mitotane could be expected to share these properties.

The genotoxic and carcinogenic potential of mitotane has not been investigated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Microcrystalline cellulose (E 460)
Macrogol 3350
Silica colloidal anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

After opening: 1 year.

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Square opaque white HDPE bottle having a thread on the mouth containing 100 tablets.
Pack size of 1 bottle.

6.6 Special precautions for disposal and other handling

This medicinal product should not be handled by persons other than the patient and his/her caregivers, and especially not by pregnant women. Caregivers should wear disposable gloves when handling the tablets.

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

7. MARKETING AUTHORISATION HOLDER

Esteve Pharmaceuticals S.A.
Passeig de La Zona Franca 109 Planta 4
08038 Barcelona
Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/273/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 April 2004
Date of last renewal: 28 April 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) https://www.emea.europa.eu/

ANNEX II

A. MANUFACTURER(S) 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(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Latina Pharma S.p.A.
Via Murillo, 7
04013 Sermoneta (LT)
Italy

or

Centre Spécialités Pharmaceutiques
76-78, avenue du Midi
63800 Cournon d'Auvergne
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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 AND THE IMMEDIATE PACKAGING

OUTER CARTON
BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Lysodren 500 mg tablets
mitotane

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 500 mg of mitotane.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet.
Bottle of 100 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral 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

Cytotoxic.
To be handled only by patients, or caregivers wearing gloves.

8. EXPIRY DATE

EXP

After opening: 1 year

9. SPECIAL STORAGE CONDITIONS

Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTORISATION HOLDER

Esteve Pharmaceuticals S.A.
Passeig de La Zona Franca 109 Planta 4
08038 Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER

EU/1/04/273/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lysodren *(Braille applies only to outer carton)*

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Lysodren 500 mg tablets
mitotane

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

What is in this leaflet

1. What Lysodren is and what it is used for

Lysodren is an antitumoral medicine that contains the active substance mitotane.

This medicine is used for the treatment of symptoms of advanced non operable, metastatic or recurrent malignant tumours of the adrenal glands.

2. What you need to know before you take Lysodren

Do not take Lysodren
- if you are allergic to mitotane or any of the other ingredients of this medicine (listed in section 6).
- if you are breast-feeding. You must not breast-feed while taking Lysodren.
- if you are being treated with medicines containing spironolactone (see "Other medicines and Lysodren").

Warnings and precautions
Talk to your doctor or pharmacist before taking Lysodren.
You should tell your doctor if any of the following applies to you:
- if you have an injury (shock, severe trauma), an infection or if you have any illness while you are taking Lysodren. Tell your doctor immediately, who may decide to temporarily stop treatment.
- if you have liver problems: Tell your doctor if you develop any of the following signs and symptoms of liver problems during Lysodren treatment: itching, yellow eyes or skin, dark urine, and pain or discomfort in the right upper stomach area. Your doctor should do blood tests to check your liver function before and during treatment with Lysodren, and as clinically indicated. Your doctor may decide to interrupt Lysodren treatment.
- if you have severe kidney problems.
- if you are using any medicines mentioned below (see "Other medicines and Lysodren").

- if you have gynaecological problems such as vaginal bleeding, menstrual disorders and/ or pelvic pain.

This medicine should not be handled by persons other than the patient and his/her caregivers, and especially not by pregnant women. Caregivers should wear disposable gloves when handling the tablets.

During treatment with Lysodren
Lysodren may temporarily lower the amount of hormones produced by your adrenal gland (cortisol) but your doctor will correct this using appropriate hormone medication (steroids).

Lysodren can cause bleeding that lasts longer than usual. If you need to have surgery or dental procedures during treatment with Lysodren, your healthcare provider will do blood tests to check for prolonged bleeding risks.

Other medicines and Lysodren
Tell your doctor or pharmacist if you are using or have recently used any other medicines, including medicines obtained without a prescription.

You must not use Lysodren with medicines containing spironolactone, often used as a diuretic for heart, liver or kidney diseases.

Lysodren may interfere with several medicines. Therefore, you should tell your doctor if you are using medicines containing any of the following active substances:
- warfarin or other anticoagulants (blood thinners), used to prevent blood clots. The dose of your anticoagulant may need adjustment.
- antiepileptics
- rifabutin or rifampicin, used to treat tuberculosis
- griseofulvin, used in the treatment of fungal infections
- herbal preparations containing St. John's wort (*Hypericum perforatum*)
- sunitinib, etoposide: to treat cancer
- midazolam, used as sedative

Lysodren with food and drink
Lysodren should preferably be taken during meals containing fat-rich food such as milk, chocolate, oil.

Pregnancy, breast-feeding and fertility
Lysodren may harm the foetus. If you are pregnant, think you are pregnant or are planning to have a baby, ask your doctor as soon as possible to know if you should stop or continue Lysodren.

If you may become pregnant, you should use an effective contraception during treatment with Lysodren and even after stopping it, ask your doctor for advice.

Because of the potential for serious adverse reactions in your baby, you must not breast-feed while taking Lysodren and even after stopping it. Ask your doctor for advice.

Driving and using machines
Lysodren has a major influence on your ability to drive and use machines. Ask your doctor for advice.

3. How to take Lysodren

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Dose and schedule
The usual starting dose for adults is 2 to 3 g (4 to 6 tablets) per day.
Your doctor may start treatment at higher doses such as 4 to 6 g (8 to 12 tablets).

In order to find the optimal dose for you, your doctor will monitor regularly the levels of Lysodren in your blood. Your doctor may decide to stop treatment with Lysodren temporarily or to lower the dose if you experience certain side effects.

Use in children and adolescents
The starting daily dose of Lysodren is 1.5 to 3.5 g/m^2 body surface area (this will be calculated by your doctor according to the weight and the size of the child). The experience in patients in this age group is very limited.

Method of administration
You should swallow the tablets with a glass of water during meals containing fat-rich food. You can divide the total daily dose in two or three intakes.

If you take more Lysodren than you should
Tell your doctor immediately if you have taken accidentally more Lysodren than you should or if a child has accidentally swallowed some.

If you forget to take Lysodren
If you accidentally miss a dose, just take the next dose as scheduled. Do not take a double dose to make up for the forgotten one.

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

4. Possible side effects

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

Tell your doctor immediately if you experience any of the following side effects:
- Adrenal insufficiency: fatigue, abdominal pain, nausea, vomiting, diarrhoea, confusion
- Anaemia: cutaneous pallor, muscular fatigability, feeling breathless, vertigo especially when standing up
- Liver damage: yellowing of the skin and eyes, itching, nausea, diarrhoea, fatigue, dark coloured urine
- Neurological disorders: movement and coordination disorders, abnormal sensations like pins and needles, memory loss, concentration difficulty, difficulty to talk, vertigo

These symptoms may reveal complications for which specific medication could be appropriate.

Side effects may occur with certain frequencies, which are defined as follows:
- very common: may affect more than 1 in 10 people
- common: may affect up to 1 in 10 people
- not known: frequency cannot be estimated from the available data

Very common side effects
- vomiting, nausea (feeling sick), diarrhoea, belly pain
- lack of appetite
- abnormal sensations like pins and needles
- movement and coordination disorders, vertigo, confusional state
- feeling sleepy, fatigue, muscle weakness (fatigue of muscle during effort)
- inflammation (swelling, heat, pain) of mucosa, skin rash
- blood disorders (bleeding time prolonged)
- increase of cholesterol, triglycerides (fats) and liver enzymes (in blood tests)

- decrease in white blood cells count
- breast overdevelopment in men
- adrenal insufficiency (may cause fatigue, abdominal pain, nausea, vomiting, diarrhoea, confusion)

Common side effects
- dizziness, headache
- peripheral nervous system disorders (association of sensory disorders, muscular weakness and atrophy, decrease of tendon reflex and vasomotor symptoms such as hot flushes, sweat and sleep disorders)
- mental impairment (such as memory loss, concentration difficulty)
- movement disorder
- decrease of red blood cells (anaemia, with symptoms such as skin pallor and fatigue), decrease in blood platelets (may make you more prone to bruising and bleeding)
- hepatitis (auto-immune) (may cause yellowing of the skin and eyes, dark coloured urine)
- difficulty of coordinating muscles

Frequency Not Known
- fever
- general aching
- flushing, high or low blood pressure, feeling of dizziness/vertigo when you suddenly stand up
- increased production of saliva
- eye disorders: visual impairment, vision blurred, double vision, distortion of images, complain of glare
- opportunistic infection
- liver injury (may cause yellowing of the skin and eyes, dark coloured urine)
- decreased uric acid in blood tests
- bladder inflammation with bleeding
- presence of blood in urine, presence of proteins in urine
- balance disorder
- distortion of the sense of taste
- impaired digestion
- ovarian macrocysts (with or without symptoms such as pelvic pain, vaginal bleeding, menstrual disorders)
- decreased androstenedione (precursor of sex hormones) in blood tests in females
- decreased testosterone (sex hormone) in blood tests in females
- sex hormone binding globulin (a protein which binds sex hormones) increased in blood tests
- corticosteroid binding globulin increased in blood tests
- thyroxin binding globulin increased in blood tests
- decreased free testosterone (sex hormone) in blood tests in males
- hypogonadism in males (with symptoms such as breast overdevelopment, libido decreased, erectile dysfunction, fertility disorders)
- allergic reactions, itching

Additional side effects in children and adolescents
In children and adolescents, thyroid problems, neuro-psychological, growth retardation and one case of encephalopathy have been observed. In addition, some signs of hormonal changes (such as breast overdevelopment in males and vaginal bleeding and/or early breast development in females) have been observed.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. 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 Lysodren

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

Store in the original package. After opening: 1 year.

Do not use this medicine after the expiry date which is stated on the carton and the bottle after EXP.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Lysodren contains
- The active substance is mitotane. Each tablet contains 500 mg of mitotane.
- The other ingredients are maize starch, microcrystalline cellulose (E 460), macrogol 3350 and silica colloidal anhydrous.

What Lysodren looks like and contents of the pack
Lysodren tablets are white, biconvex, round and scored.
Lysodren is available in plastic bottles of 100 tablets.

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Manufacturer
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or

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: https://www.emea.europa.eu/. There are also links to other websites about rare diseases and treatments.

This leaflet is available in all EU/EEA on the European Medicines Agency website.