30 May 2013
EMA/CHMP/419286/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lysodren

International non-proprietary name: MITOTANE

Procedure No. EMEA/H/C/000521/II/0014

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Laboratoire HRA Pharma, SA submitted to the European Medicines Agency on 24 December 2012 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Lysodren	MITOTANE	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for an extension of the indication for the treatment of non-functional adrenal cortical carcinoma. Consequently, the MAH proposed the update of sections 4.1, 4.2 and 5.1 of the SmPC based on final data from Study FIRM-ACT further to the assessment of FUM 008.

The Package Leaflet was proposed to be updated accordingly.

In addition, the MAH took the opportunity to update the list of local representatives with Croatia in the Package Leaflet.

Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.

Finally the MAH proposed to make some editorial changes to the SmPC.

The variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Lysodren was designated as an orphan medicinal product EU/3/02/102 EU on 12 June 2002.

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Not applicable

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice / Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Arantxa Sancho-Lopez Co-Rapporteur: Daniela Melchiorri

Submission date:	24 December 2012
Start of procedure:	20 January 2013
Rapporteur's preliminary assessment report circulated on:	26 February 2013
Co-Rapporteur's preliminary assessment report circulated on:	22 February 2013
Joint Rapporteur's updated assessment report circulated on:	15 March 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	21 March 2013
MAH's responses submitted to the CHMP on:	26 April 2013
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	13 May 2013
Joint Rapporteur's final assessment report on the MAH's responses circulated on:	24 May 2013
CHMP opinion:	30 May 2013

2. Scientific discussion

2.1. Introduction

Adrenal Cortical carcinomas (ACC) are highly malignant tumours with a very poor prognosis: a review from the Memorial Sloan-Kettering Cancer Center (USA) from 1980 to 1991 indicated a mean survival time of 9 months in patients whose tumours are unresectable. Approximately 60% of patients have a functional ACC, defined by the existence of signs of excess adrenal hormone production. ACC can be found at any age but the incidence of tumours peaks in the first and fifth decade, especially in male patients. There is an increased prevalence of ACC in females (female to male ratio: 2.5), which is more marked in patients with functional tumours. Men with ACC tend to be older than women.

Whenever possible, curative surgery is the treatment of choice: after tumour resection, the mean disease-free interval is 12 months with a wide range (1 to 175 months), with no difference between patients with functional or non-functional tumours. The existence of a regional disease significantly reduces the disease-free interval after surgery. In patients with recurrent disease, surgery should be considered and should be performed if complete removal is feasible. If surgery is not possible and in patients with metastatic disease, mitotane therapy is used either alone or associated with cytotoxic chemotherapy.

Mitotane or o, p'- DDD (1-(o-chlorophenyl)-1-(p-chlorophenyl)-2,2-dichloroethane) is an isomer and a derivative of the insecticide DDT that acts blocking several steroidogenic enzymes with consequent alteration of peripheral steroid metabolism, direct suppression of adrenal cortex and impact on cortisone metabolism.

The approved indication of Lysodren is as follows:

''Symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma (ACC). The effect of Lysodren on non-functional adrenal cortical carcinoma is not established''.

The recommended dose of Lysodren is 2 to 3 g/day divided into two or three doses.

In this application, the MAH of Lysodren proposed to change the indication by removing the sentence "The effect of Lysodren on non-functional adrenal cortical carcinoma is not established'. Further to the assessment of the CHMP and their conclusions as detailed in this report that this extension of the indication was not considered approvable, the MAH decided not to pursue the proposed change to the indication.

However, the CHMP agreed to the proposal from the MAH to update sections 4.2, 4.8 and 5.1 of the SmPC based on the results of the FIRM-ACT study. The PL has been updated accordingly.

In addition, the MAH took the opportunity to update the list of local representatives with Croatia in the Package Leaflet.

Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.

Finally the MAH made some editorial changes to the SmPC.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application.

2.2.1. Discussion on non-clinical aspects

The pharmacologic properties and the toxicological profile of mitotane have been adequately described and assessed in previous applications. No additional non-clinical studies are considered necessary. The absence of new non-clinical data was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trial was performed in accordance with GCP as claimed by the applicant.

2.3.2. Pharmacokinetics

PK FIRM-ACT (LYS-001) study

The clinical study report of the PK FIRM-ACT ancillary analysis (LYS-001 study) and additional pharmacokinetics data further to 3 months of treatment have been submitted.

A subset of 40 FIRM ACT patients were enrolled in this study, but overall 32 patients were considered for the primary PK analysis, 20 in the high dose regimen and 12 in the low dose regimen. The first patient was enrolled on 15 June 2005 and the last one was enrolled on 22 February 2010.

Results

According to the main results from PK FIRM-ACT study, the mean mitotane maximal plasma concentrations and exposure were approximately 30% superior in the high-dose regimen (15.3 ± 7.5 mg/L) in comparison to the low-dose regimen (11.8 ± 4.7 mg/L), with a higher number of patients treated with high dose mitotane reaching the effective plasma level (14 mg/L). However, the difference was not statistically significant.

Mean cumulated doses over the treatment period (12 weeks) were 60% higher in the high dose regimen when compared to the low-dose regimen with mean values of 440±142 g in the high-dose regimen versus 272±121 g in the low-dose regimen (p=0.013).

In both dose regimens, the median maximal plasma concentrations were reached after approximately 2.5 months and the steady state was not attained by the end of the study (Day 82).

In the high dose regimen, half of patients (10/20) reached at least once mitotane plasma concentrations above 14 mg/L after a median 46 days of treatment, while 4 out 12 patients in the low-dose regimen achieved this threshold with a median time of 55 days.

Further to LYS-001 study period (from Day 82 to Day 187), 7 out of 12 patients reached plasma mitotane levels >14 mg/L at least at one time point during follow-up from treatment initiation to Day 187. Among them 4 were in the initial high dose regimen group and the other 3 in the initial low dose regimen group.

2.3.3. Discussion on clinical pharmacology

Results from this study on pharmacokinetics had not been considered adequate to allow drawing any firm conclusion, as the mitotane steady-state has not been reached during the study period, and the rate of patients in each regimen (high and low dose) able to achieve the therapeutic window was unknown.

Data from additional PK analysis after the 3 months of treatment considered in the CSR of the LYS-001 study were limited to information on the dose spontaneously reported by the investigator.

The available PK data do not affect the strategy of initiating treatment either with low or with high dose and the need to regularly adjust the dose according to mitotane plasma levels and the clinical tolerability, as already indicated in the SmPC.

2.3.4. Conclusions on clinical pharmacology

The provided results of the PK analysis failed to further clarify the mitotane PK profile.

2.4. Clinical efficacy

2.4.1. Main study

FIRM ACT study

The FIRM-ACT study was a randomized phase III trial, designed to compare two regimens used for the treatment of advanced adrenocortical carcinoma (etoposide, doxorubicin, cisplatin and mitotane versus streptozocin and mitotane) (Fassnacht *et al*., 2012).

Methods

Study participants

Main Inclusion criteria

• Histologically confirmed diagnosis of adrenocortical carcinoma;

• Locally advanced or metastatic disease not amenable to radical surgery resection (Stage III-IV);

• Radiologically monitorable disease;

• ECOG performance status 0-2;

• Life expectancy > 3 months;

• Age ≥ 18 years;

• Adequate bone marrow reserve (neutrophils ≥ 1500/mm3 and platelets ≥ 100.000/mm3);

• Effective contraception in pre-menopausal female and male patients;

• Patient's written informed consent;

Main exclusion criteria

• History of prior malignancy, except for cured non-melanoma skin cancer, cured in situ cervical carcinoma, or other cancers treated with no evidence of disease for at least five years;

• Previous cytotoxic chemotherapy (prior therapy with mitotane was allowed in FIRM-ACT but excluded in LYS-001) for adrenocortical carcinoma;

• Renal insufficiency (serum creatinine ≥ 2 mg/dL or creatinine clearance ≤ 50 mL/min);

• Hepatic insufficiency / disease (serum bilirubin ≥ 2 x upper limit of normal range and/or serum transaminase ≥ 3 x upper limit of normal range);

• Pregnancy or breastfeeding;

• Known hypersensitivity to any drug included in the treatment protocol;

• Presence of active infection;

Treatments

Patients were randomized to receive therapy with Etoposide, Doxorubicin, Cisplatin plus Lysodren (EDP/M) or Streptozotocin plus Lysodren (STZ/M) as first line treatment.

The Lysodren dose regimen was left to the responsibility of the local investigator, with two possible dose regimens:

• The low starting dose approach (low-dose regimen): Lysodren was administered at a starting dose of 1 g/day and increased stepwise every 3 days by 0.5 g up to a total dose of 4.0 g and then adjusted according to plasma concentrations and tolerability.

• The high starting dose approach (high-dose regimen): Lysodren was administered at a starting dose of 1.5 g / day, then increased on day 2 to 3 g/ day, on day 3 to 4.5 g/day, and on day 4 to 6 g/day. This latter dose was administered until the first mitotane plasma level was assayed. Dose was then adjusted according to plasma concentrations and tolerability.

In both treatment schedules, mitotane was started a minimum of 1 week before the initiation of the cytotoxic treatment, with the aim to attain a blood level of 14 to 20 mg per litre.

Objectives

The primary objective of the study was to compare the efficacy of the two randomised treatments.

A secondary objective was to investigate the relationship between Lysodren dose (daily and cumulative) and mitotane plasma concentrations using one of two pre-defined treatment regimens (high-dose and low-dose).

The secondary objectives also included the evaluation of the impact of Lysodren treatment on certain hormonal parameters and the evaluation of the safety and tolerability of Lysodren treatment.

The main focus of this report is on the secondary objectives.

Outcomes/endpoints

The primary endpoint for the FIRM ACT study was overall survival, and secondary endpoints were progression-free survival, tumour response and quality of life.

Sample size and statistical considerations

The target sample size was 300 patients. The trial was designed to have a power of 80% to detect a risk reduction of 33% in the EDP–mitotane group, as compared with the streptozocin–mitotane group. Such an analysis would require the observation of up to 200 deaths on the basis of a two-sided group sequential logrank test at a type I error level of 5%. All analyses were performed on an intention-to-treat basis.

Randomisation

Patients were randomized to receive therapy with Etoposide, Doxorubicin, Cisplatin plus Lysodren (EDP/M) or Streptozotocin plus Lysodren (STZ/M) as first line treatment in a 1:1 ratio.

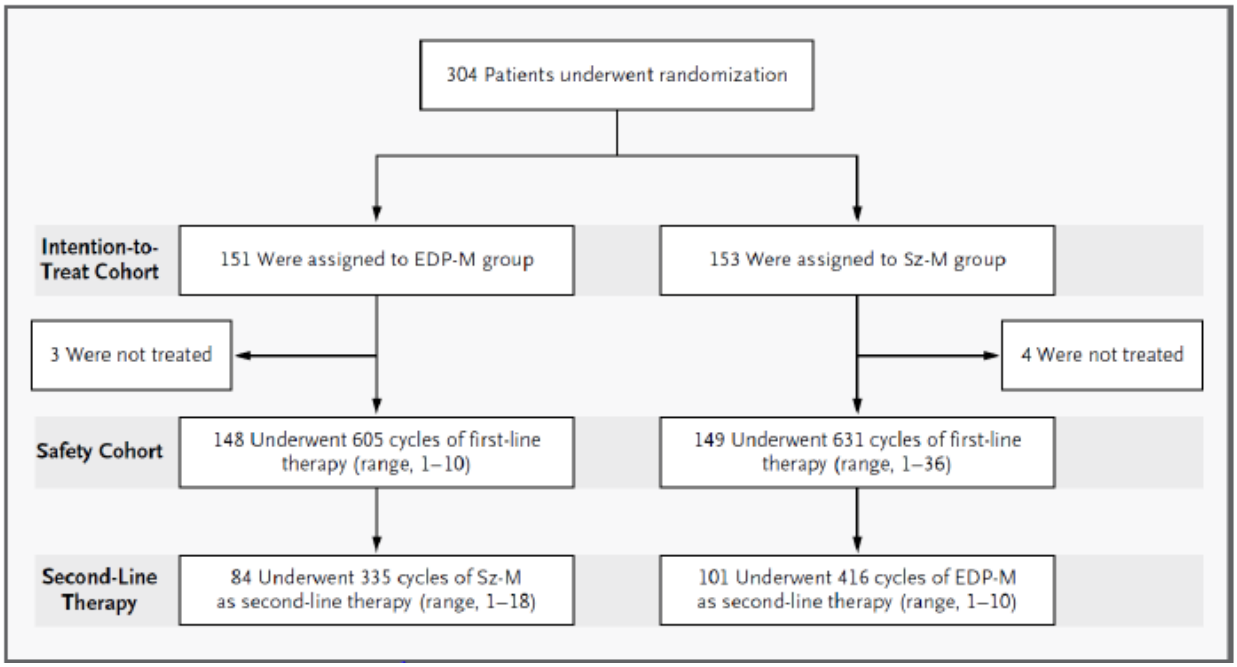
Blinding (masking)

This was an open-label study.

Results

Participant flow

Figure 1. Enrolment and treatment



Recruitment

A total of 40 centres in 12 countries participated in this trial, and 304 patients were enrolled within 5 years from June 2004 through October 2009.

Baseline data

The baseline demographic and disease characteristics are presented in the tables below.

Table 1. Baseline characteristics by mitotane levels-all patients

		Mitotane level ≥ 14mg/l at least once during the first 6 months (N=160)	Mitotane level < 14mg/l at every assessment during the first 6 months (N=144)	Total (N=304)
Age [years]	N	160	144	304
	Mean	48.5	52.2	50.3
	STD	11.4	13.2	12.4
	Min	20.4	18.8	18.8
	1st Quartile	41.2	43.5	42.2
	Median	49.4	54.1	50.8
	3rd Quartile	57.5	62.8	60.7
	Max	72.2	76.2	76.2
Sex	N	160	144	304
	Male	59 (36.9%)	62 (43.1%)	121 (39.8%)
	Female	101 (63.1%)	82 (56.9%)	183 (60.2%)
BMI [kg/m^2]	N	160	142	302
	Mean	24.8	25.9	25.3
	STD	4.5	5.1	4.8
	Min	14.5	15.8	14.5
	1st Quartile	21.5	22.3	22.0
	Median	24.1	25.2	24.6
	3rd Quartile	26.6	28.4	27.8
	Max	37.6	46.7	46.7

Table 2. Disease status at baseline by mitotane levels-all patients

		Mitotane level ≥ 14mg/l at least once during the first 6 months (N=160)	Mitotane level < 14mg/l at every assessment during the first 6 months (N=144)	Total (N=304)
Endocrine Symptoms	N	150	135	284
	No symptoms	77 (51.3%)	61 (45.2%)	138 (48.4%)
	Cushing's syndrome	64 (42.7%)	60 (44.4%)	124 (43.5%)
	Virilisation	34 (22.7%)	27 (20.0%)	61 (21.4%)
	Conn's syndrome	5 (3.3%)	10 (7.4%)	15 (5.3%)
	Feminisation	4 (2.7%)	5 (3.7%)	9 (3.2%)
ECOG	N	150	135	285
	0	88 (55.0%)	57 (39.6%)	145 (47.7%)
	1	60 (37.5%)	64 (44.4%)	124 (40.8%)
	2	12 (7.5%)	22 (15.3%)	34 (11.2%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	1 (0.6%)	1 (0.3%)
Number of affected organs	N	160	144	304
	1	36 (22.5%)	18 (12.5%)	54 (17.8%)
	2	46 (28.8%)	35 (24.3%)	81 (26.6%)
	3	43 (26.9%)	41 (28.5%)	84 (27.6%)
	4	24 (15.0%)	28 (19.4%)	52 (17.1%)
	5	6 (3.8%)	11 (7.6%)	17 (5.6%)
	6	4 (2.5%)	7 (4.9%)	11 (3.6%)
	7	1 (0.6%)	3 (2.1%)	4 (1.3%)
	8	0 (0.0%)	1 (0.7%)	1 (0.3%)

Outcomes and estimation

Primary objective

The median duration of progression-free survival was 5.0 months in the EDP–mitotane group, as compared with 2.1 months in the streptozocin–mitotane group (hazard ratio, 0.55; 95% CI, 0.43 to 0.69; P<0.001). The median duration of survival was 14.8 months and 12.0 months, respectively

(hazard ratio, 0.79; 95% CI, 0.61 to 1.02; P = 0.07). Detailed results are provided in Fassnacht *et al*. (2012).

Secondary objectives

Overall Survival

EDP/M chemotherapy arm (In patients alive at 3 months)

A total of the 151 patients were randomised to receive EDP/M. After three months, 133 patients were still surviving, of whom 65 (48.9%) had achieved mitotane levels ≥14 mg/l at least once within that time. Of those surviving at three months, 98 patients were still being treated with EDP/M, of whom 49 (50.0%) had achieved mitotane levels ≥ 14 mg/l at least once. The OS results and the corresponding Kaplan-Meier curves are presented in table 3 and figure 2 respectively.

Table 3. Overall Survival by mitotane level for the EDP/M chemotherapy arm

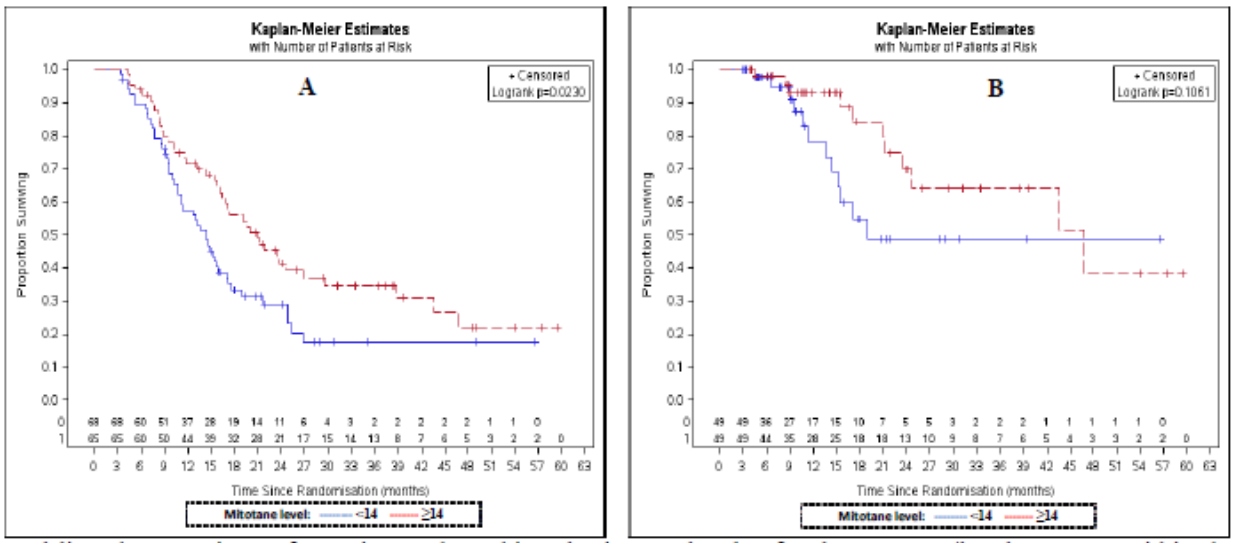
Subgroup	Mitotane level	N	Deaths	Median Time (months)	95% Confidence Interval		p-value
A) EDP/M arm*, surviving at three months	Low**	68	49	14.3	10.7	17.0	
	High***	65	41	21.0	16.2	26.8	
	Hazard Ratio			0.616	0.404	0.939	0.023
B) EDP/M arm*, surviving and still being treated with EDP/M at three months.	Low**	49	12	18.9	14.3	∞	
	High***	49	11	47.7	23.6	∞	
	Hazard Ratio			0.509	0.221	1.171	0.1061

*Includes all patients randomised to receive EDP/M as a first line treatment (N=151). Patients who changed chemotherapy arm were censored at that time

** Achieved mitotane levels ≥ 14mg/l at least once during the first three months

*** Mitotane levels < 14 mg/l at all assessments in first three months

Figure 2. K-M curves of Overall Survival by mitotane level for the EDP / M chemotherapy arm



Red line shows estimate for patients who achieved mitotane levels of at least 14 mg/l at least once within the first three months. Blue line shows estimate for patients who had mitotane levels less than 14 mg/l at all assessments within the first three months.

After six months, 120 patients were still surviving, of whom 78 (65.0%) had achieved mitotane levels ≥14 mg/l at least once within that time. Of the patients surviving at six months, 80 were still being treated with EDP/M, of whom 56 (70.0%) had achieved mitotane levels ≥ 14 mg/l at least once (data not shown).

Sz/M chemotherapy arm (In patients alive at 3 months)

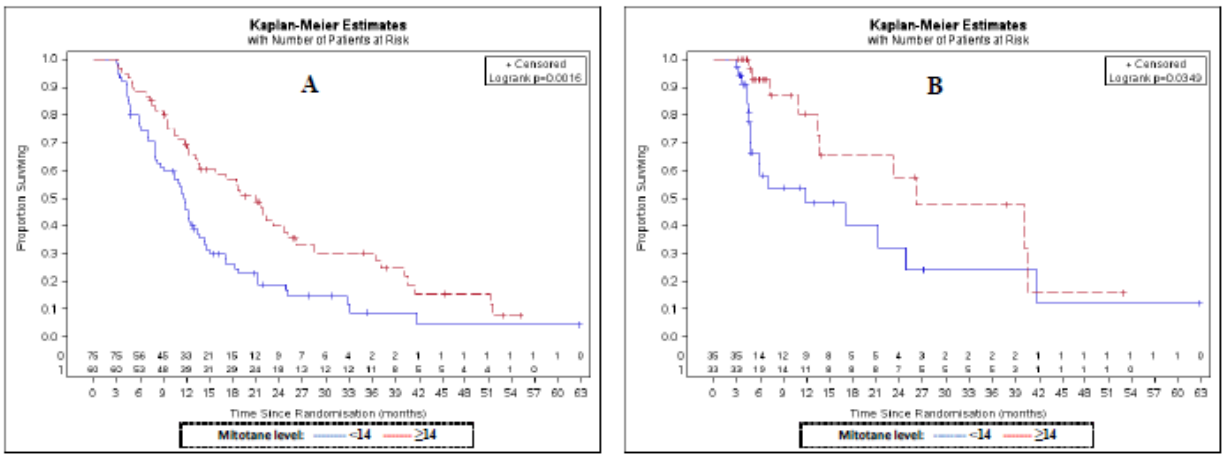
A total of 153 patients were randomised to receive Sz/M. After three months, 135 patients were still surviving, of whom 60 (44.4%) had achieved mitotane levels ≥ 14 mg/l at least once within that time. Of those surviving at three months, 68 patients were still being treated with Sz/M, of whom 33 (48.5%) had achieved mitotane levels ≥ 14 mg/l at least once. The OS results and the corresponding Kaplan-Meier curves are presented in table 4 and figure 3 respectively.

Table 4. Overall Survival by mitotane level for the Sz / M chemotherapy arm

Subgroup	Mitotane level	N	Deaths	Median Time (months)	95% Confidence Interval		p-value
A) Sz/M arm*, surviving at three months	Low**	75	62	11.7	8.7	12.8	
	High***	60	44	20.9	13.4	25.1	
	Hazard Ratio			0.534	0.359	0.793	0.0016
B) Sz/M arm*, surviving and still being treated with Sz/M at three months.	Low**	35	18	11.9	4.8	24.9	
	High***	33	10	21.0	13.4	40.6	
	Hazard Ratio			0.442	0.203	0.963	0.0349

*Includes all patients randomised to receive Sz/M as a first line treatment (N=153). Patients who changed chemotherapy arm were censored at that time.
** Achieved mitotane levels ≥ 14mg/l at least once during the first three months
*** Mitotane levels < 14 mg/l at all assessments in first three months

Figure 3. K-M curves of Overall Survival by mitotane level for the Sz / M chemotherapy arm



Red line shows estimate for patients who achieved mitotane levels of at least 14 mg/l at least once within the first three months. Blue line shows estimate for patients who had mitotane levels less than 14 mg/l at all assessments within the first three months.

After six months, 109 patients were still surviving, of whom 68 (62.4%) had achieved mitotane levels of 14 mg/l at least once. Of the patients surviving at six months, 34 were still being treated with Sz/M, of whom 23 (67.6%) had achieved mitotane levels ≥ 14 mg/l at least once (data not shown).

Progression-free survival

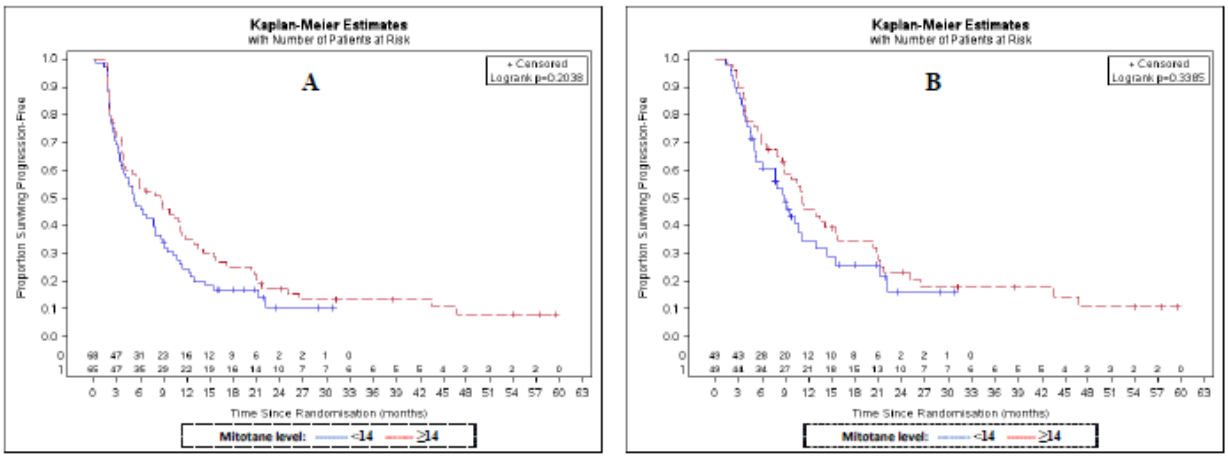
EDP/M chemotherapy arm (In patients alive at 3 months)

Table 5. Progression Free Survival by mitotane level for the EDP / M chemotherapy arm

Subgroup	Mitotane level	N	Progression	Median Time (months)	95% Confidence Interval		p-value
A) EDP/M arm*, surviving at three months	Low**	68	58	5.2	3.5	7.8	
	High***	65	57	8.5	3.9	11.2	
	Hazard Ratio			0.785	0.541	1.141	0.2038
B) EDP/M arm*, surviving and still being treated with EDP/M at three months.	Low**	49	34	8.7	5.2	11.1	
	High***	49	40	11.2	8.5	15.8	
	Hazard Ratio			0.796	0.498	1.272	0.3385

* Includes all patients randomised to receive EDP/M as a first line treatment (N=151)
** Achieved mitotane levels ≥ 14mg/l at least once during the first three months
*** Mitotane levels < 14 mg/l at all assessments in first three months

Figure 4. K-M curves of Progression Free by mitotane level for the EDP/M chemotherapy arm



Red line shows estimate for patients who achieved mitotane levels of at least 14 mg/l at least once within the first three months. Blue line shows estimate for patients who had mitotane levels less than 14 mg/l at all assessments within the first three months.

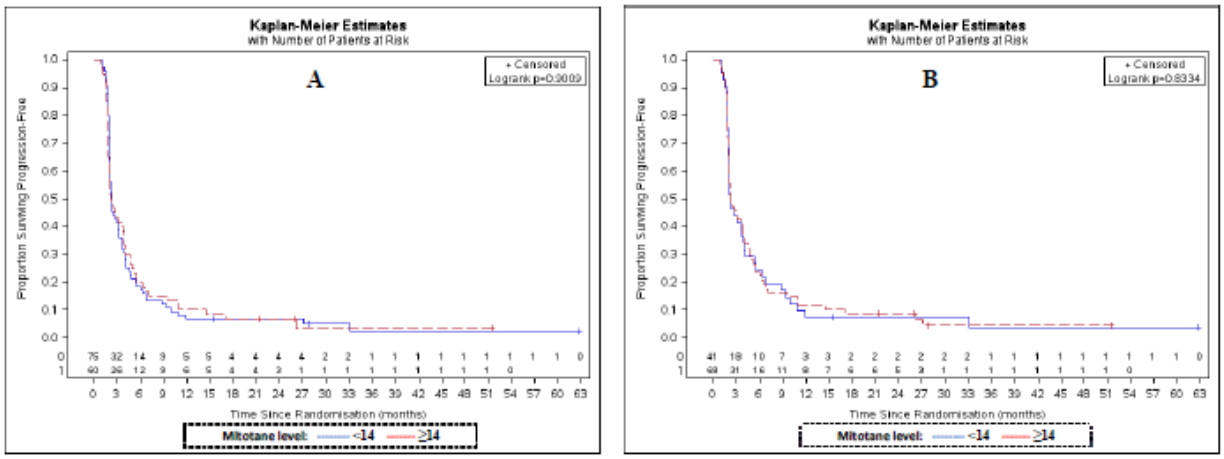
Sz/M chemotherapy arm (In patients alive at 3 months)

Table 6. Progression Free Survival by mitotane level for the Sz/M chemotherapy arm

Subgroup	Mitotane level	N	Progression	Median Time (months)	95% Confidence Interval		p-value
A) Sz/M arm*, surviving at three months	Low**	75	72	2.3	2.1	3.2	
	High***	60	57	2.2	1.9	3.8	
	Hazard Ratio			0.978	0.687	1.391	0.9009
B) Sz/M arm*, surviving and still being treated with Sz/M at three months.	Low**	35	31	4.0	3.2	4.8	
	High***	33	30	4.7	3.7	5.6	
	Hazard Ratio			0.938	0.566	1.554	0.8035

* Includes all patients randomised to receive Sz/M as a first line treatment (N=153)
** Achieved mitotane levels ≥ 14mg/l at least once during the first three months
*** Mitotane levels < 14 mg/l at all assessments in first three months

Figure 5. K-M curves of Progression Free by mitotane level for the Sz / M chemotherapy arm



Red line shows estimate for patients who achieved mitotane levels of at least 14 mg/l at least once within the first three months. Blue line shows estimate for patients who had mitotane levels less than 14 mg/l at all assessments within the first three months.

Best Overall Response (BOR) by mitotane level

Table 7. Best Overall Response (BOR) by mitotane level

Intended 1st line therapy	BOR (RECIST)	M ≥14 mg/l	M <14 mg/l	All
All	N	116	188	304
	no study therapy	0 (0%)	7 (3.7%)	7 (2.3%)
	could not be evaluated	8 (6.9%)	22 (11.7%)	30 (9.9%)
	CR	8 (6.9%)	1 (0.5%)	9 (3.0%)
	PR	16 (13.8%)	24 (12.8%)	40 (13.2%)
	SD	49 (42.2%)	38 (20.2%)	87 (28.6%)
	PD	35 (30.2%)	96 (51.1%)	131 (43.1%)
	Objective Response	24 (20.7%)	25 (13.3%)	49 (16.1%)
	Disease Control	73 (62.9%)	63 (33.5%)	136 (44.7)
EDP/M	N	67	84	151
	no study therapy	0 (0%)	3 (3.6%)	3 (2.0%)
	could not be evaluated	3 (4.5%)	14 (16.7%)	17 (11.3%)
	CR	5 (7.5%)	1 (1.2%)	6 (4.0%)
	PR	13 (19.4%)	16 (19.0%)	29 (19.2%)
	SD	33 (49.3%)	20 (23.8%)	53 (35.1%)
	PD	13 (19.4%)	30 (35.7%)	43 (28.5)
	Objective Response	18 (26.9%)	17 (20.2%)	35 (23.3%)

	Disease Control	51 (76.1%)	37 (44.0%)	88 (58.3%)
Sz/M	N	49	104	153
	no study therapy	0 (0%)	4 (3.8%)	4 (2.6%)
	could not be evaluated	5 (10.2%)	8 (7.7%)	13 (8.5%)
	CR	3 (6.1%)	0 (0%)	3 (2.0%)
	PR	3 (6.1%)	8 (7.7%)	11 (7.2%)
	SD	16 (32.7%)	18 (17.3%)	34 (22.2%)
	PD	22 (44.9%)	66 (63.5%)	88 (57.5%)
	Objective Response	6 (12.2%)	8 (7.7%)	14 (9.2%)
	Disease Control	22 (44.9%)	26 (25.0%)	48 (31.4%)

Objective Response Rate

Table 8. Analysis of objective response rate-all patients

Treatment group	Mitotane Level	N	n	%	95% CI		p-value[+]
All	High*	116	24	20.7	13.7	29.2	
	Low**	188	25	13.3	8.8	19.0	
	Difference			7.4	-1.1	16.7	0.1082
EDP/M	High*	67	18	26.9	16.8	39.1	
	Low**	84	17	20.2	12.3	30.4	
	Difference			6.6	-6.9	20.6	0.4378
Sz/M	High*	49	6	12.2	4.6	24.8	
	Low**	104	8	7.7	3.4	14.6	
	Difference			4.6	-4.9	17.3	0.3783

N total number of patients in each group
n number of patients with objective response
* Achieved mitotane levels ≥ 14mg/l at least once within six months until best response or end of first line evaluation time
** Mitotane levels < 14 mg/l at all assessments within six months until best response or end of first line evaluation time
[+] p-value for Fisher's exact test

Disease Control Rate

The results of the disease control rate are presented in Table 9.

Table 9: Analysis of disease control rate

Treatment group	Mitotane level*	N	Number of patients with disease control	%	95% CI	p-value Fisher exact test
All	≥ 14 mg/l at least once	116	73	62.9	53.5-71.7	
	<14 mg/l at all assessments	188	63	33.5	26.8-40.7	
	Difference			29.4	18.0-40.1	<0.0001
EDP/M	≥ 14 mg/l at least once	67	51	76.1	64.1-85.7	

	<14 mg/l at all assessments	84	37	44.0	33.2-55.3	
	Difference			32.1	16.6-45.9	0.0001
Sz/M	≥ 14 mg/l at least once	49	22	44.9	30.7-59.8	
	<14 mg/l at all assessments	104	26	25.0	17.0-34.4	
	Difference			19.9	3.9-35.9	0.0159

* Mitotane levels ≥ 14 mg/l at least once within 6 months until best response or end of first line evaluation time; Mitotane levels < 14 mg/l at all assessment within 6 months until best response or end of first line evaluation time

A summary of two papers recently published is reported in table 10:

Table 10. Summary of published papers

Author	N of patients	Study design	Main findings	Conclusion
Malandrino et al, 2010	55 adults	Retrospective analysis of prospectively collected data in metastatic ACC population treated with first-line mitotane and platinum-based chemotherapy. Response was assessed according to RECIST criteria and OS from the start of platinum-based chemotherapy	Fifteen out of 55 patients (27.3%) achieved an objective response. Median OS was 1 year (18 days-11 year). The mitotane level during the response was available for 39 patients, including 32 who reached a mitotane level ≥ 14 mg/l. Median OS was 13.3 and 4.0 months respectively in pts who received mitotane therapy as a single first-line or not. Median OS was 19.6 and 9.5 months for pts with a mitotane level ≥14 mg/l and <14 mg/l, respectively. In multivariate analysis, 95% CI OR=0.35 (0.14-0.89) p=0.03.	Plasma mitotane level ≥ 14 mg/l was a powerful prognostic factor in multivariate analysis. The strategy to start mitotane as first line therapy may confer a greater chance to rapidly achieve therapeutic plasma levels of mitotane. An alternative could be that this parameter identifies a subgroup of patients with lower tumour aggressiveness allowing more time to initiate mitotane
Hermsen et al, 2011	91 adults (27 patients treated with mitotane monotherapy and 64 in combination with chemotherapy)	Retrospective review data on ACC patients between 2001 and 2007. Plasma samples were collected within 3 months of best response. All available plasma samples from a given patient were collected, and the samples closest to the date of best response was selected	Median mitotane plasma level was 12.7 mg/l in the total population, 16.3 mg/l in the responders subgroup, 11.6 mg/l in patients with SD and 11 mg/l for non-responders (p=0.03). Using the ROC curve analysis, the cut-off level of 14 mg/l resulted in 65% sensitivity and 69% specificity. Cut off values of 16, 18, and 20 mg/l were associated with a lower sensitivity but a higher specificity. Survival from time to first mitotane dose was significantly longer for patients achieving the ≥14 mg/l threshold (HR 0.52, 0.28-0.97, p=0.004). The observed survival benefit was even greater for patients who received mitotane as monotherapy in univariate and multivariate analysis	Confirmation of the relevance of mitotane plasma levels ≥ 14 mg/l for responder's definition and significant improvement of survival from the time of first mitotane dose. The 14 mg/l threshold appeared as a good compromise in terms of sensitivity and specificity. Some patients below 14 mg/l may respond, however they all received concomitant chemotherapy. The benefit in this case may result from the combination of drugs.

2.4.2. Discussion on clinical efficacy

The provided results of the PK analysis failed to further clarify the mitotane PK profile, and consequently at this point an optimal dosing schedule cannot be recommended.

Mitotane plasma levels and the possible relationship with its efficacy were studied in the FIRM ACT trial, a randomized, prospective, controlled, open-label, multicentre, parallel-group study to compare the efficacy of etoposide, doxorubicin and cisplatine plus mitotane (EDP/M) to that of streptozotocin plus mitotane (Sz/M) as first-line treatment in 304 patients. The analysis of patients who achieved mitotane levels ≥ 14mg/l at least once in six months versus patients who mitotane levels were < 14 mg/l could suggest that patients with mitotane plasma levels ≥ 14mg/l could have an improvement in disease control rate (62.9% versus 33.5%; p<0.0001). However, this result should be cautiously taken since the examination of the mitotane effects was not the primary endpoint of the study (see SmPC sections 4.2 and 5.1).

Consistently with these results, in a retrospective review recently published (Hermsen, 2011), the median mitotane plasma level was 16.3 mg/l in the responders subgroup, 11.6 mg/l in patients with SD and 11 mg/l for non-responders (p=0.03).

Both in the FIRM ACT study and in the Hermsen review, patients with functional as well as non-functional ACC were included.

Even though in the FIRM ACT study 51.3 % of not symptomatic patients (77 out of the 138) seemed to have mitotane plasma level ≥14 mg/l at least once during the first 6 months, data on disease control reported in this specific patient population have not been provided. Results of subgroup analyses in patients with non-functional tumours enrolled in both treatment arms in the FIRM ACT trial have not been provided. In addition, taking into account that the FIRM-ACT was designed to compare the efficacy of etoposide, doxorubicin and cisplatin plus mitotane (EDP/M) to that of streptozotocin plus mitotane (Sz/M) as first-line treatment, the CHMP considered that based on the results of the FIRM-ACT study, the efficacy of mitotane in the treatment of patients with non-functional adrenal cortical carcinoma, cannot be defined since both arms of the trial included mitotane in combination.

2.4.3. Conclusions on the clinical efficacy

The submitted data did not provide sufficient level of evidence to establish the effect of mitotane on non-functional adrenal cortical carcinoma.

Further to the assessment of the CHMP and their conclusions as detailed in this report that this extension of the indication was not considered approvable, the MAH decided not to pursue with the proposed change to the indication.

Sections 4.2 and 5.1 of the SmPC have been updated to include the mitotane plasma levels and the possible relationship with efficacy based on the results of the FIRM-ACT study.

2.5. Clinical safety

Adverse events

In the PK FIRM ACT trial, 39 out of 40 patients presented at least one AE and 4 patients deceased in the high dose regimen following SAEs. However, none of these fatal SAEs were considered related to the administered treatments.

In the high-dose regimen, 4 patients presented treatment related SAEs (Grade 3 nausea and vomiting; Grade 2 leukopenia; Grade 2 rash; Grade 3 ASAT and Grade 4 ALAT increase, reported each in 1 patient). In the low-dose regimen, only 1 patient presented a treatment-related SAE (Grade 3 increase of liver enzymes). Eight patients reached a plasma mitotane level higher than 20 mg/l, but only 3 presented treatment-related gastrointestinal disorders and in none of them signs of neurological toxicity were reported.

An overall summary of patients who presented at least one AE and the number of AE likely or possibly treatment-related in the high and low-dose regimens is reported in the following Tables.

Table 11: Summary of all Adverse Events by System Organ Class

	All (N=40)	
SYSTEM ORGAN CLASS	**n (%)**	**AE**
ALL	39 (97.5)	208
Blood and lymphatic system disorders	1 (2.5)	1
Cardiac disorders	4 (10.0)	5
Endocrine disorders	4 (10.0)	6
Eye disorders	2 (5.0)	2
Gastrointestinal disorders	28 (70.0)	96
General disorders and administration site conditions	12 (30.0)	20
Hepatobiliary disorders	1 (2.5)	1
Infections and infestations	5 (12.5)	5
Investigations	6 (15.0)	7
Metabolism and nutrition disorders	10 (25.0)	14
Musculoskeletal and connective tissue disorders	3 (7.5)	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (2.5)	1
Nervous system disorders	12 (30.0)	19
Psychiatric disorders	6 (15.0)	8
Reproductive system and breast disorders	2 (5.0)	2
Respiratory, thoracic and mediastinal disorders	4 (10.0)	5
Skin and subcutaneous tissue disorders	6 (15.0)	6
Vascular disorders	6 (15.0)	6

N= total number of patients; n=number of patients with at least one AE; AE= number of Adverse Events

Table 12. Summary of treatment related AEs by regimen

SOC	Preferred term	Number of patients with treatment-related TEAE in the:	
		Low-dose regimen	High-dose regimen
ALL	ALL	41	69
Gastrointestinal disorders	Abdominal distension		1
	Abdominal pain	3	
	Abdominal pain upper		3
	Decrease appetite		8
	Diarrhoea	4	18
	Dysgueusia		3
	Dyspepsia	1	
	Nausea	16	14
	Oesophagitis		1
	Salivary hypersecretion		2
	Vomiting	9	4
Investigations	Gamma-glutamyltransferase increased	2	
	Hepatic enzyme increased	2	2
Nervous system disorders	Ataxia		2
	Balance disorder		1
	Clonus		1
	Disturbance in attention		1
	Dizziness	1	4
	Vertigo	3	4

An additional analysis (completed in 16 March 2013) based on the MAH's global Database was submitted for the following adverse events through the spontaneous reporting: Dyspepsia; Dysgeusia; Oesophagitis; Balance Disorders; Clonus.

- Dysgeusia

A total of six case reports involving dysgeusia coincident with the use of Lysodren were identified in the HRA Pharma pharmacovigilance database including one serious and five non-serious cases. Five reports were considered as spontaneous and the remaining case was from clinical trial; four of the 5 spontaneous cases were medically confirmed. Outcomes were reported as unknown in one report, as recovered in two reports and as not recovered in three reports.

- Dyspepsia

Four spontaneous reports were identified from the above search coincident with the use of Lysodren (2 serious and 2 non-serious reports); 3 reports were medically confirmed. Outcomes were reported as unknown in 2 reports, as recovered in 1 report and as fatal in 1 report.

- Balance Disorders

Five spontaneous reports were identified from the above search coincident with the use of Lysodren. One was serious and four were considered as non-serious; all the reports were medically confirmed. One case refers to a child patient. Outcomes were reported as recovering in two reports, as recovered in one report and as not recovered in the two remaining reports.

The literature report involves a 4-year-old patient with precocious puberty who took mitotane as adjuvant chemotherapy for left androgen-secreting adrenocortical carcinoma. The adrenocortical tumour with focal necrosis and haemorrhage was totally removed. Mitotane therapy was started with 0.5g/day and the dose was increased gradually by 0.5g/day during 1-2 weeks while monitoring the plasma level, up to 5.0g/day (plasma level, 13.43 µg/mL 3 months after initiation). The patient's concomitant medication included leuprorelin acetate. Five months after initiation of mitotane, the patient experienced an encephalopathy (anorexia, balance disorder, gait disturbance, speech disorder, apathy, memory impairment, quadriplegia, ataxia, cerebral atrophy, cerebellar atrophy, electroencephalogram abnormal) considered as due to the increased level of mitotane (34.55 µg/mL, 6 months after mitotane initiation). Mitotane was discontinued and a high dose of hydrocortisone was administered for adrenal crisis. The plasma mitotane level gradually decreased, and the neurological symptoms improved. It took 6 months for the mitotane to disappear from the plasma and for clinical recovery of the encephalopathy. No signs of tumour recurrence have been observed for 3 years since discontinuation of mitotane. All neurological abnormalities found after initiation of mitotane, including memory disturbance and motor disability, were no longer present. According to the author, there has been limited use of mitotane in children and its use remains to be established. Several side effects of mitotane are known, especially due to its narrow therapeutic range. A mitotane level of more than 20 mg/L is associated with neurological toxicity. In this patient, encephalopathy appeared after 5 months despite monthly monitoring of the plasma level after determination of the dose. This might have been caused by gradual accumulation of lipid-soluble mitotane after the determination of the therapeutic dose. The mitotane assay is not performed regularly for clinical use; in fact it took 1-2 weeks to obtain the mitotane level data and the encephalopathy developed before he noticed the high level of mitotane. A temporal relationship and a positive dechallenge were reported for all the events including balance disorders, therefore the causal relationship is possible.

- Oesophagitis

No case was identified from the above search.

- Clonus

One serious case was identified from the above search coincident with the use of Lysodren.

Serious adverse event / deaths / other significant events

Nine patients (7 in the high-dose regimen, 2 in the low-dose regimen) presented a total of 10 SAEs. none of the SAEs that resulted in death was related to the administered treatments.

In the high-dose regimen three patients presented SAEs that were not related to the study treatments: one patient presented a Grade 4 lung disorder (compression of the right pulmonary hilus due to pulmonary metastasis); one patient presented a Grade 4 gastrointestinal haemorrhage; one patient presented a Grade 3 arthralgia. Four patients presented SAEs that were related to the study treatments: one patient presented Grade 3 nausea and vomiting (considered as two different SAEs); one patient presented a Grade 2 leucopenia; one patient presented a Grade 2 rash, an allergic reaction covering the entire body; one patient presented Grade 3 ASAT and Grade 4 ALAT increase.

In the low-dose regimen, one patient presented a treatment-related SAE (Grade 3 increase of liver enzymes) and one patient presented a SAE (Grade 3 bone pain due to metastasis) that was not related to treatment (both patients received STZ).

One patient presented a Grade 3 bone pain due to metastasis, not related to treatment.

2.5.1. Discussion on clinical safety

The following treatment-related AEs were reported in the FIRM ACT study: dyspepsia, dysgeusia, oesophagitis, balance disorder and clonus. Since these events are considered as unexpected according to the current SmPC of Lysodren, an additional analysis was performed for each of these adverse events collected in the MAH's Global Database through the spontaneous reporting.

Regarding dysgeusia in all the reported cases there was a reasonable time sequence between Lysodren intake and dysgeusia, with a positive dechallenge in two of them. The causal relationship of Lysodren can be assessed as possible. Dysgeusia was added to section 4.8 of the SmPC. In addition, and based on the absence of recovery, this adverse reaction will be reviewed at the next PSUR planned in 2014 (29 April 2011-28 April 2014).

Based on the available data in the cases of dyspepsia and, due to a temporal association a causal role for Lysodren cannot be excluded. Section 4.8 of the SmPC has been updated to include dyspepsia as an adverse reaction with not known frequency.

Considering that no oesophagitis cases have been retrieved in the MAH's Pharmacovigilance Database, the CHMP agreed to review this adverse reaction in the next PSUR.

In all (5) the cases of balance disorders there is a reasonable time sequence with Lysodren intake. In 4 of these cases the event of balance disorder is reported in a context of mitotane plasma level above of the therapeutic window (> 20 mg/L in 3 reports) and a positive dechallenge reported in two of them. In addition, and based on the absence of recovery, this adverse reaction will be reviewed at the next PSUR.

One case of encephalopathy has been observed in a paediatric patient five months after initiation of the treatment; this case was considered to be related to an increased mitotane plasma level of 34.5 mg/l. After six months mitotane plasma levels were undetectable and the patient recovered clinically. The SmPC has been updated to include this information.

No follow up information is available of the clonus HCP spontaneous case. Follow-up information will be reviewed in the next PSUR.

2.5.2. Conclusions on clinical safety

Further to the assessment of the CHMP and their conclusions as detailed in this report that this extension of the indication was not considered approvable, the MAH decided not to pursue with the proposed change to the indication.

Section 4.8 of the SmPC has been updated to reflect the updated safety results.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Update of the Product information

Further to data submitted in this application the following changes have been implemented in the Product information (new text: bold, underlined, old text: strikethrough).

- SmPC Section 4.2

[..]

Dose adjustments, monitoring and discontinuation

Dose adjustment is aimed to reach a therapeutic window (mitotane plasma levels 14 - 20 mg/l) which ensures optimal use of Lysodren with acceptable safety. Indeed, neurologic toxicity has been associated with levels above 20 mg/l and therefore this threshold should not be reached. **There are some data suggesting that mitotane plasma above 14 mg/l may result in enhanced efficacy (see section 5.1).** Mitotane plasma levels higher than 20 mg/l may be associated with severe undesirable effects and offer no further benefit in terms of efficacy. Mitotane plasma levels should therefore be monitored in order to adjust the Lysodren dose and to avoid reaching toxic levels.

[..]

- SmPC Section 4.8

[..]

Table 1: Frequency of adverse reactions identified from literature data

	Adverse reaction		
System Organ Class	**Very common**	**Common**	**Not Known**
Investigations	Elevated liver enzymes Plasma cholesterol increased Plasma triglycerides increased		Blood uric acid decreased
Blood and lymphatic system disorders	Leucopoenia Bleeding time prolonged	Anaemia Thrombocytopenia	
Nervous system disorders	Ataxia Paresthesia Vertigo Sleepiness	Mental impairment Polyneuropathy Movement disorder Dizziness Headache	**Balance disorders**
Eye disorders			Maculopathy Retinal toxicity Diplopia Lens opacity Visual impairment Vision blurred
Gastrointestinal disorders	Mucositis Vomiting Diarrhoea Nausea Epigastric discomfort		Salivary hypersecretion **Dysgeusia** **Dyspepsia**
Renal and urinary disorders			Haemorrhagic cystitis Haematuria Proteinuria

[..]

Paediatric patients
Neuro-psychological retardation may be observed during mitotane treatment. In such cases, thyroid function should be investigated in order to identify a possible thyroid impairment linked to mitotane treatment. Hypothyroidism and growth retardation may be also observed. **One case of encephalopathy has been observed in a paediatric patient five months after initiation of the treatment; this case was considered to be related to an increased mitotane plasma level of 34.5 mg/l. After six months mitotane plasma levels were undetectable and the patient recovered clinically.**

- SmPC Section 5.1

[..]

Mitotane plasma levels and the possible relationship with its efficacy were studied in the FIRM ACT trial, a randomized, prospective, controlled, open-label, multicentre, parallel-group study to compare the efficacy of etoposide, doxorubicin and cisplatine plus mitotane (EDP/M) to that of streptozotocin plus mitotane (Sz/M) as first-line treatment in 304 patients. The analysis of patients who achieved mitotane levels ≥ 14mg/l at least once in six months versus patients who mitotane levels were < 14 mg/l could suggest that patients with mitotane plasma levels ≥ 14mg/l could have an improvement in disease control rate (62.9% versus 33.5%; p<0.0001). However, this result should be cautiously taken since the examination of the mitotane effects was not the primary endpoint of the study.

The Package Leaflet was updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, which were accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Croatia.

3. Recommendations

Further to the assessment of the CHMP and their conclusions as detailed in this report that this extension of the indication was not considered approvable, the MAH decided not to pursue with the proposed change to the indication.

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Update of sections 4.2, 4.8 and 5.1 of the SmPC based on the results of the FIRM-ACT study. The PL has been updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives with Croatia in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 9. Finally the MAH made some editorial changes to the SmPC.

The requested variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.