

SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Lysodren. For information on changes after approval please refer to module 8.

1. INTRODUCTION

Malignant neoplasms of the adrenal cortex are rare; they account for 0.05 to 0.2 per cent of all cancers, and show a bimodal age distribution, with the first peak occurring before the age of 5 years and the second in the fourth to fifth decade. There is a female predominance, accounting for 55 to 85 per cent of the cases, particularly among functional tumours. Men with adrenal cortical carcinoma tend to be older than women (Third national cancer survey, National Cancer Institute, 1975).

Approximately 60 percent of patients have a functional adrenal cortical carcinoma, defined by the existence of signs of excess adrenal hormone production. Among functional tumours, Cushing's syndrome is evidenced in half of the patients and virilization in one third of them, whereas hyperaldosteronism, feminisation or the combination of Cushing's syndrome and virilization account for a minority of patients. Nearly half of adult carcinomas are non-functional, and these patients present clinically with abdominal or flank pain or as an adrenal mass incidentally discovered. Metastatic disease to the lungs, liver, or bone may cause symptoms before the primary diagnosis is made.

The staging criteria of adrenal cortical carcinoma allow identifying 4 stages (Grossman 2002, Flack et al. 1997, (Liou and Kay 2000), which actually correspond to 3 stages of the disease (Ng and Libertino 2003): local disease (stages I and II), regional disease (stage III), and advanced disease (stage IV). About 40% of patients have stage IV disease at diagnosis, and the incidences of stage I, II and III is 20% each.

Surgical resection is the only therapy that has consistently shown to prolong survival and be curative in some cases, particularly if disease is detected at early stages and local or distant metastases are absent (< 50% of patients). Radical excision with en bloc resection is the procedure of choice (ipsilateral adrenalectomy with/without nephrectomy and/or splenectomy). The recurrence rate after complete resection is 35-85%, and no adjuvant treatment (radiotherapy, chemotherapy immunotherapy or hormonal treatment) has demonstrated to be beneficial.

Resectable recurrences are usually operated on, and a number of patients remain disease-free thereafter. The role of surgery when the tumours cannot be completely excised is more controversial. A drug therapy is often administered to patients whose tumour is unresectable at presentation or at relapse and radiotherapy is only indicated as palliative treatment for patients with bone metastases. Mitotane is the most commonly prescribed medicinal product. Other chemotherapeutic agents frequently used are cisplatin, etoposide or doxorubicin (the list is not exhaustive). These are usually used in combination regimens (cisplatin-etoposide, cisplatin-doxorubicin-5-FU, ...) and are able to induce short lived objective responses in about 20-30% of patients. Their toxicity is however remarkable in this palliative setting and their impact in disease progression, survival or quality on life remain unproven.

The prognosis of adrenal cortical carcinoma tumours is generally poor in adults and somehow better in children. In a recent review of seven large series, the mean survival was 18 months. Most series showed no statistically significant differences based on patients' age, gender or tumour functional status. However, stage was an important prognostic predictor. For stages I to IV tumours, approximate 5-year survival was 30-45%, 12.5-57%, 5-18% and 0%, respectively. Surgical resection was the only therapy that significantly prolonged survival, particularly when disease was detected at stages I and II. Median survival in patients with unresectable tumours was 3 to 9 months, whereas after complete resection median survival was 13 to 28 months.

Mitotane or o,p'-DDD (1-(o-chlorophenyl)-1-(p-chlorophenyl)-2,2-dichloroethane), is an isomer of DDD, an insecticide analogue of DDT, which was shown to produce adrenal atrophy in dogs. By causing alterations in the mitochondrial function and blocking adrenal steroid 11- β -hydroxylation and altering the extra-adrenal metabolism of cortisol and androgens, mitotane acts as an adrenolytic agent. These observations led to the discovery of the potential value of mitotane in the treatment of adrenal cortical carcinoma.

Surgery seems to be the preferred option of treatment of adrenal carcinoma (whenever possible). Nevertheless, medical treatment may be necessary in case of failure of surgical intervention, when it is impossible or in case of relapse. In these circumstances, mitotane appears to be the most commonly used treatment. Nowadays, there is no authorised drug therapy for the treatment of adrenocortical carcinoma.

On 12 June 2002, mitotane was granted an orphan designation by the European Commission, based on the low prevalence of the disease (0.1 in 10,000 persons, corresponding to less than 4000 cases in the European Union), where the indication is pursued (adrenal carcinoma).

Well-established medicinal use

This Marketing Authorisation Application for Lysodren was a full marketing authorisation application. All non-clinical and clinical documentation presented in modules 4 and 5 for this application, consisted of publications. The Applicant did not provide data from own tests. The submission of bibliographical non-clinical and clinical data is justified with reference to Article 10(1)(a)(ii) of Directive 2001/83/EC, as amended and to Part II.1 of Annex I to Directive 2001/83/EC, as amended by Directive 2003/63/EC. These require that the applicant demonstrates that the constituent of the medicinal product has a well-established medicinal use, with recognised efficacy and an acceptable level of safety.

The claim of 'well-established medicinal use' of mitotane has been based on the time over which the substance has been used, on quantitative aspects of the use of the substance, the degree of scientific interest in the use of the substance, and the coherence of scientific assessments. The applicant has submitted bibliographical data covering all aspects of the safety and efficacy assessment and which reflect information available at that time. At the time when the Marketing Authorisation Application for Lysodren was submitted no epidemiological study assessing the efficacy or safety profile of this product had been published. The Applicant addressed, whenever possible, the relevance of data submitted concerning products or formulations different from the product (Lysodren) intended to be authorised in the Community. The Applicant submitted a five years Periodic Safety Update Report (for the third countries where the product is authorised covering the period from 8 July 1997 to 7 July 2002).

Overview of the development of mitotane

Mitotane was shown to produce adrenal atrophy in dogs in 1948. Mitotane has been used as an adrenolytic agent for the treatment of adrenocortical carcinoma since 1960 (Bergental, Hertz et al. 1960). Lysodren is currently approved in seven countries and marketed in six non-EU countries (these countries are Brazil, Canada, Hong Kong, Malaysia, South Korea and United States of America). Mitotane is available in Australia and New Zealand to individual patients under a SAS (Special Access Scheme).

Mitotane was granted by the European Commission on 12 June 2002 an orphan designation in the EU, based on the low prevalence of the adrenal carcinoma (0.1 in 10,000 persons, corresponding to less than 4000 cases in the European Union), where the indication is pursued.

Time over which mitotane has been used in the Community

The extent and the period over which mitotane was used in the Community is documented by the publication of clinical reports (on uncontrolled and open series of patients) treated with the product for an adrenocortical carcinoma (see table below).

Country	Bibliographical reference	Period over which the product had been used	Number of patients included in the study.
Belgium	(Van Geertruyden, De Myttenaere et al. 1980)	One patient reported to be treated at the Hôpital Brugmann, Bruxelles and Hôpital de Braine-l'Alleud, Waterloo.	Exact trade name of the product containing mitotane not specified in the publication.
France	(Luton, Cerdas et al. 1990)	The patients were referred to the Endocrine Department of the Hôpital Cochin between 1963 and 1987.	105 patients were studied (75 female and 30 male; mean age, 46 years) with adrenocortical carcinoma. Mitotane (Roussel-UCLAF) was used.
France	(Bonacci, Gigliotti et al. 1998)	Between 1993 and 1997, eighteen patients were included in this study.	These eighteen patients received mitotane. Mitotane treatment was maintained during chemotherapy in 14 patients, mitotane from Pharmacie Centrale de l'Assistance Publique-Hôpitaux de Paris was used. Authors refer to the products used in a previous published study (Luton, Cerdas et al. 1990).
France	(Teinturier, Pauchard et al. 1999)	Between 1973 and 1993, paediatric patients were studied at Saint Vincent de Paul Hospital (Paris) and at the Institut Gustave Roussi (Villejuif)	Twenty one patients received mitotane (7-12 mg/m ² /day), and an additional eighteen patients received the product after surgery (5-9 mg/m ² /day) exact trade name of the product containing mitotane not specified in the publication.
France	(Baudin, Pellegriti et al. 2001)	Since 1995, patients with ACC who were referred to the Gustave-Roussy Institute were enrolled prospectively in the study.	Twenty-four patients with adrenal cortical carcinoma were studied, mitotane from Pharmacie Centrale de l'Assistance Publique-Hôpitaux de Paris was used in this study.
France	(Icard, Goudet et al. 2001)	Between 1978 and 1997, patients with adrenal cortical carcinoma were treated in six different centres in France (Caen, Lille, Paris and Marseille). Study conducted by the French Association of Endocrine Surgeons. Preliminary results of this study were reported in 1992 (Icard, Chapuis et al. 1992).	One hundred and thirty five of the patients were treated with mitotane, exact exact trade name of the containing mitotane not specified in the publication.

France	(Andres, Vinzio et al. 2001)	Case report of a patient treated in Strasbourg.	Exact trade name of the product containing mitotane not specified in the publication.
Germany	(Kornely and Schlaghecke 1994)	Case report of a female treated in the 1980's the Heinrich Heine Universität, Düsseldorf Hospital.	Case report of a woman treated with mitotane, exact trade name of the product containing mitotane not specified in the publication.
Greece	(Ilias, Alevizaki et al. 2001)	Two patients were treated in the first endocrine section "Alexandra" University Hospital, Athens.	Case report of two patients treated for more than ten years with mitotane, exact trade name of the product containing mitotane not specified in the publication.
Italy	(Barzon, Fallo et al. 1997)	These patients were referred to the Division of Endocrinology of the University of Padova between 1978 and 1995.	Forty-five patients with adrenocortical carcinoma (13 non-functioning and 32 functioning carcinomas) were retrospectively studied. Lysodren (Bristol Myers Squibb) was used.
Italy	(Berruti, Terzolo et al. 1998)	The study began in 1993 in a single institution in Italy and from July 1994 onwards became an Italian multicentre Phase II trial. The study was conducted until June 1997 by the Italian Group for the Study of Adrenal Cancer.	Twenty-eight patients (18 women and 10 men; median age, 47 years; range, 27-65 years) were enrolled in the study.
Italy	(Terzolo, Pia et al. 2000)	From 1994 to 1999 fifteen patients with adrenal cortical carcinoma were treated with mitotane in the Dipartimento di Medicina Interna, Università di Torino.	Eight patients with adrenocortical cancer were included in the study, Lysodren (Bristol Myers Squibb) was used.
Italy	(Favia, Lumachi et al. 2001)	From 1980 until 1998, 31 patients with adrenal cortical carcinoma underwent adrenalectomy in the Endocrine Surgery Unit, Department of Surgical and Gastroenterological sciences, University of Padua, Padova.	These thirty one patients were subsequently treated with mitotane, exact trade name of the product containing mitotane not specified in the publication.
The Netherlands	(van Seters and Moolenaar 1991)	Precise period not specified in the article.	Four patients treated in the Department of Endocrinology, University Hospital, Leiden were included in this study, exact trade name of the product containing mitotane not specified in the publication.

The Netherlands	(Bollen and Lanser 1992)	Case report of a patient treated in the Departement of Neurology, University Hospital, Leiden.	One patient is reported to have been treated with mitotane (exact trade name of the product not specified).
The Netherlands	(Haak, Hermans et al. 1994)	Ninety-six patients with adrenal cortical carcinoma were evaluated and followed-up in the Department of Endocrinology of the University Hospital of Leiden from 1959 until 1991. Forty two patients described in a previous study are included in this publication	Ninety-six patient were treated with mitotane (Calbiochem and Bristol-Myers).
The Netherlands	(Feller, Hoekman et al. 1997)	Case report of a patient with adrenal cortical carcinoma treated in the Free University Hospital, Boelelaan.	Exact trade name of the product containing mitotane not specified in the publication.
Sweden	(Khan, Imam et al. 2000)	Over the past 20 years before the article was published (2000), the Departments of medicine, surgery and pathology of the University Hospital in Uppsala and the department of Surgery, Karolinska Hospital in Stockholm evaluated and treated 40 patients with adrenal cortical carcinoma.	A phase II study was conducted in 40 patients with adrenal cortical carcinoma, Lysodren (Bristol Myers Squibb) was used.
Sweden	(Khorram-Manesh, Ahlman et al. 1998)	Eighteen consecutive patients were treated at our unit over a 22-year period (1975-1997) in the Sahlgrenska University Hospital in Göteborg.	These 18 patients were treated with mitotane, exact trade name of the product containing mitotane not specified in the publication.
United Kingdom	(Hague, May et al. 1989)	Case reports of two patients treated in the Royal Hallamshire Hospital, Sheffield between 1974 and 1982.	These two patients received mitotane, exact trade name of the product containing mitotane not specified in the publication.
United Kingdom	(Maher, Trainer et al. 1992)	Series of patients treated with mitotane since 1982 in the Hammersmith Hospital (MRC lipoprotein team) and St Bartholomew's Hospital in London.	Two of these patients had adrenal cortical carcinoma and received mitotane. Exact trade name of the product containing mitotane not specified in the publication.

The table above shows that the first documented use of mitotane in the Community is dating back from 1959 in the Netherlands (Haak, Hermans et al. 1994). Apart from some isolated cases of lasting responses, the efficacy of mitotane in bringing about objective tumor regression has been explored in large retrospective studies conducted for some of them in EU countries. Since the beginning of the nineties, the studies published in the scientific literature included large series of patients treated by mitotane. In France, Luton et al. studied the benefit of mitotane administration in 105 patients (75 female and 30 male; mean age, 46 years) with adrenocortical carcinoma who were referred to this

hospital between 1963 and 1987 (Luton, Cerdas et al. 1990). In Italy, the survival rate of forty-five patients treated or not with adjuvant with mitotane was studied between 1978 and 1995. In the Netherlands, the use is documented in a large series of patients for a period of time exceeding forty years (Haak, Hermans et al. 1994). Mitotane has been used in Sweden for more than 20 years (Khan, Imam et al. 2000) and in the United Kingdom for approximately 30 years.

Most of these articles do not mention the exact trade name of the product used in the studies. However, Lysodren is explicitly quoted in four of the studies (Haak, Hermans et al. 1994; Barzon, Fallo et al. 1997; Khan, Imam et al. 2000; Terzolo, Pia et al. 2000). None of these articles explain the method of access by which the product was made available to the patients.

Bristol Myers Squibb sent a letter to the Applicant indicating that no change has been made to the Lysodren formulation since July 1970.

The Applicant has been able to get more information on the formulation used in the clinical trials after contacting the authors of the articles:

- All investigators from the USA have used Lysodren, which is the only commercially available formulation in this country, and references reviewed in the present review encompass approximately 500 patients.
- In the EU, papers corresponding to the following references of the present application have used Lysodren with certainty (personal confirmation by the authors to the Applicant, or indication in the publication):
 - o Ilias et al. in Greece.
 - o Terzolo et al. and Beruti et al. in Italy;
 - o Barzon et al. in Italy
 - o Ahlman et al. in Sweden;
 - o Khan et al. in Sweden;
 - o Haak et al. in the Netherlands;

Finally, five years Periodic Safety Update Report (PSUR) submitted to the third countries were Lysodren is authorised and covering the period from 8 July 1997 until 7 July 2002 was included in the Marketing Authorisation Application for Lysodren. This PSUR contained spontaneous adverse drug reaction reports observed in the EU confirming that mitotane is currently used in the EU for the treatment of adrenocortical carcinoma.

In conclusion, the Applicant mentioned that the product was currently used and prescribed in compassionate use programmes in several EU member states. The Applicant did not provide other evidence than the articles published in the scientific literature (i.e. it is mentioned in the articles published in France that mitotane was provided by the Pharmacie Centrale des Hôpitaux de Paris which belonged to the Assistance Publique not to a Pharmaceutical Company) and the Periodic Safety Update Report to support this claim but these elements of information confirm the existence of a compassionate use in the EU. Some CPMP members confirmed the existence of compassionate use programmes supervised by their National Competent Authority during the discussions at the CPMP.

Quantitative aspects of the use of mitotane

Adrenocortical carcinoma is a rare tumor, its true incidence was estimated to be approximately between 0.5 and 2 cases per million per year according to the Third National Cancer Survey conducted in 1975 (National Cancer Institute 1975, Finnish Cancer Registry and National Board of Health and Welfare, the Cancer Registry: cancer incidence in Sweden 1984 (the last two references are quoted in Barzon, Fallo et al. 1997). Therefore, assuming an annual incidence of a maximum of 2 cases/million persons per year, in the European Union (350 million inhabitants) an estimated 700 new patients per year may potentially benefit from a treatment with mitotane.

Based on this incidence and taking into account all stages of the disease, considering that the 5 years and 10 years survival of the patients are respectively 35 and 20% (Pommier and Brennan 1992), the

calculated prevalence of adrenal cortical carcinoma can be estimated to a maximum of 0.1 cases per 10,000 inhabitants. Extrapolating to the European Union population (377 million in 2001), the estimated number of patients with adrenal cortical carcinoma is approximately equal to 3,770 patients.

The calculation of the estimate of the number of patients treated with mitotane in the EU was based on two sources of information: the articles published in the scientific literature and the worldwide sales figures. This estimate has to be put into perspective with the incidence and prevalence of the disease. None of these sources can provide an exact estimate of the number of patients who benefited from a treatment with mitotane. The number of patients reported in the articles probably suffers from an underestimation of the real number of patients treated with the product; in addition these worldwide sales figure only concern Lysodren (and no other mitotane containing medicinal products). The estimate based on the sales figures is made under some assumptions concerning the dose administered to the patients and the duration of treatment, both dose and duration and treatment are not known with certainty.

The Applicant estimated that approximately 665 patients with adrenal cortical carcinoma were reported in the literature and were treated with mitotane since 1959 (i.e. more than 10 years) in the European Union. The five years Periodic Safety Update Report covering the period from 8 July 1997 until 7 July 2002 contained an estimate of the exposure to mitotane in the EU based on the bulk of worldwide sales. Assuming that all patients are adults with normal hepatic function receiving mitotane for inoperable adrenal cortical carcinoma, and that each patient received 10 grams daily for 365 days, the Applicant estimated that slightly more than 1,700 patients benefited from a treatment with mitotane a year in the United States of America and Canada (Lysodren is authorised in these two countries) over the period covered by the PSUR. From the previous five years Periodic Safety Update Report covering the period from 1992 until 1997, the Applicant estimated that 991 patients were treated with mitotane a year in the USA and in Canada. Using the same bulk worldwide sales and based on the estimates of the number of patients treated in the USA and in Canada, the Applicant estimated that more than 2,500 patients might have benefited from a one-year treatment by mitotane in the last 10 years in the EU.

In conclusion, the data published in the peer-reviewed scientific literature demonstrates that an estimated 665 patients with adrenal cortical carcinoma were treated with mitotane since 1959 (i.e. more than ten years) in the European Union. The sales figures included in the PSUR showed that approximately 250 patients-year may benefit from a treatment with Lysodren in the community. The incidence and prevalence of the disease in the EU suggest that the estimated number of patients who may potentially benefit from a treatment with mitotane in the EU is approximately 700 new patients per year.

Scientific interest

A bibliographical research made in MEDLINE on the criteria “mitotane”, “o,p'-DDD” combined with “adrenocortical carcinoma” showed that 529 and 549 articles referencing mitotane or o,p' DDD had been listed in this database. The combination of two criteria “mitotane” or “o,p'-DDD” with “adrenocortical carcinoma” showed that 98 and 118 articles containing these key words were listed in the database. These articles illustrate that over the past forty years, several teams of worldwide medical researchers tried to define the place of mitotane (alone or in combination with other chemotherapeutic agents) in the treatment of adrenal cortical carcinoma, to assess its efficacy on the control of hormonal secretion and its possible effect on overall survival. Finally, during the past 10 years some teams tried to establish a possible pharmacokinetic/pharmacodynamic relation for mitotane. The clinical relevance of the results of the data published in the literature and its implications on the use of mitotane in the treatment of adrenal cortical carcinoma are further discussed in the clinical efficacy and safety parts of this report.

Coherence of scientific assessments

The coherence of scientific assessment is further discussed in the clinical efficacy/clinical safety sections of this report. As stated above, the exact indication of mitotane in the treatment of adrenal cortical carcinoma has to be defined. However, since its first use in the treatment of patients with

adrenal cortical carcinoma in 1960 the published literature consistently insisted on the potential therapeutic interest of this product in the treatment of patients with adrenal cortical carcinoma in adults (see for example (Luton, Cerdas et al. 1990; Pommier and Brennan 1992; Haak, Hermans et al. 1994; Barzon, Fallo et al. 1997; Khorram-Manesh, Ahlman et al. 1998; Kasperlik-Zaluska 2000; Terzolo, Pia et al. 2000; Baudin, Pellegriti et al. 2001; Favia, Lumachi et al. 2001), or in children (Teinturier, Pauchard et al. 1999; Ciftci, Senocak et al. 2001).

Discussion on ‘well-established medicinal use’

The Applicant submitted an Application in which all the contents of the dossier relating to safety and efficacy of the product were bibliographical. In addition, the Applicant demonstrated that the use of mitotane is well established in the medical practice in a known indication (i.e. adrenocortical carcinoma) with a strength and a pharmaceutical form in which mitotane has always been used, in view of the period of time over which it has been used and the information publicly available about its safety and efficacy (i.e. since 1960).

The applicant has submitted the relevant literature covering all aspects of the safety and efficacy assessment, taking into account pre- and post-marketing studies and published scientific literature on the experience with mitotane. The use of bibliographic reference to the experience with mitotane to support the efficacy and safety profile has been justified satisfactorily. The relevance of the data submitted which concern a product different from Lysodren has been addressed satisfactorily.

Systematic use of mitotane in the Community has been documented for more than ten years, starting in 1960. Ever since, patients with adrenal cortical carcinoma were treated on compassionate use programmes and in clinical trials trying to establish the clinical benefit that may be obtained with mitotane and the existence of a possible pharmacokinetic/pharmacodynamic relation with this product.

The exact indication of mitotane in the treatment of this disease has to be defined. Although the studies published with mitotane were most of the time open, non-randomised, uncontrolled studies including at best a limited number of patients (50-100), the articles published since the sixties, and more recent works published in the nineties, established that mitotane is clinically beneficial for the patients with adrenal cortical carcinoma.

In conclusion, mitotane (the active substance contained in Lysodren) has a well established medicinal use, with recognised efficacy and an acceptable level of safety (see the scientific discussion included in the non-clinical and clinical parts of this report), as demonstrated by the time over which the substance has been used, quantitative aspects of the use of the substance, the degree of scientific interest in the use of the substance, and the coherence of scientific assessments.

2. Chemical, pharmaceutical and biological aspects

Composition

This product is presented in the form of tablets containing 500mg of the active substance mitotane, in a matrix of microcrystalline cellulose and corn starch, with polyethylene glycol 3350 and colloidal silicon dioxide as lubricant and glidant respectively. The tablets are packed in a primary container of HDPE with a metal closure.

Active Substance

The chemical name of mitotane is 1-chloro-2-[2,2-dichloro-1-(4-chlorophenyl)ethyl]benzene. It is a white to off-white crystalline powder, having a slight, aromatic odour. It is practically insoluble in water, soluble in alcohol, ether, hexane and in fixed oils and fats. These properties underline the effect of the particle size and physical form on the dissolution and hence the bioavailability of the active substance and therefore need to be tightly controlled to ensure the clinical safety and efficacy of the medicinal product. Mitotane is an ‘established’ substance which is the subject of a monograph in the USP, and full information has been provided in the form of an EDMF from the manufacturer.

Manufacture

Synthesis is a simple process starting from 2-chlorobenzaldehyde, chloroform and monochlorobenzene. The manufacturing process is carried out in 5 steps (three of them include chemical reactions and the other two correspond to recrystallizations).

The chemical structure has been briefly characterised by spectroscopic means especially GC-MS, considered sufficient in this case, as it is monographed in the USP.

Minimal toxicology data permit the qualification of the impurities and residual solvents specified at the limits proposed. However, the applicant has justified the impurity levels from a safety point of view and taking into account the therapeutic indication of the product and its use in Europe for more than 30 years, it may be considered in general that there are no additional safety concerns arising from impurities in the use of mitotane for the therapeutic indication proposed.

Specification

The active substance specification includes relevant tests for identity (IR, UV), assay (GC), dimeric related substance (HPLC), residual solvents etc. The routine tests are performed in accordance with the USP monograph. The additional in house analytical methods have been adequately validated. However, the omission of relevant tests for relevant physical properties particularly particle size was noted and recommended to be resolved after the opinion as a followup measure.

Other ingredients

All materials used are of non-animal origin and comply with Eur. Ph requirements. Magnesium stearate is of vegetable origin.

The tablets are packaged in white high-density polyethylene (HPDE) bottle closed with a screw metal closure system.

Stability

Long term and accelerated stability studies have been carried out according to the CPMP/QWP/556/96 Guideline. Four batches have been studied. Taking into account the results submitted, it could be concluded that no significant changes have occurred in the active substance content.

However, there is some doubt as to whether the analytical methods can be regarded as stability indicating. The proposed re-test period of 3 years is not acceptable since degradation products have not been controlled, and hence the active substance should be tested immediately before use in the manufacturing of the finished product, until such time as a validated retest period can be agreed.

Medicinal Product

Product development and finished product

Limited data have been provided for the development pharmaceuticals. However this could be accepted based on the fact that the medicinal product is well known and has been marketed in the EU for many years.

The manufacturing process for the finished product is a conventional process consisting of the following steps: milling of the drug substance and blending it with microcrystalline cellulose. Milling and blending of the mixture with the remaining ingredients, slugging, screening, blending of the slugs and finally compressing. The process is monitored by appropriate in process controls.

The process validation of Lysodren tablets was performed on three production batches. The validation data concern critical parameters like the blending time and the tableting operation. The results obtained confirm the suitability of the process to produce a product of consistent quality that meets the pre-defined acceptance criteria.

Product specification

The product specifications include tests by validated methods for the description, uniformity of content (UV), identification (IR), disintegration, loss on drying, assay (UV, HPLC) and impurities (HPLC). The limits for each specification test are supported by data derived from stability studies. However, according to ICH guidelines since the active substance is practically insoluble in water the

relationship between disintegration and dissolution needs to be further investigated to guarantee the release of the active substance. This issue will be addressed as a follow up commitment.

Batch analysis data from six stability and one commercial scale batches of the finished product have been provided. All batches met the test limits as defined in the release specification.

Stability of the product

Three batches of the finished product in the proposed for marketing packaging have been placed under stability studies in long term (25°C, 60%RH) and accelerated conditions (40°C, 75%RH) according to ICH guidelines for up to two years. Results from supportive stability studies on three batches packaged in glass bottles and stored in long term conditions have also been presented.

The tests used to evaluate the product at the end of shelf life were the routine ones (except uniformity of content and identification) and two new tests: loss on drying and impurities determination. All methods employed were stability indicating.

All the results from the stability and supportive batches were within specifications. Based on the results of the above-mentioned studies it has been concluded that the proposed shelf life for the commercially packaged product under the conditions specified in the SPC is acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Despite the fact that this is an established substance described in the USP, some deficiencies in the quality dossier have been identified at the time of the CPMP opinion. The most important is perhaps the absence of physical characterisation and routine control of such a poorly soluble active substance. It may be unethical to perform bioavailability studies in humans with such a toxic substance in order to confirm *in vitro* – *in vivo* correlations. On the other hand, this makes it all the more necessary to fully control as many *in vitro* characteristics as possible, especially the physical ones, by means of relevant and validated methods.

A number of other minor quality issues were also not resolved at the time of the opinion.

On balance, the CPMP has reached their opinion on the basis of an ‘overall’ benefit/risk balance, taking into account the clinical usefulness of this product in the proposed indication, and accepting that some quality deficiencies have not been fully resolved at the time of the opinion. Consequently the applicant has been required to give a commitment to resolve these outstanding quality concerns within a defined timeframe, as post-opinion followup measures.

3. Toxicopharmacological aspects

Introduction

Lysodren contains the active substance mitotane or o,p'-DDD (1-(o-chlorophenyl)-1-(p-chlorophenyl)-2,2-dichloroethane). Mitotane is an isomer of an insecticide, DDT or 1,1,1-trichloro-2,2-bis(4chlorophenyl)ethane (p,p'-DDD). The potential of mitotane to affect the adrenals was first noted by Nelson and Woodard (1948); these authors, working with technical grade DDD, observed adrenocortical atrophy in dogs. Subsequent studies showed that the active component was o,p'-DDD, an impurity in technical grade product.

Pharmacology

Since these initial observations, several publications confirm the adrenalytic activity of mitotane, particularly in dogs. Histological examination showed a disruption of normal cellular structure and arrangement in the innermost zones of the adrenal cortex (zonas fasciculata and reticularis). The earliest observable ultrastructural change in the dog adrenal cortex was the swelling, dissolution and rupture of mitochondria in the zona fasciculata-reticularis area. These changes were correlated with a reduction of the adrenal output of 17-hydroxy steroid and an inhibition of ACTH-induced steroid production.

Studies on the mechanism underlying this action on the adrenals have suggested metabolism within the adrenals to generate reactive intermediates, which are capable of covalent binding to mitochondrial macromolecules. Thus, *in vitro* studies with bovine adrenal cortex homogenates, as well as those of dog, rat and human, identified 2,4-dichlorodiphenyl acetic acid (*o,p'*-DDA) as a metabolite of mitotane. It was demonstrated that the mitochondrial fraction of dog adrenal cortex homogenates were responsible for the metabolism of mitotane and generation of *o,p'*-DDA. Moreover, metabolism of mitotane in adrenal mitochondria was seen to correlate with the generation of covalent binding species. By correlating the generation of *o,p'*-DDA and covalent binding by adrenal homogenates across different species with the recognized sensitivity of these species to the adrenolytic effect of mitotane and comparing the generation of the corresponding DDA isomers from mitotane and its *m,p'* and *p,p'* isomers, data emerged consistent with an acyl chloride being the reactive intermediate, leading to both the DDA metabolite and binding to adrenal cortical bionucleophiles.

In addition to these effects within the adrenal gland, mitotane also induces enzymes involved in the metabolism of drugs that could affect the levels of circulating steroids. Enhanced cortisol metabolism has also been reported in rats and guinea - pigs.

Studies with well-characterised cell lines as regards genotype and biochemistry are limited. This lack of data can be justified taking into account the clinical experience.

In vivo studies to assess the activity of mitotane in different tumour cell lines as requested in the Guideline CPMP/SWP/997/96 (Note for Guidance on the pre-clinical evaluation of anticancer medicinal products) have not been conducted. The lack of such data can be justified taking into account the clinical experience gathered with this product over the past 30/40 years.

Primary pharmacodynamics (in vitro/in vivo)

Hart et al (1973) studied the effects in dogs of single intravenous doses of 60 mg/kg of mitotane (*o,p'*-DDD) and its *m,p'*- and *p,p'*-isomers on ACTH-induced steroid production and histology of the adrenal cortex. All 3 compounds eventually inhibited ACTH-induced steroid production but the order of onset of inhibition was *m,p'*-DDD>mitotane>*p,p'*-DDD with inhibition reaching 50% of control values at 27 minutes, 87 minutes and 4-18 hours, respectively. The order of onset of histological and ultrastructural changes within the adrenals was also in the same order. There was a marked temporal correlation between the percentage inhibition of ACTH-induced steroid production, the disruption of normal cellular structure and arrangement in the zonae fasciculata and reticularis, and the severity of the DDD-induced mitochondria damage in the cells of the inner two zones of the adrenal cortex by each of the 3 isomers of DDD. The ultrastructural damage to mitochondria was detected prior to the observation of histological lesions. Cai et al (1995) studied the same three isomers in bovine adrenocortical homogenates for their transformation into the corresponding bis-dichlorodiphenyl acetic acid (DDA) and the generation of covalent binding species. The order of both DDA formation and covalent binding was mitotane>*m,p'*-DDD>*p,p'*-DDD. Moreover, the effects of the three isomers on cell growth and cortisol production with the human adrenocortical carcinoma cell line, NCI H-295, followed the same order as their DDA formation and tissue binding. In addition to these data correlating effect and covalent binding across isomers of mitotane, as mentioned above, Martz and Straw (1980) correlated covalent binding *in vitro* with the recognized differences in susceptibility of different species to the adrenolytic effect of the drug. Thus, levels of metabolism and covalent binding of ¹⁴C-*o,p'*-DDD measured in human adrenal mitochondria were intermediate between levels measured in dogs and rabbits and those measured in the least responsive species, i.e., rats and guinea pigs. Rabbits are moderately sensitive to the adrenocorticolytic effect and rats are essentially unresponsive.

Taken together, these data are supportive of the formation of reactive metabolites within the adrenal cortex, leading to covalent binding, suppression of adrenal function and the observed histological changes.

Studies of mitotane metabolism *in vivo*, as discussed further below, identified 2,4-dichlorodiphenyl acetic acid (*o,p'*-DDA) as a major metabolite of mitotane. This was also observed in *in vitro* studies with bovine adrenal cortex homogenates (Cai et al, 1995), as well as those of dog, rat and human (Cai

et al, 1995). Working with perfused dog adrenals *in vitro*, Sinsheimer and Freeman (1987) also identified *o,p'*-DDA as a metabolite. Martz and Straw (1977) demonstrated that the mitochondrial fraction of dog adrenal cortex homogenates were responsible for the metabolism of mitotane and generation of *o,p'*-DDA, whilst the microsomal and soluble fractions were inactive. Examining possible routes to generate *o,p'*-DDA from mitotane, Cai et al (1995) proposed that there is hydroxylation of the methane hydrogen followed by spontaneous dehydrohalogenation leading to a reactive acyl chloride which subsequently transforms into *o,p'*-DDA in the presence of water. The reactive acyl chloride could lead to both DDA metabolite formation and binding to adrenal cortical bionucleophiles.

Touitou et al (1978) examined human adrenal glands *in vitro*, from both mitotane treated and untreated patients with Cushing's syndrome (adrenal adenomas, hyperplasias or carcinoma) and from normal subjects who died following road accidents (control adrenals). As compared to adrenals from untreated Cushing's patients, those from mitotane treated patients produced markedly reduced quantities of cortisol and cortisone from 11-deoxycortisol (1.1-3.4 and 0.5-0.9% conversion of precursor to cortisol and cortisone, respectively, as compared to 34-64 and 2.5-7.3% in untreated patients; conversion in control adrenals were 11-12 and 1.5-2.2%). Synthesis of aldosterone and 18-hydroxycorticosterone from corticosterone were also reduced in adrenals from treated patients. These data are consistent with inhibition of both 11 β -hydroxylase and 18-hydroxylase activities Hart and Straw (1971) and Hart et al (1971) also showed inhibition of 11 β -hydroxylase activities, but also suggested an inhibitory effect on the transformation of cholesterol into pregnenolone.

Overall, these data are consistent with formation of a reactive metabolite within the adrenal gland and covalent binding to macromolecules resulting in an inhibitory effect on steroid synthesis. Moreover, it is clear from the histological evidence that this metabolism within the adrenal gland results in a targeted adrenolytic effect. However, in addition to these effects within the adrenal, mitotane also induces drug metabolizing enzymes, which could affect the levels of circulating steroids. Kupfer et al (1964) treated guinea pigs with 300 mg/kg/day of mitotane intraperitoneally for 5 days followed by 50 mg/kg/day for 7 days. An initial fall in urinary cortisol levels was seen without any concomitant effect on cortisol metabolites. This progressed on continued treatment to a sustained decrease in cortisol levels with an increase in metabolite levels; in particular, there was an increase in 6 β -hydroxy cortisol, an inactive metabolite of cortisol. A similar increase in urinary 6 β -hydroxycortisol excretions has been reported in mitotane treated humans (Bledsoe et al cited by Kupfer & Peets, 1966). Enhanced cortisol metabolism has also been reported in the rat (Kupfer & Peets, 1966), together with a more general liver enzyme induction as shown by effects on barbiturate metabolism (Kupfer & Peets, 1966; Straw et al, 1965). However, these effects in rat and guinea pig were seen in species, which are resistant to the adrenolytic effects of mitotane. Similar inducing effects have been reported for *p,p'*-DDD (Azarnaoff et al, 1966).

Impact on the adrenals

The original observations of Nelson and Woodard (1948; 1949) arose from a study in eleven dogs, which received doses of technical grade DDD of 50 to 200 (usually 50 or 80) mg/kg/day orally for periods of 1 to 38 months. Ten of the animals died or were sacrificed during this period; an unusually consistent and severe atrophy of the adrenal cortex was observed in each animal at post-mortem. Histological examination of the adrenals showed the adrenal cortical parenchyma to be one-third to one-half its usual thickness, with much distortion of the normal architecture and alteration of the normal cellular appearances. The adrenal medulla appeared unaffected. These authors also commented (Nelson & Woodard, 1948) that rats and monkeys given DDD did not show the same changes, nor were they seen in dogs administered the related insecticide DDT.

Kaminsky et al (1962) administered 200 mg/kg/day of technical grade DDD to dogs and followed the effects of DDD during the first few days of administration by a combination of adrenal biopsy and examination of adrenals after sacrifice. The earliest ultrastructural change in the adrenal cortex was observed in the mitochondria. Thus, twelve hours after the first dose, mitochondria in the zona fasciculata began to undergo dissolution and by twenty-four hours the mitochondria of the zona fasciculata were essentially destroyed with only remnants of mitochondrial membranes remaining. After 2 and 4 days treatment, findings were similar but more severe, and by 12 days the cells of the zona fasciculata were shrunken, with abnormal nuclei, altered cytoplasmic lipid droplets and sparse

intracellular organelles. At this time the zona glomerulosa was also abnormal with swollen mitochondria and abnormal lipid droplets, but this area was less severely affected than the zona fasciculata. In 2 dogs in which treatment was stopped after 3 doses, the adrenals appeared almost normal 12 weeks later.

The above findings relate to studies carried out with technical grade DDD. Nichols and Hennigar (1957) and Cueto and Brown (1958) worked with technical DDD and its fractions and identified *o,p'*-DDD (mitotane) as the active fraction, whilst purified DDD, the *p,p'*-DDD isomer, was inactive. In the experiments of Cueto and Brown (1958), 4 mg/kg/day of mitotane induced changes in the adrenals of dogs and inhibited the 17-hydroxy corticosteroid response to administered ACTH.

Vilar and Tullner (1959) administered 5 to 100 mg/kg/day of mitotane to dogs for periods of 2 to 6 days. Whilst the 5-mg/kg/day doses were inactive, the higher doses produced histological changes within the zonas fasciculata and reticularis, and did not affect the zona glomerulosa; these changes correlated with a decreased distribution of 3 β -hydroxy sterols (as detected by the digitonin reaction) in these areas. Furthermore, the adrenal venous output of 17-hydroxy steroids was reduced, both basal output and in response to ACTH injection. ACTH failed to alter the low secretion rate. Even in the presence of minimal histological lesions, the output of 17-hydroxy steroids was reduced to levels previously observed in the same laboratory in the acutely hypophysectomized dog. Komissarenko et al (1968) confirmed these findings in a study involving 30 days administration of 50 or 100 mg/kg/day of mitotane to dogs. Administration for one week decreased plasma cortisol to unmeasurable levels and completely suppressed the corticosteroid response and eosinopenic reaction to ACTH injection. Post-mortem examinations confirmed adrenal atrophy, with the zona reticularis being less affected than other areas of the cortex. Whilst the 50 mg/kg/day dose was satisfactorily supported by the animals, the 100 mg/kg/day dose caused death after 2-3 weeks treatment with muscular weakness, rejection of food, rapid emaciation, hypothermia, decrease of blood pressure and what are described as "other symptoms of adrenocortical insufficiency". Hart et al (1973) showed inhibition of ACTH-induced steroid output and ultrastructural changes in the adrenals within 2 hours of intravenous injection of 60 mg/kg to dogs.

These studies, therefore, confirm and extend the original observations of Nelson and Woodard that DDD, through its active component mitotane, causes adrenal cortical atrophy in the dog. The studies focused on the dog, the species utilized by Nelson and Woodard, but these authors had also commented on the lack of adrenolytic activity of DDD in the rat. No changes were seen in the adrenals of rats in the one month repeated dose toxicity study at dose levels of 0, 75, 150 and 300 mg/kg/day of mitotane, as discussed in Section IV.2, and Fregly et al (1968) reported no effect on adrenal weight in rats after 6 weeks dosing with 68 or 182 mg/kg/day. Although Jensen et al (1987) reported mitochondrial destruction in the adrenal zonas fasciculata and reticularis, with no effect on the zona glomerulosa after 14 days intraperitoneal administration of 300 mg/kg/day of mitotane to guinea pigs, these observations could not be confirmed by Schteingart et al (1993).

As discussed below, several studies have addressed the possible mechanism of action of mitotane in producing these changes in adrenal function. Data indicate generation of reactive metabolites within the adrenals resulting in covalent binding

Secondary pharmacodynamics

The Applicant did not submit any secondary pharmacodynamic studies. However, as described above mitotane appears to exert its therapeutic effect in adrenal carcinoma and Cushing's syndrome through a dual action with an adrenolytic effect, which is restricted to susceptible species and the consequence of metabolism within the adrenals and generation of a reactive intermediate, and an induction of liver cortisol metabolism towards inactive metabolites, an effect which is more widely observed across species. Therefore, the pharmacodynamic properties of mitotane were considered to be known.

Safety pharmacology

The Applicant did not submit any safety pharmacology studies. Taking into account that mitotane has been used for several decades, the safety profile of mitotane can be considered to be characterised through the therapeutic use.

Pharmacodynamic drug interactions

The Applicant did not submit any pharmacodynamic drug interactions studies. The interaction profile of mitotane is characterised and is described in the relevant sections of the summary of product characteristics for Lysodren.

Pharmacokinetics

Absorption- Bioavailability

Moy (1961) has described the pharmacokinetics of mitotane in a series of patients treated with various doses of drug for different durations. Overall, he estimated that approximately 35 to 40% of the product was absorbed after an oral administration.

Limited data are available on plasma levels of mitotane in animals. Watson et al (1987) studied absorption of mitotane in dogs after a single oral dose under various conditions (see Table below). Mitotane was given by mouth at 50 mg/kg and plasma o,p'-DDD concentrations were determined by gas-liquid chromatography. A single dose of 50 mg/kg gave low plasma levels (AUC_{0-12h} of 2.39 mg.h/l; C_{max} of 0.4 mg/l) when administered as tablets to fasted dogs but levels were higher with pure drug dissolved in maize oil given by stomach tube. The levels were highest with ground tablets mixed in oil poured on dog food. When intact tablets were given in food, plasma levels were high (AUC_{0-12h} of 48.78 mg.h/l; C_{max} of 13.0 mg/l). Maximal plasma concentrations were reached 2.5 to 4 hours after dosing and the apparent elimination half-life was approximately 2 hours. There were no differences between males and females with respect to AUC, C_{max} or t_{max}.

species	n	dose (mg/kg)	route	Dosage method	C _{max} (mg/l)	t _{max} (h)	AUC ₀₋₁₂ (mg.h/l)
Dog	6	50	oral	Tablets, fasting	0.4 (0.1)	4.5 (0.3)	2.39 (1.06)
				Pure drug in maize oil	11.0 (0.6)	2.8 (0.2)	40.09 (3.15)
				Ground tablets in oil with food	15.4 (2.5)	3.3 (0.6)	63.90 (5.82)
				Tablets in food	13.0 (1.5)	3.7 (0.4)	48.78 (2.79)

Distribution

Working with technical grade DDD, which is likely to behave similarly to o,p'-DDD itself, Finnegan et al (1949) found high levels in adipose tissue of both rats and dogs. Moy (1961) also found high levels of mitotane in adrenals in humans. The presence of mitotane was also observed in the adrenals, fat, liver and kidney following 25 days treatment of dogs with 80 mg/kg/day of mitotane; levels were the highest in fat tissues, followed by adrenals, then liver and kidney (Cueto and Brown (1958). It is interesting to note that o,p'-DDD was concentrated at a higher level in the tissues analysed than p,p'-DDT, after administration of the same dose. Cueto and Brown states that the greater activity of o,p' as compared to p,p'-DDD could be explained on the basis of the differences in distribution and storage of the isomers in tissues.

Metabolism (in vitro/in vivo)

As discussed above, several studies have addressed the metabolism of mitotane as part of investigations aimed at determining its mechanism of action. Thus, 2,4-dichlorodiphenyl acetic acid (o,p'-DDA) has been identified as a major circulating and/or excreted metabolite in several species, including rats, rabbits and man (Reif & Sinsheimer, 1975); Sinsheimer et al, 1972; Andersen et al, 1999) and also, in studies with technical grade DDD, in mice (Gold and Brunk, 1982). o,p'-DDA was present in human plasma at levels 3 to 10 times those of mitotane itself. The metabolite o,p'-DDE (1,1-(o,p'-dichlorodiphenyl)-2,2 dichloroethene) was also determined in human plasma by High-

Performance Liquid Chromatography (Andersen et al, 1999). No animal studies involving monitoring of plasma levels of o,p'-DDA and o,p'-DDE have been reported.

In addition, hydroxylated derivatives of o,p'-DDA have been reported in urine of both rats (Reif & Sinsheimer, 1975) and man (Reif et al, 1974). Several other minor metabolites and conjugates have also been reported.

Several reports indicate that the adrenolytic effect of o,p'-DDD may be due to metabolic activation and subsequent covalent modification of macromolecules in the adrenal cortex. Cai et al (1995) have suggested that the reactive intermediate is an acyl chloride leading to both binding to macromolecules in the adrenal cortex and the generation of o,p'-DDA. In vitro studies have correlated the species differences in ability to metabolise mitotane by adrenal preparations and generate reactive metabolites with the recognised in vivo differences in adrenolytic effects between these species.

The factors that determine the tissue-selective bioactivation of o,p'-DDD in different species are little understood.

Excretion

Following the administration of a 100 mg oral dose of ¹⁴C-mitotane to rats, an average of 7.1% of the dose was excreted in urine and 87.8% in faeces within 8 days, with the majority appearing within the first 3 days (Reif & Sinsheimer, 1975). Autoradiographic studies in mice following intravenous administration of ¹⁴C-mitotane showed a high concentration of radioactivity in bile and intestinal contents, indicating significant biliary excretion (Lund et al, 1986).

Pharmacokinetic drug interaction

Enzyme induction

As already noted, mitotane is able to induce the metabolism of steroids, particularly enhancing the transformation of cortisol to its inactive 6 β -hydroxy metabolite (Kupfer et al, 1964; Kupfer & Peets, 1966). This induction effect is, however, more general and has also been reported with barbiturates. Thus, Straw et al (1965) reported that 3 days administration of 100 or 300 mg/kg/day of mitotane to rats reduced pentobarbital sleeping time (86.9 \pm 9 minutes in controls as compared to 29 \pm 3 and 20 \pm 2 minutes after 100 and 300 mg/kg/day, respectively); corresponding increases in liver weight and in vitro hepatic metabolism of pentobarbital were noted. Azarnoff et al (1966) showed a reduction in hexobarbital sleeping time after 3 days administration of 100 mg/kg/day to rats (142 \pm 8 and 20 \pm 4 minutes in control and treated animals, respectively); similar effects were reported for m,p'-DDD and p,p'-DDD, and for p,p'-DDA. Kupfer and Peets (1966) studied in vitro metabolism of hexobarbital in liver microsomes obtained from rats treated with 300 mg/kg/day of mitotane; metabolic activity was increased more in immature (about 60g body weight) than adult (about 200g body weight) animals.

The effects of mitotane in repeated dose toxicity studies in rats are further discussed in this report but both studies performed suggested hepatic enzyme induction. Fregly et al (1968) administered 68 and 182 mg/kg/day in the food for 6 weeks and observed an increase in thyroid weight, an increase in thyroidal uptake of administered ¹³¹I and an increase in excreted faecal radioactivity. The unpublished 4 weeks toxicity study in rats (0, 75, 150 and 300 mg/kg/day by gavage) did not measure thyroid weights; livers weights were not increased although electron microscopic examination did show increased smooth endoplasmic reticulum at the 300 mg/kg/day dose level.

Working with hepatocytes from Wistar-Furth rats, Ganem et al (1999) showed mitotane to share with phenobarbital the ability to increase the expression of the native CYP2B1/2B2 gene.

Administration of mitotane to man can result in a reversible hypercholesterolaemia, mainly due to an increase in LDL-cholesterol levels (Maher et al, 1992). Stacpoole et al (1982) showed mitotane to induce 3-hydroxy-3-methylglutaryl-coenzyme A reductase activity in hepatic microsomes both in

vitro and ex vivo after 4 days dosing with 50 or 200 mg/kg/day. The findings suggest that o,p'-DDD causes hypercholesterolaemia by increasing cholesterol synthesis.

Toxicology

Single dose toxicity

Mitotane does not appear to have adrenal specific toxicity in rat and mouse. The analogues p,p'-DDD and p,p'-DDE were slightly toxic with oral LD50 values after oral dosing in mice of 1466-1507 and 810-846 mg/kg, respectively (Tomatis et al, 1974). p,p'-DDT was moderately toxic with rat oral LD50 of 116 mg/kg.

Smith (Handbook of Pesticide Toxicology, Vol. 2, W. J. Hayes and E. R. Laws, Jr., Academic Press, New York, 1991) indicated that the primary acute toxicity, noted in animals and humans following excessive exposures to chlorinated insecticides, is neurological hyperactivity. With DDT and related compounds the effects progress gradually from mild tremors to convulsions.

Taking into account the clinical experience with mitotane and the fact that the dose dependent adverse reactions associated with mitotane administration are known the performance of single dose toxicity studies was not considered necessary.

Repeat dose toxicity (with toxicokinetics)

Two published studies have been provided, one in rats with 6 weeks administration (Fregly et al, 1968) and one in dogs with 4 weeks administration (Komissarenko et al, 1968). In addition, in order to provide data for the registration of mitotane in the USA, four-week studies were performed in the rat and dog; the reports on these studies are included in this application.

Fregly et al (1968) studied the effect of isomers of DDD on thyroid and adrenal function in rats. They administered 68 or 182 mg/kg/day of mitotane in the diet (1 and 3 mg per kg of food) to rats for 6 weeks. There were 8 male rats per dose level. Thyroid and adrenal glands were weighed at the end of treatment and whilst adrenal weights were unaffected by treatment, thyroid weights were increased (41 and 57% increase in thyroid to body weight ratios at 68 and 182 mg/kg/day, respectively, as compared to control animals). The rate of oxygen consumption (measured the second week of treatment) and gain in body weight were unaffected by treatment. There was an increased intake into the thyroid of injected ¹³¹I, which was dose-related. The rate of loss of ¹³¹I from the thyroid gland was significantly faster for both treated groups than for controls, in a dose-related fashion. These results suggest that the chronic administration of o,p'-DDD at the doses used resulted in a compensated hypothyroidism in rats. There was no change in urinary ¹³¹I excretion although the faecal excretion of radioactivity was increased at the high dose. The increase in thyroid weight may be associated with increased hepatic metabolism of thyroxine, but specific effects on the thyroid gland have not been excluded. This publication also contains data on m,p'-DDD and p,p'-DDD administered to female rats for 24 weeks; increased thyroid weights were again observed.

A study conducted in rats was not carried out under GLP, groups of 10 male and 10 female rats received 75, 150 or 300 mg/kg/day of o,p'-DDD by gavage for 4 weeks, with parallel control groups receiving vehicle. The drug o,p'-DDD was administered to the rats in corn oil. At the end of treatment 6 rats per group were killed and the other 4 were kept for a 4-week recovery period. The following parameters were measured: alkaline phosphatase, serum glutamic oxalacetic transaminase (SGOT), creatinine, glucose, haematology including haematocrit, haemoglobin, differential, bleeding and clotting time, white blood cell count. There was no effect of treatment on body weight or haematological parameters. Blood biochemistry showed no effect on SGOT, but there was an elevation of serum alkaline phosphatase in the three dose levels, which was dose-related and partially reversible during the recovery phase. The rats receiving a dose of 33 mg/kg/day exhibited a 63 % increase in the serum alkaline phosphatase activity (week 4). This finding is generally observed whenever chlorinated hydrocarbons are administered to animals. There were no changes in 17-keto or 17-hydroxy corticosteroid excretion patterns. Organ weights, including adrenals, were unchanged by treatment. Thyroid weight was not assessed in this study. Macroscopic post-mortem examinations did not show drug-related changes, nor did histopathological examinations of the liver or adrenals.

Electron microscopic examination of adrenals and livers from high dose animals at the end of treatment did not show any changes in the adrenals, but livers revealed consistently elevated quantities of smooth endoplasmic reticulum and reduced glycogen content as compared to controls, features consistent with induction of drug metabolising enzymes.

Komissarenko et al (1968) studied the effect of o,p'-DDD on the function and morphology of the adrenal cortex as well as on hematormorphology in dogs. They administered mitotane, 50 and 100 mg/kg/day, to 4 and 5 dogs respectively, for 30 days. After one week, plasma cortisol levels were decreased to below the level of detection in both treated groups and the corticosteroid response and eosinopenic reaction to ACTH administration were absent. Eosinophilia, basophilia and lymphocytosis were observed. At the end of the o,p'-DDD treatment was observed a rise of the absolute number of neutrophils. The authors indicated that these changes in blood composition resemble those observed in adrenalectomized dogs, i.e. a sharp increase of eosinophils and a gradual rising of lymphocytes. The difference found was the significant increase of the absolute number of neutrophils in dogs which received o,p'-DDD for 30 days. The 50 mg/kg/day dose level was reasonably well tolerated for the full 30 days, but animals receiving 100 mg/kg/day died after two to three weeks treatment. At autopsy, treated animals showed no pathological changes in the liver, kidney, brain or other organs, although mesenteric lymph nodes were somewhat enlarged. The adrenal cortex was atrophied, but the medulla was unaffected. The effect was greater at 100 mg/kg/day for 15 days than at 50 mg/kg/day for 30 days.

A study was conducted for the National Cancer Institute. The doses in the non-GLP 28-day dog study were 0, 10, 50 and 100 mg/kg/day, administered by capsule to groups of three male and three female animals per dose level. Two animals per group were killed after 28 days and the remaining animal kept for a 28-day recovery period. Five animals receiving 100 mg/kg/day died during the dosing period (days 1, 14, 15, 16 and 17) and the dose level in the sixth was reduced to 75 mg/kg/day after 17 days; one animal receiving 50 mg/kg/day died on day 23. Animals that died showed a decrease in appetite and water intake in the days prior to death. There was no marked effect on body weight, whether the animals survived or not. The following parameters were observed: alkaline phosphatase, serum glutamic oxalacetic transaminase (SGOT), creatinine, glucose, haematology including haematocrit, haemoglobin, differential, bleeding and clotting time, white blood cell count. White blood cell numbers were dose-relatedly and reversibly increased, being most pronounced in animals which died; there were no other changes in haematological parameters. Serum glucose, SGOT and creatinine were unchanged by treatment, but serum alkaline phosphatase was dose-relatedly increased. Alkaline phosphatase activity is still elevated 28 days after cessation of o,p'-DDD administration. There was no marked effect on organ weights, although adrenal weights were slightly lower at the mid and high doses. Histopathology showed several changes in animals that died, but in examining all animals the major changes were seen in the adrenals, particularly at the high dose. In addition to the adrenal changes, the dogs on high dosage had involvement of the liver, with atrophy of cells and centro-lobular and midzonal congestion. The changes in the adrenals were confirmed by electron microscopy with adrenals at 50 and 100 mg/kg/day being readily distinguishable from controls because of the massive accumulation of electron dense material in the region of the zona reticularis and increased quantities of connective tissue and leukocytic infiltration. Cells of the zona fasciculata in dogs examined immediately after the final dose had mitochondria, which had a highly transparent matrix. The zona glomerulosa did not appear to be affected.

Data on repeated-dose toxicity is limited to studies with a duration of 4-6 weeks: this absence of repeated-dose toxicity studies longer than 4-6 weeks duration can be considered to be acceptable in the light of the clinical experience involving longer term treatments.

Genotoxicity in vitro and in vivo (with toxicokinetics)

One report in the literature indicates a negative effect in the Ames test in *Salmonella typhimurium* strains TA100 and TA98, using rat liver or mouse lung and liver S9 fractions as metabolic activating systems (Lund et al, 1990). Thus, in a series of initial experiments, the mutagenic effect of o,p'-DDD was investigated in an Ames test, using rat S-9 to find suitable conditions for the further testing with mouse lung and liver homogenates. o,p'-DDD was shown to be non-mutagenic in TA98 and TA100, without metabolic activation in concentrations up to 25 µg/plate, and with a rat liver homogenate as

metabolizing system in concentrations up to 150 µg/plate. Above these concentrations, no Salmonella cells survived. In the presence of S-9, 25 and 3 µg/plate were the highest concentrations tested without any signs of toxicity towards TA98 and TA100, respectively. In a subsequent Ames test, using S-9 from mouse lung and liver as activating system (0.375-1.5 mg protein/plate), the results were negative (Table 1).

Table 1: Incidence of revertants using mouse liver and lung S9 for metabolic activation (concentration-response to quantity of S9).

Strain	Concentration of mitotane (µg/plate)	S9 concentration (protein mg/plate)	Revertants per plate with liver S9	Revertants per plate with lung S9
TA98	0	0.375	38 ± 6	45 ± 7
	25	0.375	36 ± 7	33 ± 5
	25	0.75	43 ± 7	37 ± 10
	25	1.5	45 ± 8	45 ± 8
TA100	0	0.375	151 ± 11	145 ± 10
	3	0.375	156 ± 18	156 ± 17
	3	0.75	141 ± 17	145 ± 25
	3	1.5	136 ± 9	126 ± 11

Carcinogenicity (with toxicokinetics)

Taking into account that the life expectancy in the indicated population is short, carcinogenicity studies are considered not required (see ICH S1A: Guideline on the need for Carcinogenicity studies of pharmaceuticals).

Lund and co-authors (1990) detected the ability of o,p'-DDD to induce cell proliferation in the mouse lung. They studied the effects of o,p'-DDD on the DNA synthesis in the C57B1 mouse lung and liver. As determined by 3H-thymidine incorporation into DNA, a selective increase in the lung DNA synthesis (+59%) was observed 2 days after a single intraperitoneal injection of 100 mg/kg o,p'-DDD. Using microautoradiography, a 9 times higher rate of cell proliferation was observed in the lung 4 days after an intraperitoneal injection of 500 mg/kg o,p'-DDD. The induced cell proliferation may indicate a tumour-promotor activity of o,p'-DDD in the mouse lung. Moreover, a long-term study of the isomer p,p'-DDD demonstrated an increased incidence of lung and liver tumours in mice, while p,p'-DDT and p,p'-DDE, a stable DDT metabolite, induced liver tumours (Innes et al., 1969; Tomatis et al., 1974).

Reproductive and developmental studies

Polychlorinated hydrocarbons compounds are known to have potential estrogenic activities. Mitotane has been reported to bind to the rat uterine estrogen receptor (Nelson cited by Johnson et al, 1992). Johnson et al (1992) studied two estrogenic actions, initiation of implantation and maintenance of pregnancy, using the hypophysectomized, delayed-implanting rat model. The animals were exposed to several polychlorinated hydrocarbons. o,p'-DDD was nearly devoid of estrogenic activity for initiating implantation. Chen and co-authors (1997) determined whether the DDT isomers p,p'-DDT, o,p'-DDT, p,p'-DDD, o,p'-DDD, p,p'-DDE, o,p'-DDE, and p,p'-DDA, could bind to and transcriptionally activate the human estrogen receptor. The results from competitive binding assays showed that o,p'-DDD, o,p'-DDE, and p,p'-DDT, as well as the established estrogenic o,p'-DDT, were able to bind specifically to the hER with approximately 1000-fold weaker affinities of the hER than that of estradiol. The relative affinities of o,p'-DDT, o,p'-DDD, o,p'-DDE, and p,p'-DDT for the receptor were similar. In contrast, only o,p'-DDT, but not p,p'-DDT, bound to the rat estrogen receptor. Moreover, two yeast expression-reporter systems, constructed to test if the DDT isomers and metabolites could transcriptionally activate the human estrogen receptor (hER), demonstrated that an o,p'-DDT metabolite could transactivate the hER with a 140- to 300-fold weaker potency than that of estradiol. The DDT isomers and metabolites that bound the hER in vitro, including o,p'-DDD,

triggered estrogen receptor-mediated transcription of the lacZ reporter gene in the yeast systems. These compounds also stimulated two estrogenic endpoints in estrogen-responsive human mammary MCF-7 cells: the induction of the progesterone receptor and the down-regulation of the hER. The studies with DDT isomers and metabolites conducted in rodent models may not represent the true potency of these compounds in humans. The difference in binding of DDT isomers and metabolites to the rat versus the human ER might be explained by the eight amino acid differences in the ligand binding domain of the two receptors.

In general, cytotoxic/cytostatic substances are assumed to cause reproductive disturbances (see the CPMP Note for Guidance on the preclinical evaluation of anticancer medicinal products (CPMP/SWP/997/96). In relation to the possible teratogenicity of mitotane in humans, Leiba et al (1989) reported on a Cushing's patient who had a therapeutic abortion and the embryo on examination was observed to show some abnormalities in the adrenal cortex. Thus, the histopathological examination of the embryo, aged about 42 days, revealed a dysmorphogenetic event in the cortical primordia characterized by pycnotic sympathoblasts.

DDT and related polychlorinated biphenyls are known to have unwanted effects on pregnancy and the foetus. Mitotane should be used during pregnancy only when clearly needed and if the clinical benefit clearly outweighs any potential risk to the foetus. Women of childbearing potential should be advised to use effective contraception during treatment. The prolonged elimination of mitotane from the body after treatment discontinuation should be considered.

DDT and related polychlorinated biphenyls have been detected in human milk (Polishuk Z. W. et al., 1977, Pesticides Monitoring 10, 121-129) as well as in the placenta of pregnant rabbits, in the cord blood of newborns and in stillborn tissues (Polishuk Z. W. et al., 1977, Environ Res. 13, 278-284). Decreases in fetal body and organ weights were observed in rabbits following dosing of 1 mg/kg/day of DDT to maternal animals (Fabro S. et al., 1984, Am. J. Obstet. Gynecol., 148, 929). Other studies were reported that indicated decreased lengths of gestation, increased resorption rates, preweaning mortality, learning impairment in mice (Agency for Toxic Substances and Disease Registry, U.S. Dept. of Commerce, NTIS PB90-182171, 1989). Moreover, Leiba et al (1989) reported on a Cushing's patient who had a therapeutic abortion after o,p'-DDD treatment and the embryo on examination was observed to show some abnormalities in the adrenal cortex. Therefore, mitotane is expected to be embryotoxic/teratogenic and to cause reproductive disturbances.

Other toxicity studies

In a series of studies, Lund et al (1986, 1989, 1990) studied covalent binding to tissues following *in vivo* administration of ¹⁴C-mitotane to mice and rabbits, as well as in *in vitro* systems. Autoradiographic studies in mice showed selective accumulation of radioactivity in the lung (Lund et al, 1986). Exhaustive extraction of lung tissue showed a large fraction of the radioactivity to be covalently bound to protein; binding was also shown in the liver, though at levels 20-30 times lower. Inhibition of binding in metyrapone treated animals indicated formation of cytochrome P450 catalysed reactive metabolites. Further *in vitro* studies with mouse lung and liver S9 preparations (Lund et al, 1989) demonstrated an oxidative cytochrome P450 mediated formation in both lung and liver of mitotane metabolites that bound covalently to proteins, phospholipids and to added naked DNA. The apparent Km value for covalent binding was lower in lung than liver and, moreover, glutathione addition decreased binding more efficiently in liver than lung fractions; both factors could contribute to the difference in binding between these tissues, observed both *in vivo* and *in vitro*. The studies on mouse lung were extended to the rabbit, allowing a more detailed examination of the cell types involved. Clara cells had the highest capacity to bind radioactivity following *in vitro* incubation with ¹⁴C-mitotane, followed by alveolar type II cells and a fraction of mixed unidentified lung cells; no binding was observed in alveolar macrophages (Lund et al, 1990).

The possible consequences of this covalent binding remain unexplained although Lund et al (1990) have shown increased DNA synthesis in mouse lung and liver following a single intraperitoneal administration of 100 or 500 mg/kg of mitotane and have suggested this may indicate a tissue selective promoter activity in the mouse lung.

Discussion on the non-clinical aspects

The potential of mitotane to affect the adrenals was first noted by Nelson and Woodard (1948). Since these initial observations, several publications confirmed the adrenolytic activity of mitotane, particularly in dogs. Histological examination showed a disruption of normal cellular structure and arrangement in the innermost zones of the adrenal cortex (zonas fasciculata and reticularis). The earliest observable ultrastructural change in the dog adrenal cortex was the swelling, dissolution and rupture of mitochondria in the zona fasciculata-reticularis area. These changes were correlated with a reduction of the adrenal output of 17-hydroxy steroid and an inhibition of ACTH-induced steroid production.

The bibliographical data are consistent with formation of a reactive metabolite within the adrenal gland and covalent binding to macromolecules resulting in an inhibitory effect on steroid synthesis. Moreover, it is clear from the histological evidence that this metabolism within the adrenal gland results in a targeted adrenolytic effect.

In addition to these effects within the adrenal gland, mitotane also induces enzymes involved in the metabolism of drugs, which could affect the levels of circulating steroids. Enhanced cortisol metabolism has also been reported in rats and guinea - pigs.

2,4-dichlorodiphenyl acetic acid (o,p'-DDA) has been identified as a major excreted metabolite in several species, including rats, rabbits and man and also, in studies with technical grade DDD, in mice. o,p'-DDA was present in human plasma at levels 3 to 10 times those of mitotane itself.

Moy (1961) has described the pharmacokinetics of mitotane in a series of patients treated with various doses of drug for different durations. Overall, he estimated that approximately 35 to 40% of the product was absorbed after an oral administration.

Watson et al (1987) studied absorption of mitotane in dogs after a single oral dose under various conditions (see Table below). Mitotane was given by mouth at 50 mg/kg. A single dose of 50 mg/kg gave low plasma levels (AUC_{0-12h} of 2.39 mg.h/l; C_{max} of 0.4 mg/l) when administered as tablets to fasted dogs but levels were higher with pure drug dissolved in maize oil given by stomach tube. Maximal plasma concentrations were reached 2.5 to 4 hours after dosing and the apparent elimination half-life was approximately 2 hours. Mitotane distributes in the adrenals, fat, liver and kidney.

2,4-dichlorodiphenyl acetic acid (o,p'-DDA) has been identified as a major circulating and/or excreted metabolite in several species, including rats, rabbits and man. o,p'-DDA was present in human plasma at levels 3 to 10 times those of mitotane itself. The metabolite o,p'-DDE (1,1-(o,p'-dichlorodiphenyl)-2,2 dichloroethene) was also determined in human plasma. In addition, hydroxylated derivatives of o,p'-DDA have been found in urine of both rats. Several other minor metabolites and conjugates have also been reported.

Following the administration of a 100 mg oral dose of ^{14}C -mitotane to rats, an average of 7.1% of the dose was excreted in urine and 87.8% in faeces within 8 days, with the majority appearing within the first 3 days. Autoradiographic studies in mice following intravenous administration of ^{14}C -mitotane showed a high concentration of radioactivity in bile and intestinal contents, indicating significant biliary excretion.

The data suggest that mitotane could provoke metabolic interactions with concomitant medication and care should thus be taken in its clinical use.

Target organs identified in the toxicity studies in rats and dogs were thyroid and liver.

The published 6 week study in rats focuses on the effect of o,p'-DDD on thyroid and adrenal function. An increase was observed in thyroid weight, an increase in thyroidal uptake of administered ^{131}I and an increase in excreted faecal radioactivity were also observed.

The published 4 week study in dogs focuses on the effect of o,p'-DDD on the function and morphology of the adrenal cortex as well as on hematomorphology. After o,p'-DDD administration. Plasma cortisol levels were decreased to below the level of detection in treated groups and the corticosteroid response and eosinopenic reaction to ACTH administration were absent. Eosinophilia, basophilia and lymphocytosis were observed. At the end of the o,p'-DDD treatment was observed a rise of the absolute number of neutrophils. At autopsy, the adrenal cortex was atrophied, but the medulla was unaffected.

In the 28 days dog study a dose-dependent and reversible increase of white blood cell numbers was observed, this effect was most pronounced in animals that died. A dose-related increase of serum alkaline phosphatase was also observed. Alkaline phosphatase activity was still elevated 28 days after cessation of o,p'-DDD administration. Histopathology showed major changes in the adrenals, particularly at the high dose. Moreover, the dogs on high dosage had involvement of the liver, with atrophy of cells and centro-lobular and midzonal congestion. The changes in the adrenals were confirmed by electron microscopy with massive accumulation of electron dense material in the region of the zona reticularis and increased quantities of connective tissue and leukocytic infiltration. Cells of the zona fasciculata in dogs examined immediately after the final dose had mitochondria which had a highly transparent matrix. The zona glomerulosa did not appear to be affected.

One report in the literature indicates a negative effect in the Ames test in *Salmonella typhimurium* strains TA100 and TA98, using rat liver or mouse lung and liver S9 fractions as metabolic activating systems. Carcinogenicity studies have not been performed with mitotane but considering that the life expectancy of the patients with adrenocortical carcinoma is short, carcinogenicity studies are considered not required. Lund and co-authors (1990) detected the ability of o,p'-DDD to induce cell proliferation in the mouse lung. The induced cell proliferation may indicate a tumour-promotor activity of o,p'-DDD.

Formal studies on the possible effects of mitotane on reproductive functions have not been performed. Polychlorinated hydrocarbons as a class are recognized as having potential estrogenic activities. Mitotane is expected to be embryotoxic/teratogenic and to cause reproductive disturbances. Therefore, since animal studies with similar substances have shown reproductive toxicity, some warnings were included in the relevant sections of the summary of product characteristics for Lysodren. Lysodren is contraindicated with breastfeeding. Lysodren should be given to pregnant women only if the expected clinical benefit clearly outweighs any potential risk to the foetus. Women of childbearing potential should be advised to use effective contraception during treatment.

The non-clinical data submitted correspond to old publications, which do not specify the GLP fulfilment. The CPMP considered that the lack of information regarding compliance with the current GLP did not impact on the validity of the results of these studies.

4. Clinical aspects

As already stated in the introduction of this report, malignant neoplasms of the adrenal cortex such as adrenal cortical carcinoma are rare; they account for 0.05 to 0.2 per cent of all cancers, and show a bimodal age distribution, with the first peak occurring before the age of 5 years and the second in the fourth to fifth decade. There is a female predominance, accounting for 55 to 85 per cent of the cases, particularly among functional tumours. Men with adrenal cortical carcinoma tend to be older than women.

Approximately 60 percent of patients have a functional adrenal cortical carcinoma, defined by the existence of signs of excess adrenal hormone production. Among functional tumours, Cushing's syndrome is evidenced in half of the patients and virilization in one third of them, whereas hyperaldosteronism, feminisation or the combination of Cushing's syndrome and virilization account for a minority of patients. Nearly half of adult carcinomas are non-functional, and these patients present clinically with abdominal or flank pain or as an incidentally discovered adrenal mass.

Metastatic disease to the lungs, liver, or bone may cause symptoms before the primary diagnosis is made.

Resectable recurrences are usually operated on, and a number of patients remain disease-free thereafter. A drug therapy is often administered to patients whose disease is unresectable at presentation or at relapse. An overview of the published data with different products is given below (see table below). Radiotherapy is only indicated as palliative treatment for patients with bone metastases.

As stated in the well-established use justification of this document, mitotane is commonly prescribed for the treatment of patients with adrenal cortical carcinoma. Other chemotherapy agents used in this indication are cisplatin, etoposide, doxorubicin and other. These are usually employed in combination regimens (cisplatin-etoposide, cisplatin-doxorubicin-5-FU, ...) able to induce short lived objective responses in about 20-30% of patients (or even higher in when administered concurrently with mitotane). The toxicity is however remarkable in this palliative setting and their impact in disease progression, survival or quality on life remain unproven.

Chemotherapy agents used in the treatment of adrenocortical carcinoma

<u>Investigations</u>	<u>Drug</u>	<u>Patients</u>	<u>Efficacy</u>
Gutierrez and Crooke, 1980 Luton et al., 1990 Van Soolten et al., 1984	Mitotane	37	22-33% PR
Venkatesh et al., 1989	Mitotane	72	29% PR
Haak et al., 1994	Mitotane		60% PR, few CR
Kornely and Schlanghecke, 1994	Mitotane + Streptozocin	2	CR with surgery plus chemotherapy
Decker et al., 1991	Mitotane	36	22% PR
Stein et al., 1989 Arit et al., 1994 LaRocca et al., 1990	Suramin	21 9	3 PR 3 PR
Stein et al., 1989	Doxorubicin	16	19% PR
Schlumberger et al., 1991	5-Fluorouracil + Doxorubicin + Cisplatin	13	1 CR, 2 PR
Berruti et al., 1992	Etoposide + Doxorubicin + Cisplatin	3	1 CR 2 PR
Avico et al., 1992	Oncovin + Cisplatin Epipodophyllotoxin Cytosin	1	1 CR
Berruti et al., 1998	Mitotane + Etoposide + Doxorubicin + Cisplatin	28	2 CR 13 PR
Zidan et al., 1996	Mitotane + Cisplatin	1	1 CR

CR, complete remission; PR, partial remission.

Norton JA, Le Hop N. Adrenal tumors. De Vita VT, Hellman S, Rosenberg SA. Cancer: Principles & practice of oncology. 6th ed. Lippincott Williams & Wilkins, Philadelphia 2001, page 1779.

The prognosis of adrenal cortical carcinoma tumours is generally poor in adults and somehow better in children. In a recent review of 7 large series, the mean survival was 18 months. Most series showed no statistically significant differences based on patients' age, gender or tumour functional status. However, stage was an important prognostic predictor. For stages I to IV tumours, approximate 5-year

survival was 30-45%, 12.5-57%, 5-18% and 0%, respectively. Surgical resection was the only therapy that significantly prolonged survival, particularly when disease was detected at stages II and I. Median survival in patients with unresectable tumours was 3 to 9 months, whereas after complete resection median survival was 13 to 28 months.

Therefore in this context it is important in the light of the data published with mitotane to define the actual place and effectiveness of mitotane in the treatment of patients with adrenal cortical carcinoma.

Pharmacokinetics

Available information is very limited, and derives mainly from a study published in 1961 (Moy et al 1961).

Absorption

In the study published in 1961, absorption and excretion and tissue levels of mitotane were investigated in 18 patients with metastatic adrenal cancer. The patients ranged in age from 8 to 56 years. The intake dosage varies among patients, but the mean regimen schedule was 10 g of mitotane per day (13 patients). For oral use, mitotane was given in tablets (Lysodren) or in capsules containing 0.5 g of the dry powder. Some patients received intravenous mitotane (courses up to 5 g/day). As it was frequently necessary to stop or lower the dosage of mitotane because of side effects or changes in the patients' clinical status, the parameters were not calculated within all 18 patients. The number of patients used for the parameters calculation is shown in the table below. Samples were obtained from fat, tumour, adrenal, brain, and liver, in 7 cases brought to autopsy, and 13 samples of subcutaneous abdominal fat from 10 patients by autopsy/biopsy. The determination of the mitotane plasma concentrations was performed with a spectrophotometric method.

Study characteristics

<u>Number of patients</u>	<u>Dose</u>	<u>Age range</u>	<u>Samples</u>	<u>Study design</u>	<u>Type of disease</u>
18	10* g/day	8-56	Serum, urine, stool emulsion, bile and cerebrospinal fluid. Tissue samples: fat, tumour, adrenal, brain and liver.	There has not been an optimal sampling time.	Metastatic adrenal cancer

* Some patients received intravenous mitotane (courses up to 5 g/day).

The blood levels of mitotane from 13 patients, who were able to maintain a dose of approximately 10 g per day during a stage of treatment, were plotted against the quantity of mitotane administered (expressed in grams). It was not possible to find a relationship between blood levels and patient's response or toxicity. Variable blood levels were achieved (up to 140 mg/l in a child who received large doses and did not respond to the treatment). In 4 patients in whom the drug was discontinued, serum levels could not be detected with the spectrophotometric method after 6 to 9 weeks.

The main conclusions of this study were that 35 to 40 percent of the substance is absorbed from the gastro-intestinal tract.

Use of different formulations in the clinical trials and bioequivalence.

The same patients excreted about 10% of the daily dose as urinary metabolites. When this percentage was compared with that excreted by some patients receiving courses up to 5g/day mitotane intravenously (urinary excretion was about 25%), it appeared that about 40% of the oral dose was absorbed from the gastrointestinal tract. Accordingly, faecal excretion amounted to 66.5, 63.2 and 62% in three patients taking 5, 10 and 15g/day of mitotane, respectively (Moy et al 1961).

The main formulation used in this study was the 0.5g capsules of the dry powder. However, tablets of mitotane (Lysodren) and other formulations were also briefly tested, without apparent therapeutic advantage (Moy et al 1961).

Literature reports often do not indicate the formulation of mitotane used. However, all publications from North America relate to Lysodren (product subject to of the present application). Similarly, in some European countries (Italy, Netherlands), publications explicitly refer to Lysodren. The various formulations in the other European countries are unknown, except for France where a capsule formulation of mitotane has been provided by the Central Pharmacy galenic department.

Distribution

In tissue samples, it was not possible to find a relationship between tissue levels and response. Analysis of tissue samples obtained by biopsy or at autopsy showed that mitotane distributed in most tissue but stored primarily in fat-containing tissues (Moy et al 1961).

Elimination

The presumed activating metabolic pathway for mitotane involves biotransformation to an acyl chloride, which may bind covalently to macromolecules in the adrenal cortex or hydrolyse to form o,p'-DDA (Cai et al 1995). Other metabolic pathway include glycine conjugation of o,p'-DDA, and hydroxylation in the 3-, 4- and 5-position and dihydroxylation in the 3,4- and 4,5-position (Sinsheimer et al 1972; Reif et al 1974).

Published studies indicate that in adrenal carcinoma patients the o,p'-DDA plasma concentrations are about 10 times higher than those of the parent compound (Andersen et al 1999; Inouye et al 1987).

Patients treated intravenously and orally excreted the equivalent of about 25 and 10 per cent of their daily dose as urinary metabolite over 24 hours, respectively. A smaller percentage was identified also in a metabolised form in the faeces (Moy et al 1961).

Approximately 25% of the amount absorbed each day (about 40%) appeared in the urine in a metabolised form (possibly o,p'-DDA). Unchanged mitotane was not detected in the urine (Reif. et al 1974). A variable amount of metabolite(s) (1% to 17%) was also excreted in the bile. No unchanged mitotane appeared in bile too (Moy et al 1961).

Terminal plasma half-life was estimated to be ranging from 18 to 159 days.

Dose proportionality and time dependencies

Non-linearity (dose-proportionality and time dependency) was never studied as such. However, in a prospective study in 24 patients with adrenocortical carcinoma taking mitotane as first-line therapy (n = 13), or as adjuvant therapy (n = 11), a correlation was observed between the highest plasma trough concentration and the cumulative daily dose of mitotane ($r^2 = 0.346$; $p = 0.0025$) (Baudin et al 2001) suggesting a dose-proportionality.

Special populations

No publication investigating the pharmacokinetics properties of mitotane in patients with impaired renal or liver function were submitted in the Application. No specific pharmacokinetic study was conducted in children. The summary of product characteristics for Lysodren reflects the limited amount of clinical data in the paediatric population: “*the safety and efficacy in patients under the age of 18 years have not been established and, at present only very limited data are available in this age group*”.

Intra- and inter-individual variability

As mentioned before (Baudin et al 2001), the daily dose of mitotane in patients was associated with the highest plasma trough levels. No correlation was found between plasma concentration and age, gender or body mass index. This suggested that the daily dose accounted for a substantial part of the inter-patient variability in the plasma of mitotane concentrations.

Interaction studies

Mitotane stimulates the clearance of warfarin by hepatic enzyme induction, leading to an increase in dosage requirements for the anticoagulant (Cuddy and Loftus 1986).

A report in the literature suggests that, in a single patient bilateral adrenal hyperplasia, the antiminerlocorticoid spironolactone blocks the effect of mitotane and that, therefore the two products should not be used together (Wortsman and Soler 1977). Therefore, this association has been contraindicated in the summary of product characteristics for Lysodren.

Pharmacodynamics

The action of mitotane on the adrenals appears to result from both a direct effect leading to decrease in cortisol production, and an increase in cortisol metabolism. Most available information is based on animal studies.

Mechanism of action

Data suggest that the drug acts as an adrenal cytotoxic agent suppressing the adrenal cortex, and it can also modify the peripheral metabolism of steroids. Its biochemical mechanism of action is unknown.

Mitotane appears to selectively inhibit adrenocortical function by a direct cytotoxic effect and, as a consequence, inhibits production of corticosteroids. The product causes focal degeneration in the zona fasciculata and reticularis of the adrenal cortex with resultant atrophy. Technical grade DDD has long been shown to induce adrenocortical atrophy and hepatic damage in dogs (Nelson and Woodward 1948; Nelson and Woodward 1949). This species is much more sensitive to the adrenocortical actions of mitotane than others like the mouse, rabbit, monkey or rat. The atrophy involved mainly the inner zones of the adrenal cortex and not the zona glomerulosa (Vilar and Tullner 1959; Kaminsky, Luse et al. 1962). The active component was shown to be *o,p'*-DDD (mitotane) an isomer and an impurity in the technical grade DDD (Nichols and Hennegar 1957; Cueto and Brown 1958), being *p,p'*-DDD itself inactive.

This effect may be mediated through covalent binding of mitotane metabolites to mitochondrial proteins. The metabolism of mitotane was seen to correlate with the generation of covalent binding species. The potential of the insecticide DDD (2,2-bis (parachlorophenyl)-2,2-dichloroethane) to affect the adrenals was first noted by Nelson and Woodard; these authors, working with technical grade DDD, noted adrenocortical atrophy in dogs. In animals, there is evidence that mitotane is transformed to an acyl chloride by a mitochondrial P450-mediated hydroxylation and that the acyl chloride covalently combines with specific bionucleophiles within the adrenal cortical cell for the adrenolytic effect to take place. In human, *o,p'*-dichloro-diphenyl acetic acid (*o,p'*-DDA) has been identified as a metabolite of mitotane (Sinsheimer, Guilford et al. 1972). The generation of *o,p'*-DDA by adrenal homogenates across different species (bovine, dog, rat and human glands) has been correlated with the recognised sensitivity of these species to the adrenolytic effect of mitotane (Cai, Counsell et al. 1995).

Mitotane has also been demonstrated to inhibit ACTH-induced steroidogenesis in the dog adrenals by preventing the intramitochondrial-induced conversion of cholesterol to pregnenolone. This is due to the generation of reactive intermediate metabolites that are capable of covalent binding to mitochondrial macromolecules.

Mitotane has also been shown to induce the metabolism of corticosteroids in animals (Kupfer, Balazs et al. 1964; Straw, Waters et al. 1965), thus reducing their active concentrations and possibly alleviating any effects consequent to their excessive production in cases of adrenal carcinoma.

Such mechanisms of action imply that steroid compensation may be necessary when treating patients with mitotane.

Therefore, the action of mitotane on the adrenals thus appears to be result of both a direct effect resulting in a decrease in cortisol production and an increase in cortisol metabolism. In practical terms,

such mechanism implies that steroid compensation may be necessary when treating patients with mitotane.

Primary pharmacology

The Application included sixteen references dealing with human pharmacodynamics, only three of these references (Sinsheimer, Guilford et al. 1972; Bukowski, Wolfe et al. 1993; Cai, Counsell et al. 1995) actually presented studies in humans. Sinsheimer et al identified o,p'-dichlorodiphenyl acetic acid as the principal urinary metabolite of the insecticide p,p'-dichlorodiphenyltrichloroethane in three patients. Cai et al explored the relationship of the metabolism of mitotane and its binding adrenal cortex tissue from several sources, including normal adrenal cortex and tumour homogenates. The objective was to detect the mitotane moiety responsible for its covalent binding. An acyl chloride appeared to be the reactive moiety of mitotane, which led to both DDA metabolite formation and binding adrenal cortex bionucleophiles. (Bukowski, Wolfe et al. 1993) conducted a phase II study of chemotherapy with and without mitotane in 37 patients with adrenal cortex carcinoma. The combined regimen has activity but moderate to severe toxicity too. Finally, Van Geertruyden and coll. (Van Geertruyden, De Myttenaere et al. 1980) report on one case of adrenal cortex carcinoma with hypercorticism, in whom treatment with mitotane led to temporary clinical and biological remission.

(Feller, Hoekman et al. 1997) reported a case of a patient with adrenal carcinoma, whose single-cell suspensions highly expressed a glycoprotein (Pgp) implicated in drug multiresistance. In vitro, mitotane was able to block the expression of the protein as well as the related Pgp resistance. However, according to the Applicant "these results did not translate in clinical use since in this patient mitotane has been reported to be inactive". Interestingly enough, this paper reports that mitotane normalised cortisol production but failed to induce tumor regression.

Secondary pharmacology

The Applicant did not submit any data exploring the secondary pharmacological properties of mitotane in humans. The absence of such studies was justified by the fact that mitotane has been used for several decades.

Conclusion on pharmacokinetic/pharmacodynamics

The only available pharmacokinetic data comes from a study performed in the early sixties providing information that, at present, is clearly insufficient. Approximately 40% of the drug is absorbed, and approximately 10% of the dose is recovered in the urine as a water-soluble metabolite. Active metabolite excreted in the bile varies from 1-17%. The substance is apparently stored in fat tissues, but mitotane can be found in most tissues. Many important aspects of the pharmacokinetics of mitotane have not been investigated, therefore the CPMP requested the Applicant to commit to further characterise the pharmacokinetic profile of mitotane as a post-authorisation commitment.

As far as the pharmacodynamic interactions are concerned, mitotane may increase the metabolism of warfarin, causing a decrease in levels. It can also interact with spironolactone, which may decrease mitotane effect. Finally, central nervous system depressants may potentiate its toxicity.

The mechanism of action of mitotane is described in its general aspects. Mitotane apparently causes adrenal inhibition without cellular destruction. The exact mechanism of action is unknown. It inhibits cholesterol side-chain cleavage and 11-beta-oxyhydrase reactions. It also appears to reduce the peripheral metabolism of steroids. Alteration of extra-adrenal metabolism of cortisol induces measurable 17-hydroxy corticosteroid while stimulating the formation of 6-beta-hydroxy cortisol.

Clinical efficacy

Dose response studies

The Applicant suggested the existence of a relation between the plasma concentrations of mitotane and the pharmacodynamic properties of the product. These publications suggest that the therapeutic

window for mitotane would lie in plasma concentrations between 14 and 20 mg/l. Although there are some published data supporting such relation, this hypothesis is far from being demonstrated.

These data suggest that serum mitotane concentrations greater than 14 mg/l may induce a tumour regression in patients with adrenocortical carcinoma, in addition serum concentrations greater than 20 mg/l may be associated with central nervous system adverse reactions. However, interestingly, the appropriate serum levels can be achieved with lower daily doses of mitotane as Lysodren formulation (2 to 3 g/daily) and some reports suggest that monitoring the plasma levels of mitotane leads to lower daily administration, hence a better tolerance.

The data that might be considered as pivotal for supporting this pharmacokinetic/pharmacodynamic (PK/PD) relationship was published in a French study using a different formulation of mitotane whose pharmacokinetic profile seems to be considerably different than the one for Lysodren. The same study (Baudin, Pellegriti et al. 2001) showed that the cumulative mitotane dose was the only parameter possibly correlated with plasma level, while the daily mitotane dose explained only 35% of the variability between patients in the plasma level.

Therapeutic window. Kopf, Goretzki et al. 2001 suggests a dose-response relationship between mitotane serum level and survival. Another original publication (Haak, Hermans et al. 1994) suggests that mitotane is effective only when high serum levels can be achieved. However, the same paper also reports that

1. 62 patients received mitotane and only 30 achieved levels ranging 14-50 mg/l.
2. Among the 29 patients with measurable tumour size, a tumour response was seen in only 6 out of 14 patients with high mitotane serum levels
3. 6 out of the 11 patients treated with mitotane after apparently complete resection had serum levels >14 mg/l and a median survival of 51 months compared with 61 months in those with no adjuvant therapy
4. 5 mg/l appears to be the threshold serum level for gastro-intestinal toxicity and 15 mg/l the threshold for neuropsychological toxicity.
5. Therefore, there appears to be no therapeutic window; if any, it is achieved in few patients only.
6. High doses (12-14g/day) are also needed to control hypercortisolism in 50-60% of the patients (Latronico & Chrousos, 1997).

Although many authors seem to support this relationship, monitoring of mitotane serum levels is not common practice in many European centres.

Dose-efficacy relationship. Recent publications (Kasperlik-Zaluska 2000; Ahlman, Khorram-Manesh et al. 2001; Baudin, Pellegriti et al. 2001; Favia, Lumachi et al. 2001; Heilmann, Wagner et al. 2001) stress the importance of monitoring the plasma levels of mitotane: they suggest that efficacy is observed for plasma levels comprised between 14 and 20 mg/l. Intolerance is more often observed with the highest concentration (above 20mg/l). However, the dose-efficacy relationship is not so clear. For instance, Baudin et al. 2001 report that six out of 24 patients achieved the threshold therapeutic plasma level of 14mg/l: four of these six patients had a response (though three only hormonal), but 8 out 11 patients given mitotane as adjuvant therapy had recurrences even though mitotane plasma level was >14mg/l in six of them.

The range of doses used in published studies is considerably wide (from 2 g to 19 g per day). In the view of some authors, the highest tolerated dose is recommended, while other publications advocate for a dosing schedule in the lower bound of the tested range (2-4 g/day). In any case, due to the high affinity of mitotane for the fat tissue, the time to reach the proposed target plasma levels can be as long as 3-5 months. The applicant should justify the selection of the 2-6 g/day dosing schedule and how plasma drug levels should be monitored in order to get the proposed therapeutic window. This is again of primary importance taking into account that monitoring of plasma levels of mitotane is not available in many centres.

Finally, with respect to plasma levels, some authors (Haak, van Seters et al. 1990; Baudin, Pellegriti et al. 2001) questioned the bioavailability of some preparations used in clinical trials (e.g. enteric-coated

capsules) and suggest that tablets (as in the present application) may constitute the optimal form of administration.

In conclusion, this possible relationship reinforces the need of obtaining further knowledge on the pharmacokinetic profile of mitotane, in order to define an optimal dosing schedule allowing for reaching the mentioned therapeutic levels.

Main study(ies)

The Applicant has not conducted clinical efficacy and safety studies. The available clinical information on mitotane in adrenal carcinoma comes from published reports of uncontrolled studies.

For an update of clinical information, the Applicant performed a search in MEDLINE, using “mitotane” as the search term. A total of 220 articles were published after 1990. The clinical data identified from these 220 references have been reviewed, taking into account that some publications report the same series of patients at different follow-up stages. Some of the publications also refer to patients treated for Cushing’s syndrome of other origin than Adrenal Carcinoma, e.g. adrenal bilateral hyperplasia, benign adrenal tumours, or hypothalamic-pituitary Cushing which are not the indications claimed by the Applicant. However, these publications were reviewed to seek possible information related to safety of mitotane.

A number of publications have reported the clinical experience with mitotane for the treatment of adrenocortical carcinoma. In the vast majority of the cases, these publications report retrospective uncontrolled studies. It is not possible to sum up the total number of patients studied, since in several of these publications patients previously reported were included. Overall, these studies encompass experience in more than 500 patients followed for various time periods. In most of the publications, the actual formulation used for the treatment of patients is not reported.

The assessment of mitotane efficacy has the difficulties associated with an uncontrolled study design. It differs from study to study, as efficacy was variably judged based on survival, on remission time, or on tumour size reduction.

In addition, it was quite difficult to compare the results of the different studies, because most of them are retrospective studies and there are various discrepancies between the series by different factors: the stage of the disease (the response depends on the stage of the disease), the time of treatment initiation (at the time of surgery or later), associated treatments, and dose regimen.

The table below summarises the most pertinent available clinical data published in the English, French or German literature since 1990 in adults as identified by the bibliographic search as indicated above. Other publications are available in the literature but relate to series published before 1990 and have not been included in this clinical overview since they did not bring additional information in terms of efficacy or safety compared to the literature published since 1990. Some of these publications indicate that mitotane has been used in Europe well before 10 years ago.

Primary endpoints/assays. Efficacy was variably judged based on survival, on remission time, or on tumour size reduction.

Table 1: Main findings from literature survey of the treatment of adrenocortical carcinoma with mitotane alone in adults (data published from 1990, onwards)

Study Identifier	Study Design and Type of Control	Test product(s): Dosage Regimen Route of administration	Number of Subjects	Main results
Haak HR 1994	Open-label	Mitotane (Lysodren) 4 - 8 g/d in 4 divided doses	96 patients	No effect of mitotane on overall survival after total resection. However, when high plasma levels of mitotane were achieved, survival was improved.
Barzon L 1997	Open-label	Mitotane (Lysodren) 4-8 g/d	45 (27 received mitotane) In certain patients, chemotherapy was added.	No effect of mitotane on disease-free interval after resection or survival. In patients given chemotherapy + mitotane, survival was significantly longer than in patients given mitotane alone.
Dickstein G 1998	Open-label	Mitotane (formulation unknown) 1.5 to 2.0 g/d	4 patients followed for 21 to 68 months after surgery	At the time of publication, 2 patients are disease free (after 21 and 57 months on treatment). One patient died after 68 months on treatment of unrelated reason without tumour recurrence or metastasis. The fourth patient had 2 lung metastases after 48 months of treatment and is still doing well and is disease free 6 months after removal of metastases.
Wooten MD 1993	Open-label (retrospective) + literature survey	Mitotane (Lysodren), dose not reported	8 patients (4 treated with Lysodren®)	The result of the search indicated 64 reports (551 patients) treated with mitotane. One-third of the patients had least a partial response to mitotane.
Luton JP 1990	Open-label	Mitotane (capsule formulation): initial dose 10g/d (4 to 16 g/d) Maintenance dose : 7 g/d (3 to 20g/d)	105 patients	All patients (47) with functional AC had adrenal insufficiency during mitotane treatment. 27 % of patients with measurable tumour size had tumour progression, 2 had stabilisation of disease for 36 and 56 months respectively, and 8 had tumour regression. Overall, mitotane had no impact on survival.

Pommier RF 1992	Open-label	Mitotane (Lysodren) dose unreported	73 patients (29 patients received Lysodren® either alone or in combination with various agents)	No clear-cut benefit from mitotane treatment.
Kasperlik-Zaluska AA 2000	Open-label	Mitotane (formulation unknown) dose adapted to plasma levels, as a mean 6 g/d	82 patients. 59 patients received mitotane: in 32 it was started immediately after surgery, and 27 with a delay of 2 to 24 months.	56 % of patients survived for several months (4 to 118 months) in the group treated immediately after surgery. There were only 22 % survivors in patients treated after a delay following surgery.
Berruti A 1998 and Ref. 10 Terzolo M 2000	Open-label Prospective	Mitotane (Lysodren) 2 - 3 g/d plus chemotherapy	28 patients	Overall response rate 53.5 % (95 % CI: 35 – 72 %). Stable disease in 8 patients; progressive disease in 5. In responding patients, time to progression was 24.4 months.
Ilias I 2001	Open-label Retrospective	Mitotane (formulation unknown) : initial dose 3 to 6 g/d, decreased to 1 g/d	2 patients with metastatic AC followed respectively for 14 and 16 year under low dose mitotane.	In both patients, the disease was stabilised at the time of publication
Icard P 2001	Retrospective survey	Mitotane (capsule formulation ?). Initial dose 12g/d reduced to 3 - 4 g/d in 3 divided doses	253 patients with AC reviewed. Mitotane as an adjuvant therapy to 135 patients (53.5 %), postoperatively in 103 cases (76 %) and pre and postoperatively in 27 cases (20 %).	Significant improvement of survival in metastatic (stage IV) patients receiving mitotane after surgery.
Vassilopoulou-Sellin R 2001	Retrospective survey	Mitotane Unknown formulation 2 to 5 g/d	217 patients with AC. 74 patients received mitotane (evaluable response in 43 only).	52.4 % of the patients improved on mitotane. Overall survival time significantly higher in patients who responded to mitotane than in those who had disease progression on mitotane. Trend towards a significant increase (P = 0.07) in survival in patients who received mitotane.

Baudin E 2001	Open-label Prospective study	Mitotane (capsule formulation) 6 -12 g/d in 3 divided doses, in function of plasma levels	24 patients. First- line treatment in 13 patients with metastatic disease, adjuvant treatment in 11 patients from surgery.	In 58 % of patients, plasma mitotane level were above 14 mg/L. Objective response (1 complete, 3 partial) in 4/13 patients with metastatic disease. No response to patients who had persistently low plasma levels (outlining that formulation may be an important factor for efficacy). 8/11 patients with mitotane as adjuvant therapy had disease recurrence despite plasma levels > 14 mg/L. Neurologic toxicity was found in patients with levels > 20 mg/L.
Favia G 2001	Open-label	Mitotane (Lysodren) 4 - 5 g/d	31 patients with functional or non- functional AC. 18 of them had adjuvant post surgical mitotane treatment.	20 to 25 % of patients responded to mitotane (need for titration of the drug).
Khorram- Mannesh A 2001	Open-label	Mitotane Formulation unknown. 2 -6.5 g/d (mean dose 4 g/d, in function of plasma levels)	18 patients with AC. After surgery, 12 patients received mitotane with plasma level monitoring for a median duration of 12 months.	Few side effects were observed on mitotane because of plasma monitoring, allowing lower doses to be used (median dose: 4 g/d). Actual efficacy of mitotane impossible to evaluate in this study.
Heilmann P 2001	Retrospective survey	Mitotane Formulation unknown. 3 -8 g/d in function of plasma levels	9 patients (8 with metastasised AC) treated with Lysodren in Germany with plasma monitoring of mitotane.	Mean survival time significantly longer in patients who had plasma levels above 14 mg/L vs. those who failed to reach such level (41.2 ± 16.2 vs. 6.3 ± 3.6 months, $p < 0.01$). The dose of mitotane necessary to reach this level differed from one patient to another. Major side effects were observed in patients with plasma levels above 20 mg/L.
Kornely E 1994	Open-label	Mitotane Formulation unknown. 12 g/d (initial dose, decreased to 1.5 to 3 g/d	1 female patient with metastasised AC followed for 4 years on mitotane treatment	Daily treatment from 1989 to 1994: prolonged remission. GI side effects controlled when decreasing the dose of mitotane.

Wajchen-berg BL 2000	Retrospective study	Mitotane Formulation unknown. 6 to 15 mg/kg/day in 3 o 4 intakes.	47 patients (22 children) with AC followed for the last 17 years in Brazil. 15 patients have received mitotane.	Only one patient had metastasis regression after 2 months on mitotane. No clear-cut effect in the other patients and no indication of survival increase.
Kasperlik- Zaluska AA 1998	Retrospective survey	Mitotane Formulation unknown. Initial dose 8 - 10 g/d decreased to 3 - 5 g/d in function of plasma levels	21 cases. 17 patients received mitotane as adjuvant therapy with plasma monitoring	9 of 13 survivors treated with mitotane were free of disease at the time of publication. One patient remained free of disease for 13 moths and mitotane was discontinued. 2 months later he had a recurrence and reintroduction of mitotane resulted in a decrease in tumour size. In general, mitotane appeared to improve prognosis in these AC diagnosed early.

Targeted population. Mitotane is frequently used for patients with unresectable adrenal carcinoma. However, the claimed indication (treatment of adrenal carcinoma) includes all the stages of the disease, such as inoperable adrenal carcinoma (metastases or recurrent local tumour) and the adjuvant treatment at the time of surgery (prior to, or after surgery), both for adult and paediatric population. No controlled prospective study evaluating the benefit of mitotane was published. In addition, in a number of publications mitotane was initiated systematically at the time of surgery. The first approach is confirmed by published review (Libertino 1988). Some articles are actually very critical in this respect (Khorram-Manesh, Ahlman et al. 1998) a vast review of 253 patients showing that mitotane benefited only the group of patients not operated. Moreover, an article not included in the Marketing Authorisation Application (Vassilopoulou-Sellin, Guinee et al. 1993) does not support the conclusion that adjuvant mitotane is beneficial in patients with localised or regional adrenocortical cancer: in this study mitotane improved neither the disease-free interval nor survival.

Effect on survival. There are only few studies assessing the efficacy of mitotane on survival rates: In four studies (Barzon, Fallo et al. 1997; Heilmann, Wagner et al. 2001; Icard, Goudet et al. 2001; Vassilopoulou-Sellin and Schultz 2001) there was an increase in survival rate whereas in two (Pommier and Brennan 1992; Haak, Hermans et al. 1994) no such improvement was reported. Finally, (Vassilopoulou-Sellin and Schultz 2001) there was a non-significant ($p=0.07$) survival advantage, which is defined as modest but has not been quantified; in any case the authors call for caution on this finding due to possible selection bias of the treatment option. In five patients who had mitotane serum levels $\geq 14\text{mg/l}$, mean survival was longer than in those with lower drug plasma levels, which does not necessarily prove that mitotane prolongs survival (Heilmann, Wagner et al. 2001). One publication (Barzon, Fallo et al. 1997) reports that the survival rate observed in patients receiving mitotane in association with chemotherapy was similar to that observed in patients given chemotherapy alone, and significantly longer than in patients given mitotane alone. This suggests a possible interaction of mitotane and chemotherapy. Most of the studies report tumoral regressions or stabilisation of the disease, and the percentage of responders varies widely from one study to another. It is stated a rate of 20 to 30 percent responders like a realistic estimate.

In their review of the literature on efficacy of mitotane, Kopf et al. 2000 explained the various discrepancies between the series by different factors: the stage of the disease, the time of treatment initiation (at the time of surgery or later), associated treatments, and dose regimen. Regarding the latter, the Applicant supported the existence of a dose-response relationship between mitotane level in serum and survival (Haak, Hermans et al. 1994; Kopf, Goretzki et al. 2001). Finally, therapeutic drug

monitoring may be helpful to target serum levels above 14 mg/l or even better above 20 mg/l if tolerance allows it, taking into account that side effects are dose-dependent.

In a retrospective series over 33 years from Poland (Kasperlik-Zaluska 2000), 82 patients with adrenal cortical carcinoma were treated with mitotane, 32 of them immediately after surgery, and 27 after a delay of 2 to 24 months. At the time of publication, there were 18 survivors (56%) in the group treated immediately after surgery, and 6 survivors (22%) in the other group.

In a retrospective study from the USA, mitotane was associated with a 24% response rate in patients with metastatic or unresectable adrenal cortical carcinoma, with no clear-cut increase in survival time (Pommier and Brennan 1992).

In a French large retrospective study (Luton et al., 1990), mitotane was able to control hormonal secretion in 75% of the patients. Some patients had tumour stabilisation for up to 56 months and a few (8 out of 37 patients treated with mitotane) had tumour regression, a fact, which was never observed among patients not treated with mitotane. Overall, however, the effect of mitotane on survival was not significant.

Dosage recommendations. As indicated in the above literature survey, the recommended dosage for adrenal carcinoma treatment varies from 8 to 12g/day in three divided doses. The time of treatment initiation depends on the investigator but a number of studies suggest that treatment should be initiated at the time of surgery for those patients undergoing surgical removal. Daily dosage must be adapted in function of the desired plasma levels: efficient plasma levels range between 14 and 20mg/l. Plasma levels above 20mg/l may be associated with severe side effects and bring no further therapeutic advantage. In children, the recommended daily dose varies from 7 to 12g/m²/day. As in adults, plasma levels between 14 and 20mg/l may be desirable. This point appears to be in line with what has been experienced in literature. However, the US product information for Lysodren recommends starting treatment at 2 to 6g per day and then increasing it incrementally up to 9 to 10g per day; if severe side effects appear, the dose should then be reduced until the maximum tolerated dose is achieved. Experience has shown that the maximum tolerated dose in literature has been varying from 2 to 16g per day, but has usually been 9 to 10g. It is true that based on the available literature data the time of treatment initiation depends on the investigator, but the lack of scientific evidence on the best time to commence therapy should further stress the need for more comprehensive testing of this product.

Combination with chemotherapy. The literature survey also provides some information on the use of mitotane in combination with other drugs used for controlling tumour growth: a variety of cytostatic agents have been tried for the treatment of adrenal cortical carcinoma, such as cisplatin, doxorubicin, suramin, 5 fluorouracil and etoposide. Interestingly, mitotane in combination with these agents may increase their efficacy, a fact that is related to the finding that mitotane is able to reverse *in vitro* multidrug resistance (Dogliotti, Berruti et al. 1995; Berruti, Terzolo et al. 1998). Streptozocin in combination with mitotane has also been found to have some effect on disease-free interval in patients with adrenal cortical carcinoma (Khan, Imam et al. 2000). A prospective US study evaluating the efficacy of mitotane combined with cisplatin in 37 evaluable patients with metastatic or residual AC concluded that the combination could be efficient (Bukowski, Wolfe et al. 1993). However, another recent prospective study in the USA (Williamson, Lew et al. 2000) has shown that combining cisplatin and etoposide for adrenal cortical carcinoma (local or metastasised disease) had minimal activity and that adding mitotane (4g/day) without plasma level monitoring led to an objective response in only 2 out of 16 evaluable patients. Conversely, a patient with liver metastasis of an adrenal cortical carcinoma was followed for 11 months while on mitotane with only minimal response and marked gastro-intestinal side effects. Mitotane was discontinued and replaced by cisplatin and etoposide, which induced a >50 % reduction in metastasis size (Zidan, Shpendler et al. 1996). In a French evaluation of etoposide and cisplatin in combination with mitotane (at doses resulting in plasma levels >14mg/L) in 18 patients with advanced adrenal cortical carcinoma (Bonacci, Gigliotti et al. 1998), the treatment resulted in a complete response in 3 cases and in a partial response in 3 cases. Tolerance was acceptable and no treatment interruption was required. A Japanese report suggests that combining mitotane with tegafur was also an option for the treatment of metastatic adrenal carcinoma (Nakamura, Kuzuya et al. 1990). Berruti et al. (Berruti, Terzolo et al. 1998), the authors concluded that the

combination of etoposide, doxorubicin and cisplatin (EDP) with mitotane “appeared active and manageable”, that compared with EDP alone “some additional side effects due to mitotane concomitant medication, such as neurotoxicity and hyperlipidemia, were observed” and that this “combination regimen should be further explored with a larger series of patients”. Other authors concluded (Khan, Imam et al. 2000) that the combination of streptozocin and mitotane “needs further evaluation with larger patient materials in randomised trials”. Finally (Bukowski, Wolfe et al. 1993), the authors of study conclude that the combination of cisplatin and mitotane “seems to have modest antitumor activity” and consider that while “it is unclear whether the addition of mitotane increased the effectiveness of cisplatin, certainly the combination seems to have had additive toxicity. Substantial neurologic and gastrointestinal toxicity occurred during the study and led to premature discontinuation of therapy in 47% of patients”. In conclusion, the literature seems to agree that larger randomised trials are required to appropriately test the safety and efficacy of mitotane in combination with other chemotherapy agents. Certainly, there is no consensus on the efficacy of mitotane in combination with other agents for the treatment of patients with adrenal cortical carcinoma.

Clinical studies in special populations

The only available information about the use of mitotane in special populations refers to children. Other groups such as elderly, patients with hepatic or renal impairment or others are not considered in this clinical dossier.

Children. As in adults, adrenal cortical carcinoma in children is a very severe tumor: disease-free interval is approximately 9 months but regional disease at presentation is associated with a shorter disease-free interval (approximately 3 months). Mitotane treatment after excision may be associated with a longer survival. The dose usually reported varies from 7 to 12g/m²/day. However, data in children are very limited and, as indicated in their reviews, Ribeiro et al. (Ribeiro, Michalkiewicz et al. 2000) and Teinturier et al. (Teinturier, Pauchard et al. 1999) conclude that the role of mitotane for the treatment of childhood AC has not been established in comparative trials. However, there are some reports that, as in adults, mitotane treatment may be associated with prolonged remissions (Godil, Atlas et al. 2000; Ciftci, Senocak et al. 2001). Other authors (Ciftci, Senocak et al. 2001) did not find a significant effect of mitotane on survival rate and conclude that these patients “should be entered into multi-institutional trials to assess adequately effective chemotherapy and radiotherapy protocols”. In a case report (Godil, Atlas et al. 2000), the authors while acknowledging that their case responded well to mitotane therapy conceded that improved survival with mitotane is controversial in pediatric patients.

In conclusion, like in adults adrenal cortical carcinoma in children is a very severe tumour: disease-free interval is approximately 9 months but regional disease at presentation is associated with a shorter disease-free interval (approximately 3 months). Data in children are very limited and two reviews (Teinturier, Pauchard et al. 1999; Ribeiro, Michalkiewicz et al. 2000) conclude that the role of mitotane for the treatment of childhood adrenal cortical carcinoma has not been established in comparative trials. However there are some reports that showed, as in adults, that mitotane treatment might be associated with prolonged remissions.

Discussion on clinical efficacy

Adrenal carcinoma is a rare disease with no curative treatment when surgery is impossible or has failed; therefore further therapeutic options are needed for this patient population. Mitotane has been used for decades in many countries, including in Europe on a compassionate basis, for the treatment of inoperable adrenal carcinoma and it seems to constitute the main therapeutic option in such cases (see also well-established used justification). Different cytotoxic agents have also been used in the treatment of adrenal cortical carcinoma, such as cisplatin, doxorubicin, suramin, 5 fluorouracil and etoposide, with questionable efficacy results and considerable higher toxicity.

No prospective comparative study assessing efficacy and safety of mitotane in a well-defined protocol has been carried out. The clinical dossier included in this application consists on published studies of poor quality. Most of them are retrospective case-series with mitotane being evaluated as palliative

therapy in advanced stages or as adjuvant treatment to surgery. The series of cases provided in the literature review data on the use of mitotane include an extremely heterogeneous population in terms of disease stage, objective of the therapeutic intervention (adjuvant to surgery or palliative treatment in non-surgical population), associated treatments, and dose regimen. Due to the nature of the published literature, there is no information for the existing data on how GCP were followed. The evidence concerning the clinical efficacy of mitotane can be summarised as follows:

Efficacy of mitotane in advanced adrenal cortical carcinoma.

Some publications suggest that mitotane administration can provide some benefit in patients with non-resectable or metastatic adrenal cortical carcinoma.

In two papers (Haak, Hermans et al. 1994; Barzon, Fallo et al. 1997) where mitotane (Lysodren for all patients in the study conducted by Haak et al.) has been studied as a true “adjuvant” treatment, there was no clear-cut evidence that mitotane can increase the disease-free interval and delay the onset of recurrence. It is noteworthy that reference (Haak, Hermans et al. 1994) is a prospective evaluation of Lysodren either as a treatment of unresectable adrenal carcinoma, or as an adjuvant treatment, with monitoring of plasma levels of mitotane: the authors found an obvious effect of Lysodren on survival and tumour regression for unresectable tumours (see below) and no effect when used as an adjuvant treatment: it is therefore unlikely that a further trial will show a positive adjuvant effect unless new prognostic factors appear in the future to select potential responders or new means to detect micrometastases become available.

Therefore, the CPMP considered that the indication should be restricted to unresectable adrenal carcinoma (i.e. no possible surgical removal of tumour or metastases, or incomplete removal of tumour and/or metastases).

Effect on survival.

Mitotane appears to prolong the survival of those patients whose tumours regress. There have been reports of a few patients who achieved complete remissions with long-term survival (greater than 5 years), although this finding does not mean that the prolonged survival is related to mitotane response. The published data do not provide sufficient evidence to support any effect of mitotane on survival.

Tumour regression.

Most of the studies report tumoral regressions or stabilisation of the disease, and the percentage of responders varies widely from one study to another. It should also be noted that an important number of studies have not been assessed using the usual response criteria. A rate of 20 to 30 percent responders is suggested as a realistic estimate (mainly either partial or just a slight reduction of tumour size). This might not be substantially different from the response rate observed with chemotherapy (mainly platinum-based regimens), but with a considerably better tolerability profile. Although no comparative trials exist assessing the effect of mitotane on adrenal cortical carcinoma in terms of objective responses and a study has yet to be conducted with modern imaging techniques and response criteria accepted by clinical oncologists, the irremediably progressive nature of the disease makes that any tumour regression obtained after a therapeutic intervention can be considered as a proof of effect (at least some effect) on the objective response. It is difficult to determine whether the magnitude and duration of this anti-tumour effect is comparable to that obtained with conventional chemotherapeutic agents. The heterogeneity of the regimens used (although cisplatin based regimens are the most commonly used) and the stage of the disease when therapy is started make unfeasible making a sound indirect comparison between both strategies. However, and according to the expert view, the following aspects favours the choice of mitotane in front of chemotherapy with conventional agents:

- If existing, the differences in response rate and duration of response between both regimens must be considered as clinically irrelevant.
- None of the regimens have demonstrated that the anti-tumour effect is associated with an improvement in survival or an increased disease-free interval.

- The toxicity profile of conventional chemotherapy is considerably higher and the acceptability by the patients much lower.
- Last, but not least, the anti-hormonal effects of mitotane allow for a better symptomatic control of the patients (see below)

Subjective response. This is an issue of extreme importance in this advanced population with such a fatal prognosis. Clinical effectiveness consists on reducing weakness, anorexia, pain (when present) and symptoms and, in functional tumours, signs and symptoms related to excessive steroid production.

Although the data provided show a variable effect of mitotane on the control of symptoms, it has been reported that it may induce a transitory return (lasting from few weeks to several months) of hormonal findings to normal levels in up to 75% of patients. In any case, treatment is never curative, and tumour regression is transient. On the literature reports (and also in the view of the expert) the effect of mitotane on the control of symptoms is higher than that observed with conventional chemotherapy. This apparent difference is specially marked in (but not limited to) functional adrenal cortical carcinoma tumours inducing a constellation of clinical pictures that significantly impair patient's quality of life (Cushing syndrome, virilisation, feminisation and hyperaldosteronism).

Efficacy of mitotane as adjuvant therapy in adrenal cortical carcinoma.

Mitotane has been used as an adjunct following surgery removal of the primary tumour in a limited number of patients in order to delay or prevent recurrent disease. Some of the publications provided by the applicant suggest that mitotane as adjunctive therapy might be associated with an improved survival. However, available evidence (and also corroborated by the wide range of publications on this issue) suggests that its value as an adjunct to surgery has not been adequately investigated in an efficacy and safety study and cannot be considered as proven.

Efficacy of mitotane in children.

The prognosis of adrenocortical carcinoma always is guarded. Sporadic cures have been reported in patients who underwent complete removal of a small (<9 cm) encapsulated tumour. Reports of remission of metastatic disease are only anecdotal. More aggressive surgical approaches have led to an expansion of mean survival time of approximately 18 months to occasionally longer than 48 months. Few studies of aggressive surgery and early adjuvant therapy are available. In this application, there are not enough data to assess the use of mitotane in children. There are no reasons to think that the role of mitotane in the treatment of adrenal cortical carcinoma in children might be substantially different than the one for adults (palliative therapy in inoperable adrenal cortical carcinoma). However, as no clear peak incidence according to age has been described, the applicant should, on the basis of available data, further elaborate on the potential usefulness and limitations of use of mitotane as well as the potential need for different dosing schedules according to age strata. In conclusion, the efficacy in patients under the age of 18 years has not been established and, at present only very limited data are available in this age group.

There are published data suggesting that assaying mitotane levels during therapy is valuable because its therapeutic efficacy depends on achieving serum levels of at least 14 mg/l and below 20 mg/l. The proposed treatment schedule is as follows: start at doses between 3 and 6 g of Lysodren per day given in three divided doses. Monitoring the plasma level of mitotane is advisable in order to target the therapeutic level which is 14 mg/l or above: experience indicates that such level can be reached when the patient has received a cumulative amount of 75 g Lysodren. After such exposure to Lysodren, plasma mitotane levels may need to be monitored at biweekly intervals. Levels higher than 20 mg/l may be associated with severe undesirable effects and offer no further benefit in terms of efficacy. When levels of 14 mg/l or above are reached, Lysodren dose should be reduced in order to maintain plasma levels in the desired range, taking into account that levels may still raise despite dose reduction, necessitating in some cases temporary Lysodren interruption. Experience with Lysodren indicates that maintenance doses of 1–2 g per day may be sufficient to maintain the patient at the desired target dose. Data with various mitotane formulations suggest that administration with food and/or oil can enhance absorption.

Therefore in the light of the published data mitotane may be beneficial for patients unable to undergo complete resection of the tumour. An estimated 80% of the patients with functioning tumours and treated with mitotane will show a substantial diminution in hormone production. In metastatic adrenocortical carcinoma, temporary palliation of disseminated adrenocortical carcinomas can sometimes be achieved. Although measurable partial remissions are unusual and are reported in 20 to 30% of cases, excellent palliation of hormone symptoms is commonly observed. Therefore, mitotane is clinically beneficial for the symptomatic treatment of patients with advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma. There does not appear to be a role for mitotane as adjuvant therapy if the patient has undergone complete resection of the tumour.

The efficacy in patients under the age of 18 years has not been established and, at present only very limited data are available in this age group.

Clinical safety

The information concerning the clinical safety of mitotane provided by the Applicant was extracted from the published literature, from a five years Periodic Safety Update Report covering the period from 8 July 1997 to 7 July 2002 and from the US product information for Lysodren (primarily on the initial New Drug Approval application submitted to the FDA in 1969).

Patient exposure

Some data on exposure are available in the scientific literature, however these data suffer most likely from an important underreporting of the true number of patients being treated with mitotane in the EU or worldwide. In the Periodic Safety Update Report covering the period from 8 July 1997 to 7 July 2002. In this report the MAH made the assumptions that all patients are adults with normal hepatic function receiving mitotane for inoperable adrenal cortical carcinoma, each patient receives 10 grams daily for 365 days (which is a high daily dose of mitotane). Based on these assumptions and based on the bulk worldwide sales, the Applicant estimated that slightly more than 1,700 patients were treated during one year over the period covered by the Periodic Safety Update Report. These data should be taken with caution since the bulk worldwide sales figures were an underestimate of the total quantity actually sold. An estimate of the number of patients liable to benefit from a treatment with mitotane was calculated in the well-established use justification of this report.

Serious adverse reactions/deaths/other significant reactions¹

In most of the clinical studies analysed, side effects were reported with few comments, since they were expected from previous experience obtained with Lysodren mostly in the USA.

¹ In this report, the terms adverse drug reactions and adverse events are used according to the current EU legislation. An adverse drug reaction is defined by a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function. A reaction, contrary to an event, is characterised by the fact that a causal relationship between the drug and the occurrence is suspected. An adverse event does not necessarily have a causal relationship with the treatment. Finally, the term "severe" is not synonymous with serious. Severe is used to describe the intensity (severity) of a specific event (as in mild, moderate or severe). The safety profile of mitotane is described according to the MedDRA system organ classes or MedDRA terminology.

Frequencies are expressed according to the EU guideline on summary of product characteristics (Report from CIOMS Working Group III, Geneva 1995 terminology) Very common (>1/10) Common (>1/100, <1/10) Uncommon (>1/1,000, <1/100) Rare (>1/10,000, <1/1,000) Very rare (<1/10,000), including isolated reports.

A very high percentage of patients (more than 80 percent) treated with Lysodren have shown at least one type of undesirable effect. The drug discontinuations due to side effects are not described in the dossier.

The most frequently observed adverse reactions consist of gastrointestinal, neurological and skin reactions.

Gastro-intestinal disorders: Gastrointestinal disturbances, which consist of anorexia, nausea or vomiting, and in some cases diarrhoea, occur in about 80% of the patients. The thresholds for gastrointestinal and neuropsychological toxicities have been reported to be about 5mg/l and 15 mg/l respectively. Moreover, plasma concentration monitoring can be difficult for a substance with such long elimination half-life and extensive distribution, as the time period before a change in dose will have an impact on plasma concentration will be very long.

Nervous system disorders: Adverse reactions affecting the central nervous system occur in 40% of the patients. These consist primarily of depression as manifested by lethargy and somnolence (25%) and dizziness or vertigo (15%). At high doses and after prolonged utilisation, brain function impairment can occur which, however, appears reversible at treatment cessation. Therefore, behavioural and neurological assessments should be made at regular intervals when continuous Lysodren treatment exceeds 2 years. In addition, since sedation, lethargy, vertigo, and other central nervous system side effects can occur so, ambulatory patients should be cautioned about driving, operating machinery, and other hazardous pursuits requiring mental and physical alertness. The monitoring of mitotane plasma levels may help at preventing the neurological toxicity if the plasma levels are maintained below 20 mg/l.

Skin and subcutaneous tissue disorders: Skin toxicity has been observed in about 15% of the cases. The skin changes consist primarily of transient skin rashes, which do not seem to be dose related. In some instances, this side effect subsided while the patients were maintained on the drug without a change of dose.

In addition, the US product information for Lysodren lists a series of less common adverse reactions involving:

Eye disorders: visual blurring, diplopia, lens opacity, toxic retinopathy;

Renal and urinary disorders: hematuria, haemorrhagic cystitis, and albuminuria;

Cardiac disorders: hypertension, or orthostatic hypotension, and flushing;

The US product information for Lysodren is based primarily on the initial New Drug Approval application. The following table summarises the side effect profile reported in this application among 241 patients with adrenal carcinoma.

Side effect profile reported in the Initial New Drug Approval application (1969)

Side effect	Cases (n = 241)
No effect	32 (13 %)
Gastrointestinal	190 (79 %)
Anorexia	59 (24 %)
Nausea	94 (39 %)
Vomiting	86 (37 %)
Diarrhoea	76 (31 %)
Other	31 (13 %)
Neuromuscular	119 (49 %)
Depression	78 (32 %)
Dizziness or vertigo	36 (15 %)
Muscle tremors	8 (3 %)
Headache	11 (5 %)
Confusion	8 (3 %)
Weakness	29 (12 %)
Other	26 (11 %)
Skin	36 (15 %)
Rash	29 (12 %)
Other	12 (5 %)
Eye	8 (3 %)
Genitourinary	5 (2 %)
Cardiovascular	5 (2 %)
Miscellaneous	20 (8 %)

Other adverse drug reactions are listed in the US product information for Lysodren. These reactions are: transient weakness, baldness, increased pain, epigastric gnawing, nosebleed, sore tongue, loose stools, dry mouth and lips, hypertension, yellow facial pigment, osteoporosis, lack of memory, weight loss, possible esophagitis, tinnitus, blurred vision, postural hypotension, posterior polar cataracts, abdominal cramps, hot flashes, fever, irritability, enuresis, drowsiness.

The most frequently reported side effects in the published literature are gastro-intestinal disorders (nausea, vomiting) and nervous system disorders (ataxia, somnolence, lethargy, dysarthria, vertigo, mental deterioration), myasthenia.

The articles published in the scientific literature indicate that some undesirable effects appear to be dose – dependent and their incidence and severity can be decreased with a reduction of the daily dose. Some of them (including the neurological disturbances and mental retardation) seem to be reversible after treatment discontinuation (Bollen and Lanser 1992). The recent availability of a plasma assay of mitotane and its metabolites (Dickstein, Shechner et al. 1998) may allow a more precise determination of the active dose: additional clinical data (Terzolo, Pia et al. 2000; Baudin, Pellegriti et al. 2001) indicate that the appropriate serum mitotane level is about 14 mg/l and that serum levels above 20 mg/l may induce adverse reactions. Appropriate serum levels may be achieved with lower daily doses of mitotane (2 to 3 g/daily), and some reports suggest that monitoring the plasma levels of mitotane leads to lower daily administration, hence a better tolerance of Lysodren (Khorram-Manesh, Ahlman et al. 1998; Terzolo, Pia et al. 2000; Baudin, Pellegriti et al. 2001; Heilmann, Wagner et al. 2001; Ilias, Alevizaki et al. 2001).

Laboratory findings

Mitotane reversibly increases the blood level of hormone-binding proteins (SHBG, TBG, CBG and vitamin D-binding protein) (van Seters and Moolenaar 1991). The mechanism of this phenomenon is not clear but may involve estrogen excess, leading to feminising phenomena (e.g. gynaecomastia) observed during mitotane treatment. This finding has practical consequences: total serum hormone levels cannot be used as the only parameter to monitor the effects of mitotane on endocrine function.

This is especially relevant for the monitoring of cortisol substitution that therefore requires measurements of free cortisol and ACTH levels. In this respect, a literature report (Hague, May et al. 1989) indicates the occurrence of adrenal crisis in two patients treated with mitotane requiring the use of high amount of steroid substitution. These adrenal crises were associated with evidence of liver enzyme induction (shortening of antipyrine half-life during mitotane treatment), which may have played an important role in the occurrence of the steroid resistance. A substantial percentage of the patients treated show signs of adrenal insufficiency. It therefore appears necessary to institute steroid replacement in those patients. Since Lysodren increases plasma level of steroid binding proteins, free cortisol and ACTH determinations are necessary for optimal dosing of steroid substitution.

Liver function tests NOS abnormal: The hepatotoxicity of mitotane has been reviewed (Neuman, Bruckert et al. 2001) in a retrospective review of 10 patients with Cushing syndrome (no patient had an adrenal carcinoma in this series), after a mean dose of 9 g per day. In all patients a raise of plasma cholesterol was noted. Before treatment, 3 patients had an increase in plasma alanine aminotransferase (ALAT). During treatment all patients had an increase of either alanine aminotransferase (ALAT) or gamma-glutamyltransferase (gamma-GT), or both. The maximum increase was 6 times the upper normal value, for mean doses of approximately 9 grams per day. The increase was detected after 2 weeks on treatment in 4 patients, and within 4 months in the others. Treatment discontinuation led to normalisation within 4 months to one year. No case of liver failure were reported.

Blood and the lymphatic system disorders: Cases of leucopenia, decrease in leucocytes, platelets or erythrocytes were reported in some patients without any conclusion as to whether or not these effects are related to mitotane, or to the underlying disease of the patients. A reversible pancytopenia has been reported in a patient treated by mitotane (3g/day) for a paraneoplastic Cushing's syndrome (Andres, Vinzio et al. 2001).

Hypercholesterolaemia (HDL) has been reported during mitotane treatment (Vassilopoulou-Sellin and Samaan 1991; Maher, Trainer et al. 1992; Gebhardt, Moolenaar et al. 1993). The proposed mechanism of action is a blockade of cytochrome P450-mediated reactions leading to a down-regulation of hepatic cholesterol synthesis. The use of cholesterol-synthesis inhibitors (statins) reverses this effect and can be proposed in association with mitotane treatment.

Safety in special populations

No specific data addressing the safety of mitotane in children were included in the Marketing Authorisation Application. However, based on the safety profile of the product observed in adults and based on the information included in the US product information for Lysodren, the summary of product characteristics for Lysodren states that 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 during mitotane treatment.

Safety related to drug-drug interactions and other interactions

Spironolactone: Mitotane should not be given in combination with spironolactone since this product may block the action of mitotane. This association is contra-indicated.

Warfarin and coumarin-like anticoagulants: Mitotane has been reported to accelerate the metabolism of warfarin by the mechanism of hepatic microsomal enzyme induction, leading to an increase in dosage requirements for warfarin. Therefore, physicians should closely monitor patients for a change in anticoagulant dosage requirements when administering mitotane 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 products metabolised via cytochrome P450 may be modified. In the absence of information on the specific P450 isoenzymes

involved, caution should be taken when coprescribing active substances metabolised by this route such as, among others, anticonvulsants, rifabutin, rifampicin, griseofulvin and St. John's Wort (*Hypericum perforatum*).

Mitotane can give rise to 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 coprescribing medicinal products with central nervous system depressant action.

Post marketing experience

Finally, the five-year Periodic Safety Update Report covers the period from 8 July 1997 to 7 July 2002 from Bristol – Myers – Squibb submitted to the Regulatory Authorities of the third countries where Lysodren is authorised was included in the Marketing Authorisation Application for Lysodren. The conclusion of this document is that during the period covered by the report of the update, no previously unrecognised adverse reaction has been identified and that no change of the safety section of the summary of product characteristics for Lysodren or patient information leaflet was warranted.

Five severe adverse reactions were reported in the EU (one in Germany and four in the UK) where Lysodren is available on a compassionate basis and four cases came from countries where Lysodren is approved (3 cases in the USA and one in Canada).

There were two cases of death: both were related to the progression of the underlying adrenal carcinoma and none appeared related to mitotane.

The severe reactions occurring in 4 patients were reported during the period covered by the Periodic Safety Update Report. These cases are the following: death (2 cases), adrenocortical carcinoma (1 case), neoplasm progression (1 case), anaemia (1 case), hyponatremia (1 case), diarrhoea (1 case), nausea (1 case), erythema multiforme (1 case).

The cases listed in this Periodic Safety Update Report broken down by system organ class are the following:

<u>System Organ Class</u>	<u>N of cases</u>	
Blood and lymphatic system disorders	1	
Anaemia	1	
Eye disorders		1
Vision blurred		1
Gastrointestinal disorders		4
Diarrhoea	1	
Nausea		2
Vomiting	1	
General disorders and administration site conditions		4
Death		2
Fatigue		2
Lethargy	1	
Injury, poisoning and procedural complications	1	
Accidental exposure		1
Investigations		2
Liver function tests abnormal	2	
Metabolism and nutrition disorders		1
Hyponatraemia		1
Neoplasm benign, malignant and unspecified (incl. cysts and polyps)	2	
Adrenocortical carcinoma		1
Neoplasm progression		1
Nervous system disorders		2
Dizziness	1	
Memory impairment		1
Respiratory, thoracic and mediastinal disorders	2	
Dyspnoea	1	
Pleural fibrosis		1
Skin and subcutaneous tissue disorders	3	
Erythema multiforme		1
Rash erythematous	1	
Rash maculo-papular		1

Although no conclusion can be drawn from the present Safety Periodic Update Report regarding the relationship between dose of mitotane and occurrence of adverse events, literature indicates that some side effects appear to be dose-dependent and their occurrence and/or severity may be decreased when decreasing the daily dose.

Discussion on clinical safety

Regarding safety aspects, the severity of inoperable or relapsing adrenal cortical carcinoma could justify the use of a product that can induce clinically significant undesirable effects in a high proportion of patients (more than 80%). The most frequently observed adverse reactions consist of gastrointestinal, neurological toxicities and cutaneous reactions. In addition, as outlined above, the availability of plasma measurements of mitotane could help prescribers to target the optimal therapeutic plasma levels (14 – 20 mg/l) and thus avoid the risk of serious adverse reactions which are dose-related and are usually observed when plasma mitotane levels are above 20 mg/l. Hepatic reactions were reported and may be reversible when treatment is discontinued.

Mitotane is contraindicated in combination with spironolactone. Mitotane has been reported to accelerate the metabolism of warfarin by the mechanism of hepatic microsomal enzyme induction, leading to an increase in dosage requirements for warfarin. Therefore, physicians should closely monitor patients for a change in anticoagulant dosage requirements when administering mitotane to patients on coumarin-like anticoagulants.

No specific data addressing the safety of mitotane in children were included in the Marketing Authorisation Application. 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. Growth retardation may be also observed during mitotane treatment.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

At the time of the CPMP opinion, a number of quality issues were not completely resolved, particularly in the context of in vitro control measures necessary to provide a comfortable margin of confidence concerning the satisfactory and reproducible bioavailability of mitotane from this product, from batch to batch.

On balance, the CPMP has reached their opinion on the basis of an 'overall' benefit/risk balance, taking into account the clinical usefulness of this product in the proposed indication, and accepting that some quality deficiencies have not been fully resolved at the time of the opinion. Consequently the applicant has been required to give a commitment to resolve these outstanding quality concerns within a defined timeframe, as post-opinion followup measures.

Non-clinical pharmacology and toxicology

Non-clinical data on the general toxicity of mitotane is limited. Reproductive toxicity studies indicate that DDT and other polychlorinated biphenyl analogues are recognised 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 have not been investigated. The administration of mitotane is contraindicated in case of breast-feeding.

Efficacy

Mitotane is an adrenal cytotoxic active substance, although it can cause adrenal inhibition, apparently without cellular destruction. Its biochemical mechanism of action is unknown. Data are available to suggest that mitotane modifies the peripheral metabolism of steroids as well as directly suppressing the adrenal cortex. The administration of mitotane alters the extra-adrenal metabolism of cortisol in man, 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- β -hydroxyl cholesterol.

Mitotane has not been studied in a clinical therapeutic 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 plasma mitotane is above 14 mg/l. In terms of total or partial tumour and/or metastasis regression, eleven studies have shown some degree of improvement and sometimes-occasional prolonged remissions. However, in several studies, the objective criteria for evaluating tumour response are missing or not reported. There are nevertheless some studies, which provide accurate information on tumour regression or disappearance and demonstrate that the threshold of 14 mg/l appears necessary to induce an objective tumour regression. 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 hormone therapy.

Paediatric population: The efficacy in patients under the age of 18 years has not been established and, at present only very limited data are available in this age group. Clinical information comes mainly from a large retrospective trial in children (median age, 4 years) who had an unresectable primary tumor or who presented a tumor recurrence or a metastatic 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%.

Safety

Regarding safety aspects, the severity of inoperable or relapsing adrenal cortical carcinoma could justify the use of a product that can induce clinically significant undesirable effects in a high proportion of patients (more than 80%). The most frequently observed adverse reactions consist of gastrointestinal, neurological toxicities and cutaneous reactions. In addition, as outlined above, the availability of plasma measurements of mitotane could help prescribers to target the optimal therapeutic plasma levels (14 – 20 mg/l) and thus avoid the risk of serious adverse reactions which are dose-related and are usually observed when plasma mitotane levels are above 20 mg/l. Hepatic reactions were reported and may be reversible when treatment is discontinued.

Mitotane is contraindicated in combination with spironolactone. Mitotane has been reported to accelerate the metabolism of warfarin by the mechanism of hepatic microsomal enzyme induction, leading to an increase in dosage requirements for warfarin. Therefore, physicians should closely monitor patients for a change in anticoagulant dosage requirements when administering mitotane to patients on coumarin-like anticoagulants.

No specific data addressing the safety of mitotane in children were included in the Marketing Authorisation Application. 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. Growth retardation may be also observed during mitotane treatment.

Benefit/risk assessment

The three main questions concerning the clinical efficacy of mitotane were discussed on 17 November 2003 after the CPMP proposed to consult the Therapeutic Advisory Group in Oncology. Three main questions related to the indication of mitotane, the possible existence of a pharmacokinetic/pharmacodynamic relationship and the relevance of the post-authorisation commitments.

On the basis of the experience of use and published data, the CPMP asked the TAG to discuss the possible effect of mitotane in the symptomatic treatment of patients with advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma and a possible limitation of the effect to those patients with functional tumours. The TAG considered that on the basis of published data that mitotane has a clinically relevant effect in the symptomatic treatment of patients with advanced (i.e. unresectable, metastatic or relapsed) adrenal cortical carcinoma. In addition, the majority of patients (an estimated 70%) suffer from a functional adrenal cortical carcinoma. However, the TAG considered that a beneficial effect could be expected in all patients with advanced adrenal cortical carcinoma whether the tumour is functional or not. Therefore, the product should be indicated in the treatment of patients with advanced (i.e. unresectable, metastatic or relapsed) adrenal cortical carcinoma without distinction whether the tumour is functional or not.

The TAG was asked to discuss the proposal for dosing mitotane. The TAG considered that this therapeutic monitoring of plasma levels is pertinent and should be reflected in the summary of product characteristics for Lysodren. However, the TAG emphasised that the availability of a monitoring of plasma level is not a mandatory monitoring to treat and monitor the patients with advanced (i.e. unresectable, metastatic or relapsed) adrenal cortical carcinoma. On the basis of the experience of use of mitotane, the monitoring of plasma level of mitotane may help the practitioners to administer higher starting doses (4 – 6 g/day) of mitotane and achieve the desired effective plasma levels of the product (estimated to be approximately 14 mg/L) more rapidly than in the situation where this monitoring is not conducted. Therefore, the Therapeutic Advisory Group considered that this monitoring should be mentioned in the “special warnings and special precautions for use” of the summary of product characteristics for Lysodren and should be recommended when a high starting dose of mitotane (i.e. 6

g/day) is given to the patients. If such monitoring is unavailable lower starting doses of mitotane should be recommended (3-4 g/day). On the basis of the experience of use of mitotane the TAG stated that there might be a relationship between high plasma levels of mitotane (above 20 mg/L) and the occurrence of neurological toxicity. Therefore a monitoring of plasma levels of mitotane may help to prevent the occurrence of this neurological toxicity. The TAG considered again, that this should be reflected in the summary of product characteristics for Lysodren.

Finally, the TAG was requested to discuss the adequacy and feasibility of the studies the Applicant committed to perform once a marketing authorisation may be granted. The TAG considered that the Applicant should perform the prospective evaluation of mitotane and should conduct (at least) two prospective studies. The first one should be a prospective evaluation of Lysodren in the target population to characterise the pharmacokinetic properties of the product. In addition, the TAG considered that the Applicant should conduct a second prospective study (in the form of a prospective registry for example) in patients treated with mitotane to better characterise the relationship between the plasma levels and the occurrence of a neurological toxicity. Considering the incidence of adrenal cortical carcinoma (two new cases per million per year, meaning that up to 30 to 40 new patients may be treated with Lysodren a year in the EU) the TAG considered that such study could be completed within 3 to 4 years.

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by majority decision that the benefit/risk profile of Lysodren was favourable in the treatment of adrenal cortical carcinoma.