Scottish Medicines Consortium

mitotane 500 mg tablets (Lysodren®) (No. 328/06)

Laboratoire HRA Pharma

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

mitotane (Lysodren®) is not recommended for use within NHS Scotland for the symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma. The effect of mitotane on non-functional adrenal cortical carcinoma is not established.

Mitotane relieves the symptoms of advanced adrenal cortical carcinoma, but there is insufficient evidence to support an increase in survival. The economic case has not been demonstrated.

Mitotane should be used only within the context of clinical trials.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

The symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma. The effect of mitotane on non-functional adrenal cortical carcinoma is not established.

Dosing information

Starting dose should be 2-3g daily which can be reduced to 1-2g daily after two months or in case of toxicity. If plasma monitoring is available, the starting dose could be as high as 4-6g daily in divided doses until a cumulative dose of 75g is reached and then monthly monitoring until stable dosage is achieved. If no clinical benefits are observed after 3 months at optimal dose (based on empirical and/or drug monitoring criteria), and if no toxicity is observed, dose escalation up to 6g daily may be considered.

Product availability date

15 July 2004. Orphan Drug status granted in 2002.

Summary of evidence on comparative efficacy

Mitotane is cytotoxic and causes adrenal inhibition, apparently without cellular destruction. Its biochemical mechanism of action is unknown. Data suggest that mitotane modifies the peripheral metabolism of steroids as well as directly suppressing the adrenal cortex. Adrenal cortical carcinoma is a rare disease with no curative treatment when surgery is impossible or has failed. Mitotane has been widely used in patients with advanced adrenal cortical carcinoma for the past forty years.

Mitotane has not been studied in a clinical therapeutic programme. The vast majority of published studies are retrospective, uncontrolled studies in patients with adrenal cortical carcinoma (ACC). There are data for over 500 patients treated with mitotane from about 220 studies published since 1990.

Mitotane induces a state of adrenal insufficiency which leads to the disappearance of Cushing's syndrome in patients with secreting adrenal carcinoma, often necessitating steroid substitution. In one study, where 27 patients received mitotane, it was effective in the control of clinical and biochemical hypercortisolism in all those with functioning tumours. In a second, all 59 patients treated with mitotane had adrenal insufficiency which was permanent in 75%.

The published data do not provide sufficient evidence to support any effect of mitotane on survival. Five out of nine studies which reported survival data found an increase in the survival rate with mitotane, and in three of those there was a benefit only when plasma levels exceeded 14mg/L. In terms of total or partial tumour and/or metastasis regression, eleven studies showed some degree of improvement and occasional prolonged remissions.

Summary of evidence on comparative safety

No safety studies were submitted in the licence application. The European Public Assessment Report (EPAR) notes that the severity of inoperable or relapsing ACC could justify the use of a product that can induce clinically significant undesirable effects in a high proportion of patients (more than 80%). The EPAR also notes that other cytotoxic drugs have been used in the treatment of ACC with questionable efficacy and considerably higher toxicity. Serious undesirable effects appear linked to the cumulative exposure to mitotane and are most likely to occur when plasma mitotane levels are 20 mg/L or above.

Summary of clinical effectiveness issues

The licensed indication is symptomatic treatment of advanced adrenal cortical carcinoma, and subjective response includes reduction of weakness, anorexia, pain and, in functional tumours, signs and symptoms related to excessive steroid production.

Although most studies did not measure symptom relief, some measured anti-hormonal effects. The EPAR notes that although measurable partial remissions are unusual and are reported in 20 to 30% of cases, excellent palliation of hormone symptoms is commonly observed.

Although no comparative trials exist assessing the effect of mitotane on ACC in terms of objective responses, the irremediably progressive nature of the disease means that any tumour regression obtained after a therapeutic intervention can be considered as proof of at least some effect. 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 EPAR advises that mitotane is preferred over chemotherapy with conventional agents for the following reasons:

- None of the regimens has 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 patients much lower.
- The anti-hormonal effects of mitotane allow for better symptomatic control.

Although steroid synthesis inhibitors have been cited as comparator drugs, very few reports could be found in the literature and they are not mentioned in the EPAR.

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. The multi-national clinical trial currently underway, (mitotane plus etoposide, doxorubicin and cisplatin vs mitotane plus streptozotocin) and its pharmacokinetic sub-study aim to provide data on efficacy, quality of life, dosing schedules and the potential value of plasma level monitoring.

Summary of comparative health economic evidence

The manufacturer provided a decision analysis comparing mitotane treatment to chemotherapy with either carboplatin/etoposide or the EDP regimen (doxorubicin, cisplatin and etoposide). The model examined the costs and benefits over a five year period; during the course of the model patients could switch between treatments owing to non-response and patients could receive mitotane in combination with chemotherapy. An indirect comparison was necessary as there are no clinical trials comparing mitotane to these treatments. Using this method, the analysis attributed an eleven month survival advantage to mitotane. Utility scores were obtained from four UK experts and gave a value of 0.575 for a patient on mitotane monotherapy or 0.30 for a patient on the EDP regimen. The utility values were not further adjusted for adverse events.

The manufacturer's estimate for baseline cost per QALY was £29000. The results of the model were sensitive to the dose of mitotane used and the utility values assumed.

The comparators in the model were suitable although there is some use of mitotane as current treatment in Scotland. The analysis had some limitations due to limited clinical data being available on this rare disease and the model structure was not always clearly described. The model result was driven in part by an assumed survival advantage with mitotane but at present the clinical data do not exist to support it. The results were sensitive to a range of key input parameters such as resource use and utilities. In conclusion, the economics case was not demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: comparators

Cytotoxic drugs including 5-fluorouracil, etoposide, doxorubicin and cisplatin have been used in the treatment of ACC.

Additional information: costs

Combination drug therapy is often used in advanced ACC

Product	Regimen	Cost per 28 days * (£)
mitotane 500mg tablets	**1-6g daily**	**258-1547**
doxorubicin 50mg injection	40mg/m^2 on 1 day of 28 day cycle[#]	1530
cisplatin 100mg injection	40mg/m^2 on 2 days of 28 day cycle[#]	111
etoposide 200mg injection	100mg/m^2 on 3 days of 28 day cycle[#]	87
fluorouracil 250mg injection	500mg/m^2 on 3 days of 28 day cycle[##]	38

*costs accessed from eVadis drug dictionary on 22/8/06; etoposide and mitotane costs from BNF; cisplatin cost from MIMS

[#]dose regimen from FIRM-ACT trial [##]dose regimen from published trial

Doses are shown for general comparison and do <u>not</u> imply therapeutic equivalence.

Additional information: budget impact

The net budget impact of using mitotane in the treatment of ACC was estimated by the manufacturer as £28k in year one rising to a cumulative total of £480k by year five. These figures assumed 10 patients were treated in the first year rising to a cumulative total of 50 by year five and were calculated directly from the economic model. As such, the budget impact figures included drug costs, concurrently administered drugs (such as anti-emetics and hydrocortisone), inpatient and outpatient visits.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 12th October 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.