REGIMEN TITLE: Mitotane (Lysodren®)

Indication: Symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma.
Radiologically monitorable disease
ECOG performance status 0-2

All possible tumour tissues should be surgically removed from large metastatic masses before mitotane administration is instituted. This is necessary to minimise the possibility of infarction and haemorrhage in the tumour due to a rapid cytotoxic effect of mitotane.

Exclusion criteria
- Decompensated heart failure (ejection fraction <50%)
- MI or revascularisation procedure during the last 6 months

Regimen details:
Treatment to be initiated gradually (see page 4 –dosing guidance table)

Maintenance
- Mitotane PO up to 6g daily in divided daily doses (bd to qds)
- Dose escalate following High dose or Low dose regimen (see page 4. – dosing guidance table)
- Dose may be reduced to 1-2 g per day after 2 months of treatment (cumulative dose of 200g) or in case of toxicity

Administration:
- Available as 500mg tablets
- Take with meals, avoiding fatty meals

Frequency:
- Continuous therapy in treatment response, monitoring schedule until a stable dosage is achieved
- Supply 28 days treatment per cycle

Anti-emetics:
- Mildly emetogenic

Supportive medication:
- Hydrocortisone 20mg every morning and at noon, 10mg in the evening (monitor response)
- Fludrocortisone acetate 0.1mg every morning (if mineralocorticoid deficiency causes orthostatic hypotension)

Regular investigations:
- FBC Prior each cycle
- LFTs Prior each cycle
- U&Es Prior each cycle
- Mitotane levels Levelling kit provided by HRA Pharma (prescribing consultant required to register with the service)
- Serum DHEAS or 24 hr urinary cortisol After a stable tolerated dose for 4 weeks is attained, then every 3-4 months

- Behavioural and neurologic assessments (especially if levels > 20mg/L)
- Signs and symptoms of adrenal insufficiency, hypogonadism and hypothyroidism
Dose Modifications

Monitoring of plasma levels
Mitotane dose should be adjusted to achieve a therapeutic plasma level of 14 to 20mg/L.
CNS toxicity has been associated with levels above 18-20 mg/L.
Mitotane has a long half life (18 to 159days), hence dose adjustments will not result in immediate change in levels.
Levels can continue to rise on maintenance doses and dose reductions; hence levels should be taken at each 28 days cycle (see appendix for further guidance).
Target plasma concentrations may take 3 to 5 months to achieve.

Haematological Toxicity
Prolonged bleeding time with mitotane has been reported.
Monitor APTT for patients on LMWH, and INR for patients on warfarin.
It is recommended to switch warfarin to LMWH therapy.

Renal Impairment
Severe renal impairment (CrCl<30ml/min) Mitotane is not recommended
Mild to moderate renal impairment (CrCl 30-80ml/min) monitor plasma Mitotane levels

Hepatic Impairment
Mitotane is mainly metabolised via the liver.
Severe hepatic impairment
(Bilirubin levels >2 x ULN and/or serum transaminases > 5xULN) Do no use Mitotane
Mild to moderate hepatic impairment Monitor plasma mitotane levels

Gamma-GT, aminotransferase and alkaline phosphatase are commonly raised on treatment with Mitotane. Levels normalize when the Mitotane dose is decreased.

Dose modifications for other toxicities as appropriate

Adrenal insufficiency (See supportive medications list)
Because of its adrenolytic activity and its action on cortisol metabolism, mitotane treatment induces a state of potentially permanent functional adrenal insufficiency, which necessitates hormone supplementation. Hormone supplementation should be continued even after stopping Mitotane treatment unless adequate evaluation for adrenal function is performed. Since mitotane increases plasma levels of steroid binding proteins, free cortisol and corticotropin (ACTH) determinations are necessary for optimal dosing of steroid substitution. The dose of steroids should be tapered slowly when withdrawing hormone treatment.

Toxicities: In the event of shock, severe trauma or infection, stop Mitotane immediately, Full steroid replacement should be administered in such circumstances.
Prolonged bleeding time, adrenal insufficiency, CNS toxicity, hypercholesterolemia, hypertriglyceridaemia, GI symptoms, mucositis, skin rash

Drug interactions: Spironolactone- blocks the action of mitotane- do not co-prescribe
Warfarin- accelerated metabolism of warfarin
Medicines influenced by hepatic enzyme induction (anticonvulsants, rifabutin, rifampicin, St.johns wort)
Mitotane has been shown to increase plasma hormone binding protein: this should be taken into account when interpreting the results of hormonal assays.

Comments: Maximum cumulative dose of Mitotane = 200g

References:
www.medicines.org.uk, accessed May 07
BCCA Protocol summaries. Revised March 2000
CCO formulary. Revised 2006-2007

Mitotane High Dose Regimen
### Week 1

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 g</td>
<td>3 g</td>
<td>4.5 g</td>
<td>6 g</td>
<td>6 g</td>
<td>6 g</td>
<td>6 g</td>
</tr>
</tbody>
</table>

#### Week 2

<table>
<thead>
<tr>
<th>Day 8</th>
<th>Day 9</th>
<th>Day 10</th>
<th>Day 11</th>
<th>Day 12</th>
<th>Day 13</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 g</td>
<td>6 g</td>
<td>6 g</td>
<td>6 g</td>
<td>6 g</td>
<td>6 g</td>
<td>6 g</td>
</tr>
</tbody>
</table>

**From day 15 onwards drop dose down to 4.5 g/daily (1.5 g tds) and await result of plasma mitotane level**

Blood sampling for plasma mitotane after 14 days, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks and then every 4 weeks; after achieving steady state (4-12 months) mitotane levels should be monitored every 8-12 weeks, in patients with stable levels after more than 3 yrs of treatment every 6 months.

#### Weeks 3-12 and later

Dose adjustment at least every 4 weeks according to CNS/GI side effects and plasma mitotane level.

<table>
<thead>
<tr>
<th>Plasma mitotane level</th>
<th>CNS (Grade2) /GI effects (Grade 3/4)</th>
<th>Grade 3/4 CNS side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
</tr>
</tbody>
</table>

**Treatment dose decision**

- **< 14 mg/l**
  - Increase daily dose by 1.5 g for 1 week, then another 1.5 g in the second week*
  - Reduce daily dose by 1.5 g
  - Stop Mitotane #

- **14-20 mg/l**
  - Maintain dose
  - Reduce daily dose by 1.5 g
  - Stop Mitotane #

- **> 20 mg/l**
  - Reduce daily dose to 50-80% of the most recent dose
  - Stop Mitotane #

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### Low-dose regimen

#### Week 1

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 g</td>
<td>1.0</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>2.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

#### Week 2

<table>
<thead>
<tr>
<th>Day 8</th>
<th>Day 9</th>
<th>Day 10</th>
<th>Day 11</th>
<th>Day 12</th>
<th>Day 13</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>2.5</td>
<td>2.5</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0 g</td>
</tr>
</tbody>
</table>

#### Weeks 3-12 and later

Dose adjustment at least every 4 weeks according to CNS/GI side effects and plasma mitotane level.

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<th>Grade 3/4 CNS side effects</th>
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</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
</tr>
</tbody>
</table>

**Treatment dose decision**

- **< 14 mg/l**
  - Increase daily dose by 1 g*
  - Reduce daily dose by 1 g
  - Stop Mitotane #

- **14-20 mg/l**
  - Maintain dose
  - Reduce daily dose by 1.5 g
  - Stop Mitotane #

- **> 20 mg/l**
  - Reduce daily dose to 50-80% of the most recent dose
  - Stop Mitotane #

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* Maximum daily Mitotane dose permitted is 12 g

# until recovery of side effects and restart with a lower dose (50-80% of the most recent dose).