Adrenocortical carcinoma metastatic EDP (etoposide DOXOrubicin ciSplatin) and mitotane

ID: 3937 v.1 **Endorsed**

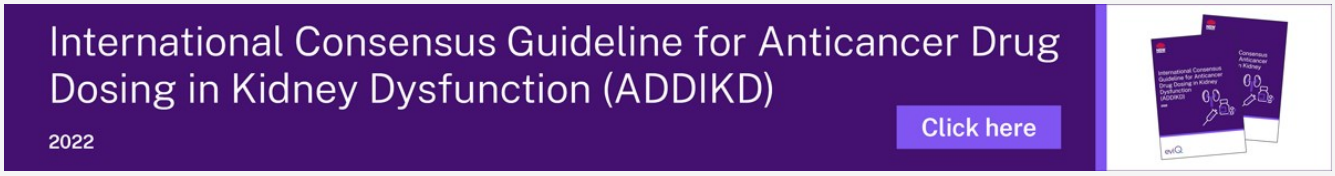
⚠ Life threatening adrenal crisis with mitotane:
Adrenal crisis, which may be life threatening or fatal, has been reported in the setting of shock, infection or severe trauma in patients treated with mitotane.

The treatment of adrenocortical carcinoma is complex and combined modality therapy is common; the involvement of a multidisciplinary team (MDT) including endocrinologists, medical oncologists familiar with the disease and urologists in the initial development and ongoing evaluation of the treatment plan, and the management of the sequelae associated with treatment is **strongly** recommended. Patients with adrenocortical carcinoma should be considered for inclusion in a clinical trial. For details of current clinical trials visit the Australian Clinical Trials website.

This protocol is not exportable and does not have a calculator.

Note: Mitotane is not TGA registered in Australia. The inclusion of mitotane on eviQ for metastatic adrenocortical carcinoma is an exceptional circumstance as per criteria set out in eviQ compliance with TGA registration and PBS listing for drugs policy. Please note the potential liability is increased when prescribing off-label and that this liability lies with the prescriber.

The anticancer drug(s) in this protocol may have been included in the ADDIKD guideline. Dose recommendations in kidney dysfunction have yet to be updated to align with the ADDIKD guideline. Recommendations will be updated once the individual protocol has been evaluated by the reference committee. For further information refer to the ADDIKD guideline. To assist with calculations, use the eviQ Estimated Glomerular Filtration Rate (eGFR) calculator.



Treatment schedule - Overview

Mitotane pre-phase

Drug	Dose	Route	Day
Mitotane	1,000 mg	PO	1 to 3
Mitotane	1,500 mg	PO	4 to 6
Mitotane	2,000 mg	PO	7

Note: Mitotane should be started a minimum of 1 week before the initiation of EDP chemotherapy as below, with the goal of attaining a blood level of 14 to 20 mg/L.[1]

Cycle 1

Drug	Dose	Route	Day
Mitotane	2,000 mg	PO	1 and 2
DOXOrubicin	40 mg/m^2	IV	1
Etoposide *	100 mg/m^2	IV infusion	2 to 4
ciSplatin	40 mg/m^2	IV infusion	3 and 4
Mitotane	2,500 mg	PO	3 to 5

Drug	Dose	Route	Day
Mitotane	3,000 mg	PO	6 to 8
Mitotane	3,500 mg	PO	9 to 11
Mitotane	4,000 mg	PO	12 to 14
Mitotane	Dose to be adjusted based on blood concentrations and tolerability **	PO	15 to 28

Cycle 2 to 6

Drug	Dose	Route	Day
Mitotane	Dose to be adjusted based on blood concentrations and tolerability **	PO	1 to 28
DOXOrubicin	40 mg/m^2	IV	1
Etoposide *	100 mg/m^2	IV infusion	2 to 4
ciSplatin	40 mg/m^2	IV infusion	3 and 4

Frequency: 28 days

Cycles: up to 6

Cycle 7 and further cycles

Drug	Dose	Route	Day
Mitotane	Dose to be adjusted based on blood concentrations and tolerability **	PO	1 to 28

* Etopophos (etoposide phosphate) 113.6 mg is equivalent to etoposide 100 mg. Doses in this protocol are expressed as etoposide.

** Mitotane dose to be adjusted based on blood concentrations and tolerability with the goal of attaining a blood level of 14 to 20 mg/L.[1]

Frequency: 28 days

Cycles: Continuous until disease progression or unacceptable toxicity

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Drug status: Doxorubicin, etoposide and cisplatin are on the PBS general schedule. Mitotane is neither TGA registered or PBS listed for this indication.

Mitotane is available as **500 mg** tablets.

Cost: not available

Treatment schedule - Detail

The supportive therapies (e.g. antiemetics, premedications, etc.), infusion times, diluents, volumes and routes of administration, if included, are listed as defaults. They may vary between institutions and can be substituted to reflect individual institutional policy.

*Antiemetics if included in the treatment schedule are based upon recommendations from national and international guidelines. These are **defaults only** and may be substituted to reflect individual institutional policy. Select here for recommended doses of alternative antiemetics.*

Mitotane pre-phase

Day 1 to 3		
Mitotane	1,000 mg (PO)	in divided doses about the same time every day with consistent timing of the doses relative to food

Day 1 to 3		
Hydrocortisone	50 mg (PO)	in divided 20-20-10 mg doses with or after food *

Day 4 to 6		
Mitotane	1,500 mg (PO)	in divided doses about the same times every day with consistent timing of the doses relative to food
Hydrocortisone	50 mg (PO)	in divided 20-20-10 mg doses with or after food *

Day 7		
Mitotane	2,000 mg (PO)	in divided doses about the same times every day with consistent timing of the doses relative to food
Hydrocortisone	50 mg (PO)	in divided 20-20-10 mg doses with or after food *

Note: Mitotane should be started a minimum of 1 week before the initiation of EDP chemotherapy as below, with the goal of attaining a blood level of 14 to 20 mg/L.[1]

Cycle 1

Day 1		
Dexamethasone	8 mg (PO)	60 minutes before chemotherapy
Palonosetron	0.25 mg (IV bolus)	30 minutes before chemotherapy
DOXOrubicin	40 mg/m^2 (IV)	over 5 to 15 minutes
Mitotane	2,000 mg (PO)	in divided doses about the same times every day with consistent timing of the doses relative to food

Day 2		
Dexamethasone	8 mg (PO)	60 minutes before chemotherapy
Etoposide **	100 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 30 to 60 minutes (if dose > 200 mg, dilute in 1000 mL sodium chloride 0.9%)
Mitotane	2,000 mg (PO)	in divided doses about the same times every day with consistent timing of the doses relative to food

Day 3		
Netupitant	300 mg (PO)	60 minutes before chemotherapy (fixed dose preparation with palonosetron)
Palonosetron	0.5 mg (PO)	60 minutes before chemotherapy (fixed dose preparation with netupitant)
Dexamethasone	12 mg (PO) ***	60 minutes before chemotherapy
ciSplatin	40 mg/m^2 (IV infusion)	in 1000 mL sodium chloride 0.9% over 60 minutes
Etoposide **	100 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 30 to 60 minutes (if dose > 200 mg, dilute in 1000 mL sodium chloride 0.9%)
Mitotane	2,500 mg (PO)	in divided doses about the same times every day with consistent timing of the doses relative to food

Day 4		
Dexamethasone	8 mg (PO)	60 minutes before chemotherapy
ciSplatin	40 mg/m^2 (IV infusion)	in 1000 mL sodium chloride 0.9% over 60 minutes
Etoposide **	100 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 30 to 60 minutes (if dose > 200 mg, dilute in 1000 mL sodium chloride

Day 4		
		0.9%)
Mitotane	2,500 mg (PO)	in divided doses about the same times every day with consistent timing of the doses relative to food

Day 5		
Dexamethasone	8 mg (PO)	ONCE a day (or in divided doses) with or after food
Mitotane	2,500 mg (PO)	in divided doses about the same times every day with consistent timing of the doses relative to food

Day 6 and 7		
Dexamethasone	8 mg (PO)	ONCE a day (or in divided doses) with or after food
Mitotane	3,000 mg (PO)	in divided doses about the same times every day with consistent timing of the doses relative to food

Day 8		
Mitotane	3,000 mg (PO)	in divided doses about the same times every day with consistent timing of the doses relative to food
Hydrocortisone	50 mg (PO)	in divided 20-20-10 mg doses with or after food *

Day 9 to 11		
Mitotane	3,500 mg (PO)	in divided doses about the same times every day with consistent timing of the doses relative to food
Hydrocortisone	50 mg (PO)	in divided 20-20-10 mg doses with or after food *

Day 12 to 14		
Mitotane	4,000 mg (PO)	in divided doses about the same times every day with consistent timing of the doses relative to food
Hydrocortisone	50 mg (PO)	in divided 20-20-10 mg doses with or after food *

Day 15 to 28		
Mitotane	Dose to be adjusted based on blood concentrations and tolerability ****	in divided doses about the same times every day with consistent timing of the doses relative to food
Hydrocortisone	50 mg (PO)	in divided 20-20-10 mg doses with or after food *

Cycle 2 to 6

Day 1		
Dexamethasone	8 mg (PO)	60 minutes before chemotherapy
Palonosetron	0.25 mg (IV bolus)	30 minutes before chemotherapy
DOXOrubicin	40 mg/m^2 (IV)	over 5 to 15 minutes
Mitotane	Dose to be adjusted based on blood concentrations and tolerability ****	in divided doses about the same times every day with consistent timing of the doses relative to food

Day 2		
Dexamethasone	8 mg (PO)	60 minutes before chemotherapy
Etoposide **	100 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 30 to 60 minutes (if dose > 200 mg, dilute in 1000 mL sodium chloride 0.9%)

Day 2		
Mitotane	Dose to be adjusted based on blood concentrations and tolerability ****	in divided doses about the same times every day with consistent timing of the doses relative to food

Day 3		
Netupitant	300 mg (PO)	60 minutes before chemotherapy (fixed dose preparation with palonosetron)
Palonosetron	0.5 mg (PO)	60 minutes before chemotherapy (fixed dose preparation with netupitant)
Dexamethasone	12 mg (PO) ***	60 minutes before chemotherapy
ciSplatin	40 mg/m^2 (IV infusion)	in 1000 mL sodium chloride 0.9% over 60 minutes
Etoposide **	100 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 30 to 60 minutes (if dose > 200 mg, dilute in 1000 mL sodium chloride 0.9%)
Mitotane	Dose to be adjusted based on blood concentrations and tolerability) ****	in divided doses about the same times every day with consistent timing of the doses relative to food

Day 4		
Dexamethasone	8 mg (PO)	60 minutes before chemotherapy
ciSplatin	40 mg/m^2 (IV infusion)	in 1000 mL sodium chloride 0.9% over 60 minutes
Etoposide **	100 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 30 to 60 minutes (if dose > 200 mg, dilute in 1000 mL sodium chloride 0.9%)
Mitotane	Dose to be adjusted based on blood concentrations and tolerability ****	in divided doses about the same times every day with consistent timing of the doses relative to food

Day 5 to 7		
Dexamethasone	8 mg (PO)	ONCE a day (or in divided doses) with or after food
Mitotane	Dose to be adjusted based on blood concentrations and tolerability ****	in divided doses about the same times every day with consistent timing of the doses relative to food

Day 8 to 28		
Mitotane	Dose to be adjusted based on blood concentrations and tolerability ****	in divided doses about the same times every day with consistent timing of the doses relative to food
Hydrocortisone	50 mg (PO)	in divided 20-20-10 mg doses with or after food *

Frequency: 28 days

Cycles: up to 6

Cycle 7 and further cycles

Day 1 to 28		
Mitotane	Dose to be adjusted based on blood concentrations and tolerability ****	in divided doses about the same times every day with consistent timing of the doses relative to food
Hydrocortisone	50 mg (PO)	in divided 20-20-10 mg doses with or after food *

* Hydrocortisone doses to be confirmed upon evaluation of adrenal function and in consultation with an endocrinologist.

Hydrocortisone to be omitted in patient with confirmed Cushing's syndrome.

** Etopophos (etoposide phosphate) 113.6 mg is equivalent to etoposide 100 mg. Doses in this protocol are expressed as etoposide.

*** The full dose of dexamethasone on day 3 may not be required and may be reduced to 8 mg at the clinician's discretion as per eviQ RC consensus. Link to ID 7 Prevention of chemotherapy induced nausea and vomiting.

**** Mitotane dose to be adjusted based on blood concentrations and tolerability with the goal of attaining a blood level of 14 to 20 mg/L.[1]

Frequency: 28 days

Cycles: Continuous until disease progression or unacceptable toxicity

Indications and patient population

Indications:

- Unresectable locally advanced or metastatic adrenocortical carcinoma
  - ECOG performance status 0 to 2.

Cautions/Exclusions:

- pre-existing neuropathies Grade 2 or greater
- moderate/severe renal impairment (creatinine clearance less than 50 mL/min)
- moderate/severe hepatic impairment (serum bilirubin ≥ 2 x ULN and/or serum transaminases ≥ 3 x ULN. For mitotane monotherapy transaminase ≤ 5 x ULN are acceptable)
- significant hearing impairment/tinnitus
- left ventricular ejection fraction less than 50%.

Clinical information

Caution with oral anti-cancer drugs	Select links for information on the safe prescribing, dispensing and administration of orally administered anti-cancer drugs. Read more about the COSA guidelines and oral anti-cancer therapy
Venous access required	IV cannula (IVC) or central venous access device (CVAD) is required to administer this treatment. Read more about central venous access device line selection
Hypersensitivity/infusion related reaction	High risk with etoposide. Read more about Hypersensitivity reaction

Emetogenicity MODERATE/HIGH	Antiemetic therapy should be administered throughout the duration of the chemotherapy protocol and to cover delayed nausea. The acute and delayed emetic risk of multi-day chemotherapy protocols will overlap depending on the individual drugs and their sequence of administration. More or less antiemetic cover may be required. NCCN antiemesis guidelines 2020 classifies mitotane as moderate to high emetic risk. A NK1 receptor antagonist and a $5HT_3$ receptor antagonist in combination with dexamethasone are available on the PBS for primary prophylaxis of cisplatin induced nausea and vomiting. Suggested default antiemetics have been added to the treatment schedule, and may be substituted to reflect institutional policy. Ensure that patients also have sufficient antiemetics for breakthrough emesis: Metoclopramide 10 mg three times a day when necessary (maximum of 30 mg/24 hours, up to 5 days) OR Prochlorperazine 10 mg PO every 6 hours when necessary. Read more about preventing anti-cancer therapy induced nausea and vomiting
Cumulative lifetime dose of anthracyclines	Cumulative doses should take into account all previous anthracyclines received during a patient's lifetime (i.e. daunorubicin, doxorubicin, epirubicin, idarubicin and mitoxantrone). Criteria for reducing the total anthracycline cumulative lifetime dose include: • patient is elderly • prior mediastinal radiation • hypertensive cardiomegaly • concurrent therapy with high dose cyclophosphamide and some other cytotoxic drugs (e.g. bleomycin, dacarbazine, dactinomycin, etoposide, melphalan, mitomycin and vincristine). Baseline clinical assessments include echocardiogram (ECHO) or gated heart pool scan (GHPS) and electrocardiogram (ECG) evaluation. Patients with normal baseline cardiac function (left ventricular ejection fraction (LVEF) > 50%) and low risk patients require LVEF monitoring when greater than 70% of the anthracycline threshold is reached or if the patient displays symptoms of cardiac impairment. Post-treatment cardiac monitoring is recommended for patients who have received high levels of total cumulative doses of anthracyclines at the clinician's discretion. Read more about cardiac toxicity associated with anthracyclines
Central nervous system (CNS) effects	A broad spectrum of CNS effects can occur in patients receiving this treatment. These reactions may or may not be reversible after treatment discontinuation. Mood effects primarily included depression as manifested by lethargy, somnolence, sedation, dizziness or vertigo. Cognitive effects included mental impairment, confusion and ataxia. Speech effects included dysarthria. Behavioural and neurological assessments should be made at regular intervals, especially when mitotane plasma levels exceed 20 mg/L.
Mitotane monitoring	Therapeutic drug monitoring recommended. Dose escalation following the protocol may lead to gastrointestinal and neurological toxicity. Mitotane plasma levels should be monitored at frequent intervals (every 3-4 weeks) until the therapeutic window (a blood level of 14 to 20 mg/L) has been reached. Once the maintenance dose has been reached, the intervals can be extended. The first 6 months after beginning mitotane therapy mitotane plasma levels should be assessed at least once every four weeks and after 6 months analysis should be done at least every 8 weeks.
Hypoadrenalism	Mitotane may cause potentially permanent hypoadrenalism. Patients should take gluco- and possibly mineralocorticoid (depending on blood pressure, serum potassium levels and plasma renin activity) replacement. Patients are likely to require steroid replacement even after mitotane is discontinued. Steroid replacement should not be discontinued without evaluation for adequate adrenal function. Additional steroids may be required in physiologic stress circumstances. In patients with functioning tumours, adrenal steroid replacement should not be started until cortisol levels are less than or equal to normal.

Adrenal crisis	Mitotane, as an adrenolytic agent, may contribute to potentially life-threatening adrenal crisis in the setting of shock, severe trauma or infection and response to shock is impaired. If shock, severe trauma or infection occurs, mitotane should be temporarily discontinued and steroids immediately given. Monitoring for escalating signs of shock is recommended.
Hypothyroidism	Thyroid dysfunction, in particular central hypothyroidism (low free T4 with low or normal TSH), may occur with this treatment. Monitor for signs and symptoms of thyroid dysfunction and manage as clinically appropriate.
Caution with higher body weight/recent weight loss	Fat tissue can act as a reservoir for mitotane. This could result in prolonged half-life and potential accumulation of mitotane in overweight or even normal weight patients. Closer monitoring in obese patients or patients with recent weight loss is recommended.
Ovarian macrocysts	Mitotane has been associated with development of ovarian macrocysts in premenopausal patients. Improvement after mitotane discontinuation has been reported in some cases. Advise patients to report any abnormal vaginal bleeding, vaginal discharge or pain or pressure in the pelvic region.
Sex hormone disturbances	Mitotane has been associated with sex hormone disturbances including decreased blood androstenedione and decreased blood testosterone in females, increased sex hormone binding globulin in females and males, decreased blood free testosterone in males. Routine monitoring of testosterone/oestrodial levels is recommended.
Etoposide conversion factor	Note: Etopophos (etoposide phosphate) 113.6 mg is equivalent to etoposide 100 mg. Doses in this protocol are expressed as etoposide.
Hydration	Hydration helps to prevent cisplatin-induced nephrotoxicity. The default regimen is appropriate for patients with normal electrolytes, kidney function, fluid status etc. and should be adjusted according to individual requirements. Read more about cisplatin hydration regimens
Ototoxicity	Ototoxicity may occur with platinum-based therapy; patients should be monitored for signs and symptoms. Platinum compounds should be used with caution in patients with pre-existing conditions or risk factors. Ototoxicity may become more severe in patients being treated with other drugs with nephrotoxic potential e.g. aminoglycosides. An audiometry test should be performed if symptoms develop. Read more about ototoxicity - tinnitus and hearing loss
Peripheral neuropathy	Assess prior to each treatment. If a patient experiences grade 2 or greater peripheral neuropathy, a dose reduction, delay, or omission of treatment may be required; review by medical officer before commencing treatment. Read more about peripheral neuropathy Link to chemotherapy-induced peripheral neuropathy screening tool
Corticosteroids	Diabetic patients should monitor their blood glucose levels closely. To minimise gastric irritation, advise patient to take immediately after food. Consider the use of a H2 antagonist or proton pump inhibitor if appropriate. Read more about acute short term effects from corticosteroids
Blood tests	FBC, EUC, LFTs, TFTs, calcium, magnesium and phosphate at baseline and prior to each cycle. DHEAS, ACTH and 24 hour urinary cortisol or serum cortisol at baseline, 4 weeks after being on stable dose, then every 3 to 4 months. Nadir FBC for every EDP cycle.
Hepatitis B screening and prophylaxis	Routine screening for HBsAg and anti-HBc is NOT usually recommended for patients receiving this treatment. Read more about hepatitis B screening and prophylaxis in cancer patients requiring cytotoxic and/or immunosuppressive therapy

Vaccinations	Live vaccines are contraindicated in cancer patients receiving immunosuppressive therapy and/or who have poorly controlled malignant disease. Refer to the recommended schedule of vaccination for immunocompromised patients, as outlined in the Australian Immunisation Handbook. Read more about COVID-19 vaccines and cancer.
Fertility, pregnancy and lactation	Cancer treatment can have harmful effects on fertility and this should be discussed with all patients of reproductive potential prior to commencing treatment. There is a risk of foetal harm in pregnant women. A pregnancy test should be considered prior to initiating treatment in females of reproductive potential if sexually active. It is important that all patients of reproductive potential use effective contraception whilst on therapy and after treatment finishes. Effective contraception methods and adequate contraception timeframe should be discussed with all patients of reproductive potential. Possibility of infant risk should be discussed with breastfeeding patients. Read more about the effect of cancer treatment on fertility

Dose modifications

Evidence for dose modifications is limited, and the recommendations made on eviQ are intended as a guide only. They are generally conservative with an emphasis on safety. Any dose modification should be based on clinical judgement, and the individual patient's situation including but not limited to treatment intent (curative vs palliative), the anti-cancer regimen (single versus combination therapy versus chemotherapy versus immunotherapy), biology of the cancer (site, size, mutations, metastases), other treatment related side effects, additional co-morbidities, performance status and patient preferences.Suggested dose modifications are based on clinical trial findings, product information, published guidelines and reference committee consensus . The dose reduction applies to each individual dose and not to the total number of days or duration of treatment cycle unless stated otherwise. Non-haematological gradings are based on Common Terminology Criteria for Adverse Events (CTCAE) unless otherwise specified. Renal and hepatic dose modifications have been standardised where possible. For more information see dosing considerations & disclaimer .

The dose recommendations in kidney dysfunction (i.e.renal impairment) displayed may not reflect those in the ADDIKD guideline and have been included for historical reference only. Recommendations will be updated once the individual protocol has been evaluated by the reference committee, with this version of the protocol then being archived. Clinicians are expected to refer to the ADDIKD guideline prior to prescribing in kidney dysfunction.
International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD).

Note:

- The dose modifications below are based on a combination of the clinical trial,[1] product information and reference committee consensus.
- All dose reductions are calculated as a percentage of the starting dose

Haematological toxicity	
ANC x 10^9/L (pre-treatment blood test)	
1.0 to less than 1.5	Refer to local institutional guidelines; it is the view of the expert clinicians that treatment should continue if patient is clinically well.
0.5 to less than 1.0	Delay treatment until recovery
less than 0.5	Delay treatment until recovery and consider reducing doxorubicin, cisplatin, etoposide and mitotane by 25% for subsequent cycles
Febrile neutropenia	Delay treatment until recovery and consider reducing doxorubicin, cisplatin, etoposide and mitotane by 25% for subsequent cycles
Platelets x 10^9/L (pre-treatment blood test)	
75 to less than 100	Refer to local institutional guidelines; it is the view of the expert clinicians that treatment should continue if patient is clinically well.

Haematological toxicity	
50 to less than 75	Delay treatment until recovery
less than 50	Delay treatment until recovery and consider reducing doxorubicin, cisplatin, etoposide and mitotane by 25% for subsequent cycles

Renal impairment	
eGFR (CKI-EPI or MDRD) or eCrCl (Cockcroft Gault) (mL/min) *	
greater than or equal to 70	No dose modifications necessary
50 to less than 70	Reduce cisplatin by 25%. Use mitotane with caution
30 to less than 50	Reduce etoposide by 25% and cisplatin by 50%. Use mitotane with caution
less than 30	Reduce etoposide by 50%; omit mitotane and cisplatin

** Each method has its limitations; refer to Nephrotoxicity associated with cisplatin for more information.*

Hepatic impairment	
Hepatic dysfunction	
Mild	Reduce doxorubicin and etoposide by 25%. Use mitotane with caution
Moderate	Reduce doxorubicin and etoposide by 50%. Use mitotane with caution
Severe	Omit doxorubicin, mitotane and etoposide

Peripheral neuropathy	
Grade 2 which is present at the start of the next cycle	Reduce cisplatin by 25%; if persistent, reduce cisplatin by 50%
Grade 3 or Grade 4	Omit cisplatin

Central nervous system toxicity	
Grade 2, Grade 3 or Grade 4	Check Mitotane plasma level. Withhold mitotane until symptoms have resolved and restart 7-10 days after symptoms resolve with a lower dose (decrease by 500-1000 mg)

Mucositis and stomatitis	
Grade 2	Delay treatment until toxicity has resolved to Grade 1 or less and reduce doses for subsequent cycles as follows: 1st occurrence: No dose reduction 2nd occurrence: Reduce doxorubicin, cisplatin and etoposide by 25% 3rd occurrence: Reduce doxorubicin, cisplatin and etoposide by 50% 4th occurrence: Omit doxorubicin, cisplatin and etoposide
Grade 3 or Grade 4	Delay treatment until toxicity has resolved to Grade 1 or less and reduce doses for subsequent cycles as follows: 1st occurrence: Reduce doxorubicin, cisplatin and etoposide by 50% 2nd occurrence: Omit doxorubicin, cisplatin and etoposide

Interactions

Drug interactions in eviQ protocols are under review and being updated to align with current literature. Further site-wide updates and changes will occur in due course. ***References & Disclaimer***

The drug interactions shown below are not an exhaustive list. For a more comprehensive list and for detailed information on specific drug interactions and clinical management, please refer to the specific drug product information and the following key resources:

- *MIMS - interactions tab (includes link to a CYP-450 table) (login required)*
- *Australian Medicines Handbook (AMH) – interactions tab (login required)*

- *Micromedex Drug Interactions (login required)*
- *Cancer Drug Interactions*
- *Cytochrome P450 Drug Interactions*

Cisplatin		
	Interaction	**Clinical management**
Nephrotoxic drugs (e.g. aminoglycosides, amphotericin, contrast dye, frusemide, NSAIDs)	Additive nephrotoxicity	Avoid combination or monitor kidney function closely
Ototoxic drugs (e.g. aminoglycosides, frusemide, NSAIDs)	Additive ototoxicity	Avoid combination or perform regular audiometric testing
Neurotoxic drugs (e.g. vincristine, paclitaxel)	Additive neurotoxicity	Monitor closely for neuropathy if combination used
Paclitaxel	Administration schedule may influence the development of myelosuppression	Minimise toxicity by administering paclitaxel first in regimens using the combination
Carbamazepine, phenytoin, valproate	Decreased antiepileptic plasma levels	Monitor antiepileptic serum levels and seizure frequency for efficacy; adjust dosage as appropriate or select alternative antiepileptic (e.g. clonazepam, diazepam, lorazepam)

Doxorubicin		
	Interaction	**Clinical management**
Cardiotoxic drugs (eg. bevacizumab, calcium channel blockers, propranolol, trastuzumab)	Increased risk of doxorubicin-induced cardiotoxicity	Avoid combination or monitor closely for cardiotoxicity
Cyclophosphamide	Sensitises the heart to the cardiotoxic effects of doxorubicin; also, doxorubicin may exacerbate cyclophosphamide induced cystitis	Monitor closely for cardiotoxicity and ensure adequate prophylaxis for haemorrhagic cystitis when combination is used
Glucosamine	Reduced efficacy of doxorubicin (due to induction of glucose-regulated stress proteins resulting in decreased expression of topoisomerase II *in vitro*)	The clinical effect of glucosamine taken orally is unknown. Avoid combination or monitor for decreased clinical response to doxorubicin
CYP2D6 inhibitors (e.g. SSRIs (esp. paroxetine), perhexiline, cinacalcet, doxepin, flecainide, quinine, terbinafine)	Increased toxicity of doxorubicin possible due to reduced clearance	Monitor for doxorubicin toxicity
CYP3A4 inhibitors (e.g. aprepitant, azole antifungals, clarithromycin, erythromycin, grapefruit juice, ritonavir etc.)	Increased toxicity of doxorubicin possible due to reduced clearance	Monitor for doxorubicin toxicity
CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort etc.)	Reduced efficacy of doxorubicin possible due to increased clearance	Monitor for decreased clinical response to doxorubicin

Etoposide and Etoposide Phosphate		
	Interaction	**Clinical management**
CYP3A4 and P-gp inhibitors (e.g. amiodarone, aprepitant, azole-antifungals, ritonavir, lapatinib, nilotinib, sorafenib, macrolides, ciclosporin etc.)	Increased toxicity of etoposide possible due to reduced clearance	Avoid combination or monitor for etoposide toxicity
CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort etc.)	Reduced efficacy of etoposide possible due to increased clearance	Avoid combination or monitor for decreased clinical response to etoposide
Glucosamine	Reduced efficacy of etoposide (due to induction of glucose-regulated stress proteins resulting in decreased expression of topoisomerase II)	Avoid combination or monitor for decreased clinical response to etoposide
Grapefruit juice	Reduced efficacy of oral etoposide possible due to possible alteration of P-gp mediated intestinal transport of etoposide	Avoid combination or monitor for decreased clinical response to etoposide

Mitotane		
	Interaction	**Clinical management**
CYP3A4 substrates (e.g. atorvastatin, benzodiazepines, calcineurin inhibitors, clarithromycin, dihydroergotamine, simvastatin, etc.)	Reduced efficacy of these drugs possible due to induction of CYP3A4 by mitotane resulting in increased clearance	Avoid combination or monitor for reduced efficacy of the interacting drugs
Warfarin	Reduced anticoagulant efficacy of warfarin due enhancement of its metabolism by mitotane	Monitor INR regularly and adjust warfarin dosage as appropriate; consider alternative anticoagulant (e.g. LMWH, unfractionated heparin)
Spironolactone	Reduced efficacy of mitotane due to unknown mechanism	Avoid combination
Central nervous system (CNS) depressants	Enhanced CNS depression due to additive effect	Use combination with caution

NK-1 antagonist e.g. aprepitant, fosaprepitant, netupitant		
	Interaction	**Clinical management**
Dexamethasone	Increased effects/toxicity of dexamethasone due to inhibition of its metabolism via CYP3A4	Reduce dose of **antiemetic dexamethasone** by approximately 50% when adding a NK-1 antagonist. For protocols that already recommend a NK-1 antagonist, the dose reduction of **antiemetic dexamethasone** has already been taken into account. If **dexamethasone is part of the chemotherapy protocol**, dose reduction as per the product information is not routinely recommended in clinical practice and no additional dexamethasone is required for antiemetic cover.
Warfarin	Reduced anticoagulant efficacy of warfarin due to increased clearance (aprepitant induces CYP2C9). *Note interaction only applicable to aprepitant/ fosaprepitant	INR should be monitored in the 2 week period, particularly at 7 to 10 days following the administration of aprepitant/ fosaprepitant
Combined oral contraceptive	Reduced contraceptive efficacy due to increased clearance. *Note interaction only applicable to aprepitant/ fosaprepitant	Alternative non-hormonal methods should be used during and for 1 month after stopping aprepitant/ fosaprepitant
CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort etc.)	Reduced efficacy of NK-1 antagonist possible due to increased clearance	Avoid combination or monitor for decreased antiemetic effect. Consider using an alternative antiemetic regimen
CYP3A4 inhibitors (e.g. azole antifungals, clarithromycin, erythromycin, grapefruit juice, ritonavir etc.)	Increased toxicity of NK-1 antagonist possible due to reduced clearance	Avoid combination or monitor for increased adverse effects of NK-1 antagonist (e.g. headache, hiccups, constipation)
Drugs metabolised by CYP3A4 (e.g. etoposide, imatinib, irinotecan, midazolam, paclitaxel, vinblastine, vincristine etc.)	Increased effects/toxicity of these drugs possible due to inhibition of CYP3A4 by NK-1 antagonist	Avoid combination or monitor for increased toxicity especially with orally administered drugs

General		
	Interaction	**Clinical management**
Warfarin	Anti-cancer drugs may alter the anticoagulant effect of warfarin.	Monitor INR regularly and adjust warfarin dosage as appropriate; consider alternative anticoagulant.
Direct oral anticoagulants (DOACs) e.g. apixaban, rivaroxaban, dabigatran	Interaction with both CYP3A4 and P-gp inhibitors /inducers. DOAC and anti-cancer drug levels may both be altered, possibly leading to loss of efficacy or toxicity (i.e. increased bleeding).	Apixaban: avoid concurrent use with strong CYP3A4 and P-gp inhibitors. If treating VTE, avoid use with strong CYP3A4 and P-gp inducers. Rivaroxaban: avoid concurrent use with strong CYP3A4 and P-gp inhibitors. Dabigatran: avoid combination with strong P-gp inducers and inhibitors. If concurrent use is unavoidable, monitor closely for efficacy/toxicity of both drugs.
Digoxin	Anti-cancer drugs can damage the lining of the intestine; affecting the absorption of digoxin.	Monitor digoxin serum levels; adjust digoxin dosage as appropriate.
Antiepileptics	Both altered antiepileptic and anti-cancer drug levels may occur, possibly leading to loss of efficacy or toxicity.	Where concurrent use of an enzyme-inducing antiepileptic cannot be avoided, monitor antiepileptic serum levels for toxicity, as well as seizure frequency for efficacy; adjust dosage as appropriate. Also monitor closely for efficacy of the anti-cancer therapy.
Antiplatelet agents and NSAIDs	Increased risk of bleeding due to treatment related thrombocytopenia.	Avoid or minimise combination. If combination deemed essential, (e.g. low dose aspirin for ischaemic heart disease) monitor for signs of bleeding.
Serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs e.g. paroxetine) and serotonin noradrenaline reuptake inhibitors (SNRIs e.g. venlafaxine)	Increased risk of serotonin syndrome with concurrent use of 5-HT3 receptor antagonists (e.g. palonosetron, ondansetron, granisetron, tropisetron, dolasetron, etc.)	Avoid combination. If combination is clinically warranted, monitor for signs and symptoms of serotonin syndrome (e.g. confusion, agitation, tachycardia, hyperreflexia). For more information link to TGA Medicines Safety Update
Vaccines	Diminished response to vaccines and increased risk of infection with live vaccines.	Live vaccines (e.g. BCG, MMR, zoster and varicella) are contraindicated in patients on immunosuppressive therapy. Use with caution in patients on non-immunosuppressive therapy. For more information; refer to the recommended schedule of vaccination for cancer patients, as outlined in the Australian Immunisation Handbook

Administration mitotane pre-phase

eviQ provides safe and effective instructions on how to administer cancer treatments. However, eviQ does not provide every treatment delivery option, and is unable to provide a comprehensive list of cancer treatment agents and their required IV line giving set/filter. There may be alternative methods of treatment administration, and alternative supportive treatments that are also appropriate. Please refer to the individual

product information monographs via the TGA website for further information.

Day 1 to 7

This is a continuous oral treatment

Safe handling and waste management

Safe administration

General patient assessment prior to each treatment.

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

Pre treatment medication

Verify premedication taken or administer as prescribed.

Chemotherapy - Time out

Mitotane

- administer orally in divided doses as prescribed on **days 1 to 7**
- to be swallowed whole with a glass of water; do not break, crush or chew
- may be taken with or without food; consistent association with food is necessary
- to be taken about the same time each day

Note: missed doses should not be replaced; if a dose is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Continue safe handling precautions until 7 days after completion of drug(s)

Discharge information

Mitotane tablets

- Mitotane tablets with written instructions on how to take them.

Steroid tablets

- Steroid tables if prescribed with written instructions on how to take them.

Patient information

- Ensure patient receives patient information sheet.

Administration cycles 1 to 6

eviQ provides safe and effective instructions on how to administer cancer treatments. However, eviQ does not provide every treatment delivery option, and is unable to provide a comprehensive list of cancer treatment agents and their required IV line giving set/filter. There may be alternative methods of treatment administration, and alternative supportive treatments that are also appropriate. Please refer to the individual product information monographs via the TGA website for further information.

Day 1

Approximate treatment time: 30 to 60 minutes.

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before commencing treatment.

Prime IV line(s).

Insert IV cannula or access TIVAD or CVAD.

Pre treatment medication

Verify dexamethasone taken or administer as prescribed.

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Doxorubicin

Administer doxorubicin (vesicant):

- over 5 to 15 minutes
  - via a minibag **OR**
  - by IV bolus via a side port of a freely flowing IV infusion
- ensure vein is patent and monitor for signs of extravasation throughout administration
- flush with ~150 mL of sodium chloride 0.9%
- potential for flare reaction during administration of doxorubicin (facial flushing and red streaking along the vein) stop infusion and exclude extravasation before continuing at a slower rate of infusion.

Although rare, cardiac arrhythmias may occur during or immediately after doxorubicin administration. If sudden onset of dyspnoea, palpitations or irregular pulse occurs, stop administration immediately and obtain urgent medical officer review.

Mitotane

This is a continuous oral treatment

- administer orally in divided doses as prescribed on **days 1 to 28**
- to be swallowed whole with a glass of water; do not break, crush or chew
- may be taken with or without food; consistent association with food is necessary
- to be taken about the same time each day
- dose to be adjusted based on blood concentrations and tolerability (see treatment schedule and clinical information)

Note: missed doses should not be replaced; if a dose is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Remove IV cannula and/or deaccess TIVAD or CVAD.

Continue safe handling precautions until 7 days after completion of drug(s)

Day 2

Approximate treatment time: 90 minutes

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before commencing treatment.

Prime IV line(s).

Insert IV cannula or access TIVAD or CVAD.

Pre treatment medication

Verify dexamethasone taken or administer as prescribed.

Chemotherapy - Time out

Etoposide

Administer etoposide (irritant):

- via IV infusion over 30 to 60 minutes
- rapid infusion may cause hypotension
- observe for hypersensitivity
- flush with ~ 100 mL sodium chloride 0.9%
- if using etoposide phosphate administer in ~ 50 mL sodium chloride 0.9% or glucose 5% over ~15 minutes.

Stop infusion at first sign of reaction:

- if symptoms are mild and resolve when infusion is stopped, consider recommencing infusion after review by medical officer at a slower rate.
- for severe reactions seek medical assistance immediately and do not restart infusion.

Mitotane

This is a continuous oral treatment

- administer orally in divided doses as prescribed on **days 1 to 28**
- to be swallowed whole with a glass of water; do not break, crush or chew
- may be taken with or without food; consistent association with food is necessary
- to be taken about the same time each day
- dose to be adjusted based on blood concentrations and tolerability (see treatment schedule and clinical information)

Note: missed doses should not be replaced; if a dose is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Remove IV cannula and/or deaccess TIVAD or CVAD.

Continue safe handling precautions until 7 days after completion of drug(s)

Day 3

Approximate treatment time: 5 hours

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before commencing treatment.

Peripheral neuropathy assessment tool.

Prime IV line(s).

Insert IV cannula or access TIVAD or CVAD.

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Verify dexamethasone taken or administer as prescribed.

Chemotherapy - Time out

Cisplatin

Commence prehydration for cisplatin:

- administer 10 mmol magnesium sulphate ($MgSO_4$) in 500 mL sodium chloride 0.9% over 60 minutes
- followed by 200 mL of mannitol 20% over 15 minutes
  - mannitol should be administered via a controlled infusion
- mannitol 10% may be used as per institutional policy; there is much variation in the use of mannitol and although there is no conclusive evidence that mannitol should be used, many sites have used it routinely without renal toxicity. The routine use of frusemide to increase urine flow is not recommended. Refer to your institutional guidelines and medical orders.
- ensure patient has passed urine prior to cisplatin administration as per institutional policy.

Administer cisplatin (irritant):

- via IV infusion over 60 minutes
- flush with 100 mL of sodium chloride 0.9%.

Post hydration:

- 500 mL sodium chloride 0.9% over 60 minutes.

Etoposide

Administer etoposide (irritant):

- via IV infusion over 30 to 60 minutes
- rapid infusion may cause hypotension
- observe for hypersensitivity
- flush with ~ 100 mL sodium chloride 0.9%
- if using etoposide phosphate administer in ~ 50 mL sodium chloride 0.9% or glucose 5% over ~15 minutes.

Stop infusion at first sign of reaction:

- if symptoms are mild and resolve when infusion is stopped, consider recommencing infusion after review by medical officer at a slower rate.
- for severe reactions seek medical assistance immediately and do not restart infusion.

Mitotane

This is a continuous oral treatment

- administer orally in divided doses as prescribed on **days 1 to 28**
- to be swallowed whole with a glass of water; do not break, crush or chew
- may be taken with or without food; consistent association with food is necessary
- to be taken about the same time each day
- dose to be adjusted based on blood concentrations and tolerability (see treatment schedule and clinical information)

Note: missed doses should not be replaced; if a dose is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Remove IV cannula and/or deaccess TIVAD or CVAD.

Continue safe handling precautions until 7 days after completion of drug(s)

Day 4

Approximate treatment time: 5 hours

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before commencing treatment.

Peripheral neuropathy assessment tool.

Prime IV line(s).

Insert IV cannula or access TIVAD or CVAD.

Pre treatment medication

Verify dexamethasone taken or administer as prescribed.

Chemotherapy - Time out

Cisplatin

Commence prehydration for cisplatin:

- administer 10 mmol magnesium sulphate ($MgSO_4$) in 500 mL sodium chloride 0.9% over 60 minutes
- followed by 200 mL of mannitol 20% over 15 minutes
  - mannitol should be administered via a controlled infusion
- mannitol 10% may be used as per institutional policy; there is much variation in the use of mannitol and although there is no conclusive evidence that mannitol should be used, many sites have used it routinely without renal toxicity. The routine use of frusemide to increase urine flow is not recommended. Refer to your institutional guidelines and medical orders.
- ensure patient has passed urine prior to cisplatin administration as per institutional policy.

Administer cisplatin (irritant):

- via IV infusion over 60 minutes
- flush with 100 mL of sodium chloride 0.9%.

Post hydration:

- 500 mL sodium chloride 0.9% over 60 minutes.

Etoposide

Administer etoposide (irritant):

- via IV infusion over 30 to 60 minutes
- rapid infusion may cause hypotension
- observe for hypersensitivity
- flush with ~ 100 mL sodium chloride 0.9%
- if using etoposide phosphate administer in ~ 50 mL sodium chloride 0.9% or glucose 5% over ~15 minutes.

Stop infusion at first sign of reaction:

- if symptoms are mild and resolve when infusion is stopped, consider recommencing infusion after review by medical officer at a slower rate.
- for severe reactions seek medical assistance immediately and do not restart infusion.

Mitotane

This is a continuous oral treatment

- administer orally in divided doses as prescribed on **days 1 to 28**
- to be swallowed whole with a glass of water; do not break, crush or chew
- may be taken with or without food; consistent association with food is necessary
- to be taken about the same time each day
- dose to be adjusted based on blood concentrations and tolerability (see treatment schedule and clinical information)

Note: missed doses should not be replaced; if a dose is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Remove IV cannula and/or deaccess TIVAD or CVAD.

Continue safe handling precautions until 7 days after completion of drug(s)

Days 5 to 28

This is a continuous oral treatment

Safe handling and waste management

Safe administration

General patient assessment prior to each treatment.

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

Chemotherapy - Time out

Mitotane

- administer orally in divided doses as prescribed on **days 1 to 28**
- to be swallowed whole with a glass of water; do not break, crush or chew
- may be taken with or without food; consistent association with food is necessary
- to be taken about the same time each day
- dose to be adjusted based on blood concentrations and tolerability (see treatment schedule and clinical information)

Note: missed doses should not be replaced; if a dose is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Continue safe handling precautions until 7 days after completion of drug(s)

Discharge information

Mitotane tablets

- Mitotane tablets with written instructions on how to take them.

Steroid tablets

- Steroid tables if prescribed with written instructions on how to take them.

Antiemetics

- Antiemetics as prescribed.

Patient information

- Ensure patient receives patient information sheet.

Administration cycle 7 and further cycles

eviQ provides safe and effective instructions on how to administer cancer treatments. However, eviQ does not provide every treatment delivery option, and is unable to provide a comprehensive list of cancer treatment agents and their required IV line giving set/filter. There may be alternative methods of treatment administration, and alternative supportive treatments that are also appropriate. Please refer to the individual product information monographs via the TGA website for further information.

Day 1 to 28

This is a continuous oral treatment

Safe handling and waste management

Safe administration

General patient assessment prior to each treatment.

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

Pre treatment medication

Chemotherapy - Time out

Mitotane

- administer orally in divided doses as prescribed on **days 1 to 28**
- to be swallowed whole with a glass of water; do not break, crush or chew
- may be taken with or without food; consistent association with food is necessary
- to be taken about the same time each day
- dose to be adjusted based on blood concentrations and tolerability (see treatment schedule and clinical information)

Note: missed doses should not be replaced; if a dose is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Continue safe handling precautions until 7 days after completion of drug(s)

Discharge information

Mitotane tablets

- Mitotane tablets with written instructions on how to take them.

Steroid tablets

- Steroid tables if prescribed with written instructions on how to take them.

Patient information

- Ensure patient receives patient information sheet.

Side effects

The side effects listed below are not a complete list of all possible side effects for this treatment. Side effects are categorised into the approximate onset of presentation and should only be used as a guide.

Immediate (onset hours to days)	
Extravasation, tissue or vein injury	The unintentional instillation or leakage of a drug or substance out of a blood vessel into surrounding tissue. This has the potential to cause damage to affected tissue. Read more about extravasation management
Hypersensitivity reaction	Anaphylaxis and infusion related reactions can occur with this treatment. Read more about hypersensitivity reaction
Flare reaction	Anthracycline flare reaction is caused by a localised allergic reaction. It is characterised by erythematous vein streaking, urticaria and pruritus which may occur during drug administration and is often associated with too rapid an infusion. Extravasation must be ruled out if flare occurs.
Nausea and vomiting	Read more about prevention of treatment induced nausea and vomiting
Red-orange discolouration of urine	Pink/red/orange discolouration of the urine. This can last for up to 48 hours after some anthracycline drugs.
Taste and smell alteration	Read more about taste and smell changes

Early (onset days to weeks)	
Neutropenia	Abnormally low levels of neutrophils in the blood. This increases the risk of infection. Any fever or suspicion of infection should be investigated immediately and managed aggressively. Read more about immediate management of neutropenic fever
Thrombocytopenia	A reduction in the normal levels of functional platelets, increasing the risk of abnormal bleeding. Read more about thrombocytopenia
Adrenal insufficiency	Adrenal insufficiency is a common side effect with mitotane. Gluco- and sometimes mineralocorticoid replacement is required. Optimal dose of steroid replacement should be determined by monitoring free cortisol and corticotropin levels.
Hypothyroidism	
Side effects of corticosteroids	Insomnia, oedema, increased risk of infection e.g. oral thrush, gastric irritation, worsening of peptic ulcer disease, increased blood sugar levels, loss of diabetic control, mood and behavioural changes - including anxiety, euphoria, depression, mood swings, increased appetite and weight gain, osteoporosis and fractures (long term use), bruising and skin fragility are associated with corticosteroid use.
Peripheral neuropathy	Typically symmetrical sensory neuropathy, affecting the fingers and toes, sometimes progressing to the hands and feet. It is associated with several classes of anti-cancer drugs. These include taxanes, platinum-based compounds, vinca alkaloids and some drugs used to treat multiple myeloma. Read more about peripheral neuropathy
Oral mucositis	Erythematous and ulcerative lesions of the gastrointestinal tract (GIT). It commonly develops following chemotherapy, radiation therapy to the head, neck or oesophagus, and high dose chemotherapy followed by a blood and marrow transplant (BMT). Read more about oral mucositis
Fatigue	Read more about fatigue
Neurological toxicities	Neurological events are a common side effect of mitotane especially when mitotane plasma levels are greater than 20 mg/L. Symptoms may include sedation, lethargy, somnolence, vertigo, depression, irritability, confusion and tremors. Close monitoring is recommended.
Diarrhoea	Read more about treatment induced diarrhoea
Anorexia	Loss of appetite accompanied by decreased food intake. Read more about anorexia
Ototoxicity	Tinnitus and hearing loss may occur due to damage in the inner ear. Tinnitus is usually reversible, while hearing loss is generally irreversible. Hearing loss is dose-related, cumulative and may be worse in those with pre-existing hearing problems. Read more about ototoxicity - tinnitus and hearing loss
Hypomagnesaemia, hypokalaemia, hypocalcaemia	Abnormally low levels of magnesium, potassium and calcium in the blood.
Nephrotoxicity	Renal dysfunction resulting from damage to the glomeruli, tubules or renal vasculature.
Photosensitivity	Increased sensitivity to ultraviolet (UV) light resulting in an exaggerated sunburn-like reaction accompanied by stinging sensations and urticaria.
Skin rash	Anti-cancer drugs can cause a number of changes in the skin with maculo-papular rash the most common type of drug-induced skin reaction. Read more about skin rash
Radiation recall	Erythematous or inflammatory skin reaction resembling severe sunburn at sites previously treated with radiation therapy can occur with certain anti-cancer drugs. Symptoms include vesiculation, desquamation and ulceration of the skin. Read more about radiation recall

Late (onset weeks to months)	
Anaemia	Abnormally low levels of red blood cells (RBCs) or haemoglobin in the blood. Read more about anaemia
Aldosterone deficiency	A reduction in aldosterone biosynthesis resulting in various clinical and laboratory test manifestations, such as hypotension, hyponatremia, hyperkalemia, and acidosis.
Ovarian macrocysts	Mitotane may cause ovarian macrocysts in premenopausal patients. Complications include adnexal torsion and hemorrhagic cyst rupture.
Alopecia	Hair loss may occur from all parts of the body. Patients can also experience mild to moderate discomfort of the hair follicles, and rarely pain as the hair is falling out. Read more about alopecia and scalp cooling
Hyperpigmentation	Darkening of an area of skin caused by the overproduction of melanin.
Nail changes	Hyperpigmentation, paronychia, onycholysis, splinter haemorrhage, pyogenic granuloma formation, subungal haematoma and subungal hyperkeratosis are some of the nail changes associated with anti-cancer drugs. Read more about nail toxicities

Delayed (onset months to years)	
Cardiotoxicity	Anthracyclines are the most frequently implicated anti-cancer drugs associated with cardiotoxicity, which typically manifests as a reduction in left ventricular ejection fraction (LVEF), cardiomyopathy, or symptomatic CHF. Anthracycline induced cardiotoxicity has been categorised into acute, early-onset chronic progressive and late-onset chronic progressive and is usually not reversible. The risk of clinical cardiotoxicity increases with a number of risk factors including higher total cumulative doses. Read more about cardiac toxicity associated with anthracyclines

Evidence

The evidence supporting this protocol is provided by a phase 3 multicentre international randomised trial (FIRM-ACT) involving 304 patients comparing etoposide-doxorubicin-cisplatin (EDP) plus mitotane with streptozocin plus mitotane in patients with unresectable locally advanced/metastatic adrenocortical carcinoma.[1]

Between June 2004 and October 2009, 304 patients were randomised in a 1:1 ratio. 151 patients were randomised to EDP (etoposide 100 mg/m^2 on days 2-4; doxorubicin 40 mg/m^2 on day 1 and cisplatin 40 mg/m^2 on days 3-4) every 4 weeks for 6 cycles. 153 patients were randomised to streptozotocin (1 g on days 1-5 in the first cycle and 2 g on day 1 in subsequent cycles) every 3 weeks for 6 cycles. All patients received mitotane continuously starting one week before initiation of chemotherapy with the goal of attaining a blood level of 14 to 20 mg/L. Crossover to alternative regimen was allowed after disease progression.[1]

The primary end point was overall survival (OS) and secondary end points were progression-free survival (PFS), tumour response and quality of life.[1]

Efficacy

At 6.5 years from study initiation, no significant difference in OS was demonstrated between EDP-mitotane (14.8 months, 95% CI 11.3-17.1) and streptozotocin-mitotane arms (12.0 months, 95% CI 10.3-13.6); HR = 0.79, 95% CI 0.61-1.02, p=0.07. Median PFS was 5.0 months (95% CI 3.5-6.9) in the EDP-mitotane group vs. 2.1 months (95% CI 2.04-2.33) in the streptozotocin-mitotane group (HR = 0.55, 95% CI 0.43-0.69, p<0.001). [1]

There was no significant difference in quality-of-life score change from baseline to evaluation according to EORTC QLQ-C30 questionnaire for both groups (-4.2 vs. 0, 95% CI -8.3–8.3, p=0.996).

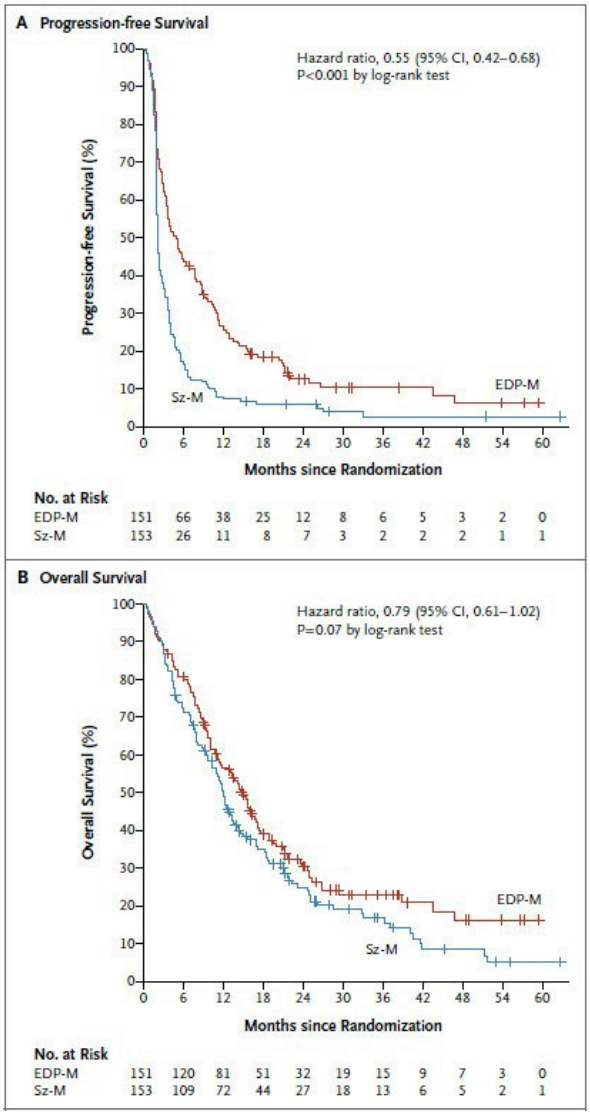
Overall response[1]

Table 2. Best Overall Response in the Intention-to-Treat Population.*

Variable	EDP-M (N=151)	Sz-M (N=153)	P Value
Type of response — no. (%)			
Complete response	2 (1.3)	1 (0.7)	
Disease-free by time of surgery†	4 (2.6)	2 (1.3)	
Partial response	29 (19.2)	11 (7.2)	
Stable disease‡	53 (35.1)	34 (22.2)	
Progressive disease	43 (28.5)	88 (57.5)	
Did not receive treatment	3 (2.0)	4 (2.6)	
Could not be evaluated for response	17 (11.3)	13 (8.5)	
Objective response§			
No. of patients	35	14	
% (95% CI)	23.2 (16.7–30.7)	9.2 (5.1–14.9)	<0.001
Disease control¶			
No. of patients	88	48	
% (95% CI)	58.3 (50.0–66.2)	31.4 (24.1–39.4)	<0.001

* Responses were rated according to the Response Evaluation Criteria in Solid Tumors (RECIST).
† Surgery was performed after a partial response to study treatment. These patients were not included in the "partial response" category.
‡ Stable disease was defined as no disease progression for at least 8 weeks and no objective response to treatment. Confirmatory scans were not required for this determination, according to the study protocol.
§ Objective response was defined as a complete or partial response.
¶ Disease control was defined as a complete response, a partial response, or stable disease.

Kaplan-Meier curves of progression-free (A) and overall (B) survival[1]



Toxicity

Rates of serious (0.092 vs. 0.099, p=0.64) and non-serious (0.54 vs. 0.49, p=0.17) adverse events per month did not differ significantly between EDP-mitotane and streptozotocin-mitotane treatment groups.[1]

Treatment-related adverse events[1]

Table 3. Serious Adverse Events during First-Line Therapy.

Event	EDP-M (N = 148)	Sz-M (N = 149)
	no. of patients (%)	
Any serious adverse event	86 (58.1)	62 (41.6)
Adrenal insufficiency	5 (3.4)	1 (0.7)
Bone marrow toxicity	17 (11.5)	3 (2.0)
Cardiovascular or thromboembolic event	10 (6.8)	0
Fatigue or general health deterioration	8 (5.4)	7 (4.7)
Gastrointestinal disorder	6 (4.1)	12 (8.1)
Impaired liver function	0	7 (4.7)
Impaired renal function	1 (0.7)	6 (4.0)
Infection	10 (6.8)	4 (2.7)
Neurologic toxicity	5 (3.4)	4 (2.7)
Respiratory disorder	9 (6.1)	5 (3.4)
Other	15 (10.1)	13 (8.7)

References

1 Fassnacht, M., M. Terzolo, B. Allolio, et al. 2012. "Combination chemotherapy in advanced adrenocortical carcinoma." N Engl J Med 366(23):2189-2197.

History

Version 1

Date	Summary of changes
15/09/2021	Protocol approved electronically by Medical Oncology Reference Committee and published on eviQ. Review in 1 year.
30/09/2022	Protocol reviewed electronically by Medical Oncology Reference Committee. no changes. Next review in 2 years.

First approved: 13 September 2021
Last reviewed: 30 September 2022
Review due: 31 December 2024

The currency of this information is guaranteed only up until the date of printing, for any updates please check:
https://www.eviq.org.au/p/3937
19 Jun 2023

Patient information - Adrenocortical carcinoma locally advanced or metastatic - Etoposide, doxorubicin, cisplatin and mitotane

Patient's name:

Your treatment

The treatment schedule below explains how the drugs for this treatment are given.

Mitotane pre-phase

This treatment is split into 3 parts. First you will start taking mitotane tablets 1 week before chemotherapy and continue until your doctor advises you to stop.

Day	Treatment	How it is given	How long it takes
1 to 7	**Mitotane** (MYE-toe-tane)	Take orally as prescribed by your doctor on days 1 to 7 with a glass of water, with or without food. Take about the same time everyday with consistent timing relative to food. Do not break, crush or chew tablets. If you forget to take a tablet or vomit a tablet, take your normal dose the next time it is due. Do not take an extra dose.	

Etoposide, doxorubicin, cisplatin and mitotane cycles 1 to 6

This is the second part. This treatment is repeated every 28 days. You will have 6 cycles of etoposide, doxorubicin, cisplatin and mitotane.

Day	Treatment	How it is given	How long it takes
1	**Doxorubicin** *(dox-oh-roo-bi-sin)*	By a drip into a vein	About 30 minutes to 1 hour
2	**Etoposide** (*e-TOE-poe-side*)	By a drip into a vein	About 1.5 hours
3 and 4	**Cisplatin** (*siss-PLAT-in*) **Etoposide**	By a drip into a vein	About 5 hours
1 to 28	**Mitotane** (MYE-toe-tane)	Take orally as prescribed by your doctor on days 1 to 28 with a glass of water, with or without food. Take about the same time everyday with consistent timing relative to food. Do not break, crush or chew tablets. If you forget to take a tablet or vomit a tablet, take your normal dose the next time it is due. Do not take an extra dose.	

Mitotane cycle 7 and further cycles

This is the third part. You will take mitotane continuously. Your doctor will advise of the number of treatments you will have.

Day	Treatment	How it is given	How long it takes

Mitotane cycle 7 and further cycles			
1 to 28	**Mitotane** (MYE-toe-tane)	Take orally as prescribed by your doctor on days 1 to 28 with a glass of water, with or without food. Take about the same time everyday with consistent timing relative to food. Do not break, crush or chew tablets. If you forget to take a tablet or vomit a tablet, take your normal dose the next time it is due. Do not take an extra dose.	

When to get help

Anticancer drugs (drugs used to treat cancer) can sometimes cause serious problems. It is important to get medical help immediately if you become unwell.

IMMEDIATELY go to your nearest hospital Emergency Department, or contact your doctor or nurse if you have any of the following at any time:	**Emergency contact details** Ask your doctor or nurse from your treating team who to contact if you have a problem
• a temperature of 38ºC or higher • chills, sweats, shivers or shakes • shortness of breath • feeling confused, weak, dizzy, or faint • uncontrolled nausea, vomiting or diarrhoea • pain, tingling or discomfort in your chest or arms • sudden pain in your stomach area • you become unwell.	Daytime: Night/weekend: Other instructions:

During your treatment immediately tell the doctor or nurse looking after you if you get any of the following problems:

- leaking from the area where the drugs are being given
- pain, stinging, swelling or redness in the area where the drugs are being given or at any injection sites
- a skin rash, itching, feeling short of breath, wheezing, fever, shivers, or feeling dizzy or unwell in any way (allergic reaction).

Other information about your treatment

Changes to your dose or treatment delays

Sometimes a treatment may be started at a lower dose or the dose needs to be changed during treatment. There may also be times when your treatment is delayed. This can happen if your doctor thinks you are likely to have severe side effects, if you get severe side effects, if your blood counts are affected and causing delays in treatment, or if you are finding it hard to cope with the treatment. This is called a dose reduction, dose change or treatment delay. Your doctor will explain if you need any changes or delays to your treatment and the reason why.

Blood tests and monitoring

Anti-cancer drugs can reduce the number of blood cells in your body. You will need to have regular blood tests to check that your blood cell count has returned to normal. If your blood count is low, your treatment may be delayed until it has returned to normal. Your doctor or nurse will tell you when to have these blood tests.

Other medications given during this treatment

- **Anti-sickness (anti-nausea) medication:** you may be given some anti-sickness medication. Make sure you take this medication as your doctor or nurse tells you, even if you don't feel sick. This can help to prevent the sickness starting.
- **Steroid supplements:** you may be given some steroid tablets to help reduce the risk of adrenal insufficiency. Your doctor or nurse will tell you how and when to take these tablets. You may need to monitor your blood sugar levels closely while you are taking steroid supplements. If you have diabetes, your diabetic medication may need to be adjusted. In cases of serious stress, infection or injuries, you might need higher doses of steroid tablets to prevent a serious adverse event called adrenal crisis. You must inform your medical team that you are taking mitotane tablets.

Side effects

Cancer treatments can cause damage to normal cells in your body, which can cause side effects. Everyone gets different side effects, and some people will have more problems than others.

The table below shows some of the side effects you may get with this treatment. You are unlikely to get all of those listed and you may also get some side effects that have not been listed.

Tell your doctor or nurse about any side effects that worry you. Follow the instructions below and those given to you by your doctor or nurse.

Immediate (onset hours to days)	
Pain or swelling at injection site (extravasation)	• This treatment can cause serious injury if it leaks from the area where it is going into the vein. • This can cause pain, stinging, swelling or redness at or near the site where the drug enters the vein. • If not treated correctly, you may get blistering and ulceration. • **Tell your doctor or nurse immediately if you get any of the symptoms listed above during or after treatment.**

Allergic reaction	• Allergic reactions are uncommon but can be life threatening.
	• **If you feel unwell during the infusion or shortly after it, or:**
	  ◦ **get a fever, shivers or shakes**
	  ◦ **feel dizzy, faint, confused or anxious**
	  ◦ **start wheezing or have difficulty breathing**
	  ◦ **have a rash, itch or redness of the face**
	
	<u>While you are in hospital:</u> Tell your doctor or nurse immediately.
	<u>After you leave:</u> Contact your doctor or nurse immediately, or go to the nearest hospital Emergency Department.

Redness and itching along vein	• You may get redness and itching along the vein where your chemotherapy is being infused. • This will usually go away within 30 minutes of stopping the injection. • **Tell your doctor or nurse as soon as possible if you get any of the symptoms listed above. Your nurse will check to make sure the drug has not leaked out of the vein.**
Nausea and vomiting	• You may feel sick (nausea) or be sick (vomit). • Take your anti-sickness medication as directed even if you don't feel sick. • Drink plenty of fluids (unless you are fluid restricted). • Eat small meals more frequently. • Try food that does not require much preparation. • Try bland foods like dry biscuits or toast. • Gentle exercise may help with nausea. • Ask your doctor or nurse for eviQ patient information - Nausea and vomiting during cancer treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have uncontrolled vomiting or feel dizzy or light-headed.**
Urine turning orange or red	• Your urine will turn an orange or red colour. • This is not harmful and should only last for up to 48 hours after treatment.
Taste and smell changes	• You may find that food loses its taste or tastes different. • These changes are likely to go away with time. • Do your mouth care regularly. • Chew on sugar-free gum or eat sugar-free mints. • Add flavour to your food with sauces and herbs. • Ask your doctor or nurse for eviQ patient information - Taste and smell changes during cancer treatment.

Early (onset days to weeks)

Infection risk (neutropenia)	• This treatment lowers the amount of white blood cells in your body. The type of white blood cells that help to fight infection are called neutrophils. Having low level of neutrophils is called neutropenia. If you have neutropenia, you are at greater risk of getting an infection. It also means that your body can't fight infections as well as usual. This is a serious side effect, and can be life threatening. • Wash your hands often. • Keep a thermometer at home and take your temperature regularly, and if you feel unwell. • Do your mouth care regularly. • Inspect your central line site (if you have one) daily for any redness, pus or swelling. • Limit contact with people who are sick. • Learn how to recognise the signs of infection. • Ask your doctor or nurse for eviQ patient information - Infection during cancer treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the following signs or symptoms:** ◦ **a temperature of 38°C or higher** ◦ **chills, shivers, sweats or shakes** ◦ **a sore throat or cough** ◦ **uncontrolled diarrhoea** ◦ **shortness of breath** ◦ **a fast heartbeat** ◦ **become unwell even without a temperature.**
Low platelets (thrombocytopenia)	• This treatment lowers the amount of platelets in your blood. Platelets help your blood to clot. When they are low, you are at an increased risk of bleeding and bruising. • Try not to bruise or cut yourself. • Avoid contact sport or vigorous exercise. • Clear your nose by blowing gently. • Avoid constipation. • Brush your teeth with a soft toothbrush. • Don't take aspirin, ibuprofen or other similar anti-inflammatory medications unless your doctor tells you to. • Tell your doctor or nurse if you have any bruising or bleeding. • **Tell your doctor or nurse immediately, or go to your nearest hospital Emergency Department if you have any uncontrolled bleeding.**
Adrenal insufficiency	• You may get: ◦ tiredness ◦ muscle pain or weakness ◦ decreased appetite ◦ weight changes ◦ pain in your stomach area ◦ nausea and vomiting • Take your steroid medication as directed by your doctor. • Do not drive or operate machinery if you are feeling dizzy or tired. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you feel confused, weak, dizzy, or faint, or get severe nausea and vomiting, diarrhoea or sudden pain in your stomach area.**

Slow thyroid gland (hypothyroidism)	• You may:
	  ◦ fatigue and low energy levels
	  ◦ depression
	  ◦ slow heart rate
	  ◦ unexplained weight gain
	  ◦ intolerance to cold temperatures
	  ◦ fatigued and aching muscles
	  ◦ dry, coarse skin
	  ◦ puffy face
	  ◦ hair loss
	  ◦ constipation
	  ◦ problems with concentration
	• You will have regular blood tests to check how well your thyroid is working
	• **Tell your doctor or nurse if you get any of the symptoms listed above.**

Side effects from steroid medication	• Steroid medication may cause:
	  ◦ mood swings and behaviour changes
	  ◦ an increased appetite
	  ◦ weight gain
	  ◦ swelling in your hands and feet
	  ◦ stomach upsets
	  ◦ trouble sleeping
	  ◦ fragile skin and bruising
	  ◦ an increase in your blood sugar level
	  ◦ weak and brittle bones (osteoporosis)
	• Take your steroid medication with food to reduce stomach upset
	• If you have diabetes, your blood sugar levels may be tested more often.
	• Tell your doctor or nurse if you get any of the symptoms listed above.

Nerve damage (peripheral neuropathy)	• You may notice a change in the sensations in your hands and feet, including:
	  ◦ tingling or pins and needles
	  ◦ numbness or loss of feeling
	  ◦ pain.
	• You may find it difficult to do everyday activities, such as doing up buttons or picking up small objects.
	• Test water temperature with your elbow when bathing to avoid burns.
	• Use rubber gloves, pot holders and oven mitts in the kitchen.
	• Wear rubber shoes or boots when working in the garden or garage.
	• Keep rooms well lit and uncluttered.
	• Ask your doctor or nurse for eviQ patient information – Nerve problems during cancer treatment.
	• Tell your doctor or nurse if you get any of the symptoms listed above.

Mouth pain and soreness (mucositis)	• You may have: ◦ bleeding gums ◦ mouth ulcers ◦ a white coating on your tongue ◦ pain in the mouth or throat ◦ difficulty eating or swallowing. • Avoid spicy, acidic or crunchy foods and very hot or cold food and drinks. • Try bland and soft foods. • Brush your teeth gently with a soft toothbrush after each meal and at bedtime. If you normally floss continue to do so. • Rinse your mouth after you eat and brush your teeth, using either: ◦ 1/4 teaspoon of salt in 1 cup of warm water, or ◦ 1/4 teaspoon of bicarbonate of soda in 1 cup of warm water • Ask your doctor or nurse for eviQ patient information - Mouth problems during cancer treatment. • **Tell your doctor or nurse if you get any of the symptoms listed above.**
Tiredness and lack of energy (fatigue)	• You may feel very tired, have no energy, sleep a lot, and not be able to do normal activities or things you enjoy. • Do not drive or operate machinery if you are feeling tired. • Nap for short periods (only 1 hour at a time) • Prioritise your tasks to ensure the best use of your energy. • Eat a well balanced diet and drink plenty of fluids (unless you are fluid restricted). • Try some gentle exercise daily. • Allow your friends and family to help. • **Tell your doctor or nurse if you get any of the symptoms listed above.**
Neurological events	• You may feel confused, agitated, dizzy, disorientated, have impaired speech or consciousness or have seizures. • This side effect can be very serious. You will be monitored very closely with regular assessment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the symptoms listed above.**
Diarrhoea	• You may get bowel motions (stools, poo) that are more frequent or more liquid. • You may also get bloating, cramping or pain. • Take your antidiarrhoeal medication as directed by your doctor. • Drink plenty of fluids (unless you are fluid restricted). • Eat and drink small amounts more often. • Avoid spicy foods, dairy products, high fibre foods, and coffee. • Ask your doctor or nurse for eviQ patient information - Diarrhoea during cancer treatment. • **Tell your doctor or nurse immediately, or go to your nearest hospital Emergency Department if your diarrhoea is not controlled, you have 4 or more loose bowel motions per day, and if you feel dizzy or light-headed.**
Appetite loss (anorexia)	• You may not feel like eating. • Try to avoid drinking fluids at meal times. • Try to eat small meals or snacks regularly throughout the day. • Try to eat food that is high in protein and calories. • If you are worried about how much food you can eat, or if you are losing weight, ask to speak to a dietitian.
Hearing changes (ototoxicity)	• You may get ringing in your ears or loss of hearing. • You may have your hearing tested before and during your treatment. • **Tell your doctor or nurse as soon as possible if you notice any changes to your hearing.**

Low blood magnesium, potassium and calcium levels (hypomagnesaemia, hypokalaemia, hypocalcaemia)	• This may be found from your routine blood tests and treated by your doctor. • If it is severe you may get: ◦ muscle cramps or twitches ◦ numbness or tingling in your fingers, toes or around your mouth ◦ constipation ◦ an irregular heartbeat ◦ sleepy, drowsy or confused • **Tell your doctor or nurse as soon as possible if you get any of the signs or symptoms listed above.**
Kidney damage	• This treatment can cause changes to how your kidneys work. • You will have blood tests to make sure your kidneys are working properly. • You may need to drink more fluids while you are having treatment. Your doctor or nurse will tell you if you need to do this. • **Tell your doctor or nurse as soon as possible if you notice that your urine changes colour or you don't need to empty your bladder as often.**
Skin that is more sensitive to the sun (photosensitivity)	• After being out in the sun you may develop a rash like a bad sunburn. • Your skin may become red, swollen and blistered. • Avoid direct sunlight. • Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and a sunscreen of SPF 50 or higher. • **Tell your doctor or nurse if you get any of the symptoms listed above.**
Skin rash	• You may get a red, bumpy rash and dry, itchy skin. • Moisturise your skin with a gentle non-perfumed moisturising cream like sorbolene or aqueous cream. • Do not scratch your skin. • Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and sunscreen of SPF 50 or higher. • **Talk to your doctor or nurse about other ways to manage your skin rash.**
Skin reaction in an area previously treated with radiation therapy (radiation recall)	• In the area that was treated with radiation therapy, your skin may become: ◦ dry, red and itchy ◦ tender and swollen • It may also: ◦ peel or blister ◦ form ulcers • This usually happens weeks or months after chemotherapy treatment. • Avoid wearing tight clothing. • Avoid direct sunlight and very hot or cold temperatures. • Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and a sunscreen of SPF 50 or higher. • Tell your doctor or nurse if you get any of the symptoms listed above.

Late (onset weeks to months)	
Low red blood cells (anaemia)	• You may feel dizzy, light-headed, tired and appear more pale than usual. • Tell your doctor or nurse if you have any of these signs or symptoms. You might need a blood transfusion. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have any chest pain, trouble breathing, or feel like your heart is racing.**
Aldosterone deficiency	• You may get: ◦ tiredness ◦ decreased appetite ◦ weight changes ◦ darkening of your skin ◦ a decrease in your blood sugar level ◦ a decrease in your blood pressure ◦ pain in your stomach area ◦ muscle or joint pain ◦ nausea, vomiting or diarrhoea ◦ irritability, depression or other behavioral symptoms • Do not drive or operate machinery if you are feeling dizzy or tired. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you feel confused, weak, dizzy, or faint, or get severe nausea and vomiting, diarrhoea or sudden pain in your stomach area.**
Gynecological problems	You may experience • unexpected vaginal bleeding • pain in your pelvic area **Tell your doctor or nurse immediately if you get any of the symptoms listed above.**
Hair loss (alopecia)	• Your hair may start to fall out from your head and body. • Hair loss usually starts 2 to 3 weeks after your first treatment. • You may become completely bald and your scalp might feel tender. • Use a gentle shampoo and a soft brush. • Take care with hair products like hairspray, hair dye, bleaches and perms. • Protect your scalp from the cold with a hat, scarf or wig. • Protect your scalp from the sun with a hat or sunscreen of SPF 50 or higher. • Moisturise your scalp to prevent itching. • Ask your doctor or nurse about the Look Good Feel Better program
Skin colour changes	• You may have darkening of your skin, especially in areas that are exposed to the sun. • You may also notice darkening of your tongue, gums and over your finger joints. • These skin changes may fade over time. • Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and a sunscreen of SPF 50 or higher.
Nail changes	• Your nails may: ◦ grow more slowly ◦ become darker ◦ develop ridges or white lines ◦ become brittle and flaky • In some cases, you may lose your nails completely. • Keep your nails clean and short. • Avoid things like biting your fingernails, getting a manicure, pedicure or false nails. • Wear gloves when you wash the dishes, work in the garden, or clean the house.

Delayed (onset months to years)	

Heart problems	• You may get:
	  ◦ chest pain or tightness
	  ◦ shortness of breath
	  ◦ swelling of your ankles
	  ◦ an abnormal heartbeat.
	• Heart problems can occur months to years after treatment.
	• Tell your doctor if you have a history of heart problems or high blood pressure.
	• Before or during treatment, you may be asked to have a test to see how well your heart is working.
	• **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the symptoms listed above.**

General advice for people having cancer treatment

Chemotherapy safety

- Learn how to keep you and your family safe while you are having anticancer drugs.
- See our patient information sheet - Chemotherapy safety at home.

Blood clot risk

- Cancer and anticancer drugs can increase the risk of a blood clot (thrombosis).
- Tell your doctor if you have a family history of blood clots.
- A blood clot can cause pain, redness, swelling in your arms or legs, shortness of breath or chest pain.
- If you have any of these symptoms go to your nearest hospital Emergency Department.

Medications and vaccinations

- Before you start treatment, tell your doctor about any medications you are taking, including vitamins or herbal supplements.
- Don’t stop or start any medications during treatment without talking to your doctor and pharmacist first.
- Paracetamol is safe to take if you have a headache or other mild aches and pains. It is recommended that you avoid taking aspirin, ibuprofen and other anti-inflammatory type medications for pain while you are having treatment. However, if these medications have been prescribed by your doctor, do not stop taking them without speaking with your doctor.
- Vaccinations such as flu and tetanus vaccines are safe to receive while having treatment. Do not have any live vaccines during your treatment or for 6 months after it finishes. If you are unsure, check with your doctor before you have any vaccinations.
- People you live with should be fully vaccinated, including having live vaccines according to the current vaccination schedule. Extra care needs to be taken with hand washing and careful disposal of soiled nappies for infants who have recently received the rotavirus vaccine.

Other medical and dental treatment

- If you go to hospital or any other medical appointment (including dental appointments), always tell the person treating you that you are receiving anticancer drugs.
- Before you have any dental treatment, talk to your doctor.

Diet

- While you are receiving this treatment it is important that you try to maintain a healthy diet.
- Grapefruit and grapefruit juice can interact with your medication and should be avoided while you are on this treatment.
- Speak to your doctor or nurse about whether drinking alcohol is safe with your treatment.
- If you have any concerns about recent weight loss or weight gain or questions about your diet, ask to speak to a dietitian.

Fertility

- Some cancer treatments can reduce your fertility. This can make it difficult or impossible to get pregnant or father a child.
- Talk to your doctor or nurse before you start any treatment. Depending on your situation there may be fertility sparing options available to you and/or your partner, discuss these with your doctor or nurse.

Pregnancy and breastfeeding

- Some cancer treatments can be dangerous to unborn babies. Talk to your doctor or nurse if you think there is any chance that

you could be pregnant.
- Do not try to get pregnant or father a child during this treatment. Contraception should be used during treatment and after stopping treatment. Ask your doctor or nurse about what type of contraception you should use.
- If you are planning pregnancy/fatherhood after completing this treatment, talk to your doctor. Some doctors advise waiting between 6 months and 2 years after treatment.
- Do not breastfeed if you are on this treatment, as anti-cancer medications can also pass into breast milk.

Sex life and sexuality

- The desire to have sex may decrease as a result of this treatment or its side effects.
- Your emotions and the way you feel about yourself may also be affected by this treatment.
- It may help to discuss your concerns with your partner and doctor or nurse.

Risk of developing a second cancer

- Some anticancer treatments can increase your chance of developing a second cancer, this is rare. Your doctor will discuss with you the specific risks of your treatment.

Quitting smoking

- It is never too late to quit smoking. Quitting smoking is one of the best things you can do to help your treatment work better.
- There are many effective tools to improve your chances of quitting.
- Talk to your treating team for more information and referral to a smoking cessation support service.

Staying active

- Research shows that exercise, no matter how small, has many benefits for people during and after cancer treatment.
- Talk to your doctor before starting an exercise program. Your doctor can advise whether you need a modified exercise program.

For more information about cancer treatment, side effects and side effect management see our Patient and carers section.

Where to get more information

Telephone support

- Call Cancer Council on 13 11 20 for cancer information and support

Rare cancer information

- Rare Cancers Australia – rarecancers.org.au

General cancer information and support

- Australian Rare Cancer (ARC) Portal – arcportal.org.au/
- Beyondblue – beyondblue.org.au
- Cancer Australia – canceraustralia.gov.au
- Cancer Council Australia – cancer.org.au
- Cancer Voices Australia – cancervoicesaustralia.org
- CanTeen – canteen.org.au
- Carers Australia – carersaustralia.com.au
- CHILL Cancer related hair loss - scalpcooling.org
- eviQ Cancer Treatments Online – eviQ.org.au
- LGBTQI+ People and Cancer - cancercouncil.com.au/cancer-information/lgbtqi
- Look Good Feel Better – lgfb.org.au
- Patient Information – patients.cancer.nsw.gov.au
- Radiation Oncology Targeting Cancer – targetingcancer.com.au
- Redkite – redkite.org.au
- Return Unwanted Medicines – returnmed.com.au
- Staying active during cancer treatment – patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/staying-active

Quit smoking information and support

Quitting smoking is helpful even after you have been diagnosed with cancer. The following resources provide useful information

and support to help you quit smoking. Talk to your treating team about any other questions you may have.

- Call Quitline on 13 QUIT (13 78 48)
- iCanQuit – iCanQuit.com.au
- Patient Information – patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/quitting-smoking
- Quitnow – quitnow.gov.au

Additional notes:

First approved: 13 September 2021
Last reviewed: 30 September 2022
Review due: 31 December 2024

The currency of this information is guaranteed only up until the date of printing, for any updates please check:
https://www.eviq.org.au/pi/3937
17 Jun 2023