Bladder/Urothelial small cell cARBOplatin and etoposide

ID: 1021 v.6 **Endorsed** Essential Medicine List

⚠ ADDIKD Carboplatin dosing:

For dosing carboplatin, ADDIKD recommends that:

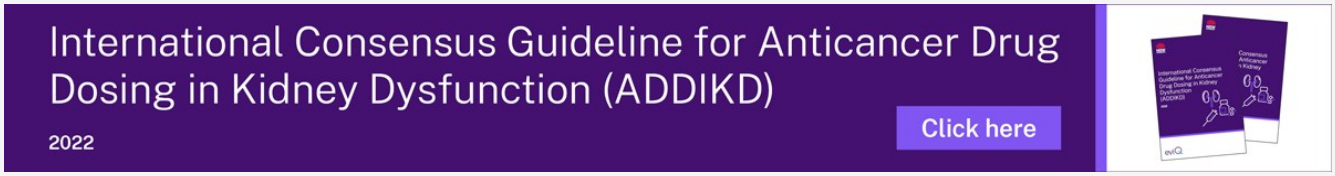
- Directly measured glomerular filtration rate (mGFR) is the preferred kidney function value in the Calvert formula, especially where estimated kidney function may be unreliable for accurate therapeutic dosing.
- Where mGFR is unavailable, eGFR adjusted to an individual's body surface area (BSA-adjusted eGFR) is a suitable alternative for use in the Calvert formula.
- Kidney function should not be capped at 125 mL/min for use in the Calvert formula.
- Recalculation of carboplatin doses at each cycle is unnecessary, except when baseline kidney function (e.g., eGFR) alters by > 20% or when there is a change in the clinical status of the patient.

For further information refer the eviQ Factsheet around carboplatin dosing and the carboplatin drug monograph within the ADDIKD guideline. To assist with calculations, use the eviQ Estimated Glomerular Filtration Rate (eGFR) and carboplatin dose calculators.

This protocol is based on limited evidence; refer to the evidence section of this protocol for more information.

Check for clinical trials in this patient group. Link to Australian Clinical Trials website

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.



Related pages:

- Bladder/Urothelial small cell ciSplatin and etoposide

Treatment schedule - Overview

Cycle 1 to 4

Drug	Dose	Route	Day
cARBOplatin	5 AUC *	IV infusion	1
Etoposide **	100 mg/m^2	IV infusion	1 to 3

*if estimated GFR is greater than 125 mL/min (i.e. 5 AUC dose greater than 750 mg), obtaining direct measurement rather than an estimated renal function and/or dose capping is strongly recommended

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

Frequency: 21 days

Cycles: 4 to 6 unless disease progression or unacceptable toxicity

Drug status: All drugs in this protocol are on the PBS general schedule

Cost: ~ $420 per cycle

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.***

Cycle 1 to 4

Day 1		
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	8 mg (PO)	60 minutes before chemotherapy
cARBOplatin	5 AUC (IV infusion)	in 500 mL glucose 5% over 30 to 60 minutes (Note: If estimated GFR is greater than 125 mL/min (i.e. 5 AUC dose greater than 750 mg), obtaining direct measurement rather than an estimated renal function and/or dose capping is strongly recommended)
Etoposide	100 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 30 to 60 minutes
Day 2 and 3		
Etoposide	100 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 30 to 60 minutes
Dexamethasone	8 mg (PO)	ONCE a day (or in divided doses) with or after food. Note: dexamethasone doses on day 2 and 3 may not be required and may be reduced or omitted at the clinicians discretion *

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

* Link to ID 7 Prevention of antineoplastic induced nausea and vomiting

Frequency: 21 days

Cycles: 4 to 6 unless disease progression or unacceptable toxicity

Indications and patient population

- Small cell bladder cancer

Clinical information

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. High risk with carboplatin. Hypersensitivity risk increases with number of cycles of carboplatin.

Emetogenicity MODERATE	Suggested default antiemetics have been added to the treatment schedule, and may be substituted to reflect institutional policy. Carboplatin AUC ≥ 4 is classified by MASCC/ESMO Antiemetic Guidelines 2016 and ASCO Antiemetic Guidelines 2017 as having moderate emetogenicity. However, a NK1 receptor antagonist and a $5HT_3$ receptor antagonist in combination with dexamethasone are available on the PBS for primary prophylaxis of carboplatin induced nausea and vomiting. 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
Etoposide conversion factor	Note: Etopophos (etoposide phosphate) 113.6 mg is equivalent to etoposide 100 mg. Doses in this protocol are expressed as etoposide.
Blood tests	FBC, EUC, LFT's (consider calcium and magnesium levels) at baseline, and prior to each cycle. Recalculate carboplatin dose if significant change in weight and/or creatinine.
Hepatitis B screening and prophylaxis	Routine screening for HBsAg and anti-HBc is recommended prior to initiation of treatment. Prophylaxis should be determined according to individual institutional policy. 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).

For dosing carboplatin, ADDIKD recommends that:

- Directly measured glomerular filtration rate (mGFR) is the preferred kidney function value in the Calvert formula, especially where estimated kidney function may be unreliable for accurate therapeutic dosing.
- Where mGFR is unavailable, eGFR adjusted to an individual's body surface area (BSA-adjusted eGFR) is a suitable alternative for use in the Calvert formula.
- Kidney function should not be capped at 125 mL/min for use in the Calvert formula.
- Recalculation of carboplatin doses at each cycle is unnecessary, except when baseline kidney function (e.g., eGFR) alters by > 20% or when there is a change in the clinical status of the patient.

*For further information refer the **eviQ Factsheet** around carboplatin dosing and the carboplatin drug monograph within the ADDIKD guideline. To assist with calculations, use the eviQ **Estimated Glomerular Filtration Rate (eGFR)** and **carboplatin** dose calculators.*

Note: All dose reductions are calculated as a percentage of the starting dose

Haematological toxicity	
ANC x 10^9/L (pre-treatment blood test)	
0.5 to less than 1.0	Delay treatment until recovery
less than 0.5	Delay treatment until recovery and reduce carboplatin and etoposide by 25% for subsequent cycles
Febrile neutropenia	Delay treatment until recovery and reduce carboplatin and etoposide 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.
50 to less than 75	Delay treatment until recovery
less than 50	Delay treatment until recovery and reduce carboplatin and etoposide by 25% for subsequent cycles

Renal impairment	
Creatinine clearance (mL/min)	
30 to 50	Reduce etoposide by 25% and recalculate carboplatin dose using Calvert formula
less than 30	Reduce etoposide by 50% and recalculate carboplatin dose using Calvert formula based on measured glomerular filtration rate (GFR) or consider omitting carboplatin

Hepatic impairment	
Hepatic dysfunction	
Mild	Reduce etoposide by 25%
Moderate	Reduce etoposide by 50%
Severe	Omit etoposide

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 carboplatin and etoposide by 25% 3rd occurrence: Reduce carboplatin and etoposide by 50% 4th occurrence: Omit carboplatin 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 carboplatin and etoposide by 50% 2nd occurrence: Omit carboplatin 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*

Carboplatin		
	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
Paclitaxel	Administration schedule may influence the development of myelosuppression	Minimise toxicity by administering paclitaxel first in regimens using the combination

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

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

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: 2.5 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.

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Verify dexamethasone taken or administer as prescribed.

Prime IV line(s).

Insert IV cannula or access TIVAD or CVAD.

Chemotherapy - Time out

Carboplatin

Administer carboplatin (irritant):

- via IV infusion over 30 to 60 minutes
- observe for hypersensitivity reactions
- flush with ~100 mL of sodium chloride 0.9%
- hypersensitivity risk increases with number of cycles administered.

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.

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.

Remove IV cannula and/or deaccess TIVAD or CVAD.

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

Day 2 and 3

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 antiemetics 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.

Remove IV cannula and/or deaccess TIVAD or CVAD.

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

Discharge information

Antiemetics

- Antiemetics as prescribed.

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)	
Hypersensitivity reaction	Anaphylaxis and infusion related reactions can occur with this treatment. Read more about hypersensitivity reaction
Nausea and vomiting	Read more about prevention of treatment induced nausea and vomiting
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
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
Anorexia	Loss of appetite accompanied by decreased food intake. Read more about anorexia
Diarrhoea	Read more about treatment induced diarrhoea

Late (onset weeks to months)	
Anaemia	Abnormally low levels of red blood cells (RBCs) or haemoglobin in the blood. Read more about anaemia
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

Evidence

A search of the literature did not find strong evidence to support the use of carboplatin or any regime in the neoadjuvant treatment of small cell bladder cancer. There is consensus from the various literature that neoadjuvant chemotherapy, if tolerated by the patient should provide the best outcome. The expert reference panel supported publication of the protocol on the basis of the information summarised below, the committee was most strongly influenced by Siefeker- Radkte et al[1], Bex et al[2] and Meijer et al[3].

This protocol has been used extensively in the treatment of small cell lung cancer.

Source	Study & Year Published	Supports Use	Is the dose and regimen consistent with the protocol?	Comments
Phase II trials	Siefker-Radtke et al 2009[1]	**Yes**	No	cisplatin 20mg/m^2 etoposide 80mg/m^2 d 1-5; alternating with ifosfamide, doxorubicin
Case Studies	-	**N/A**	-	-
Observational studies	Meijer et al 2013[3]	**Yes**	No	cisplatin 75mg/m^2
	Lynch et al 2013[4]	**Yes**	n/a	various regimens used
	Bex et al 2005[2]	**Yes**	No	cisplatin 75mg/m^2
	Siefker-Radtke et al 2004[5]	**Yes**	n/a	various regimens used
	Lohrisch et al 1999[6]	**Yes**	n/a	various regimens used
	Choong et al 2005[7]	**Yes**	n/a	various regimens used
	Mukesh et al 2008[8]	**Yes**	n/a	various regimens used
	Quek et al 2005[9]	**Yes**	No	cisplatin/etoposide/doxorubicin

Source	Study & Year Published	Supports Use	Is the dose and regimen consistent with the protocol?	Comments
	Asmis et al 2004[10]	**Yes**	n/a	either carboplatin/etoposide or EP doses not specified
Guidelines	**Date published/revised**	**Supports Use**	**Is the dose and regimen consistent with the protocol?**	**Comments**
NCCN	v.1 2012	**Yes**	no doses	refers to small cell lung cancer
BCCA	April 2013	**Yes**	Yes	
CCO	-	**N/A**	-	

Efficacy

Author/Year	No. of patients	Treatment	Overall survival	Response Rate	Cancer specific free survival	5 y sur
Meijer 2013[3]	27	MVAC, IEP, EP, Cyclophosphamide/doxorubicin/etoposide, or carboplatin/etoposide followed by EBRT	24 months (5 year OS 22.2%)	-	complete responders- 52 months; incomplete responders- 22 months	45
Lynch 2013[4]	48 (36 pt with <pT2N0M0)	IA/EP (54%), EP (15%), MVAC (10%) followed by surgery, RT or chemoradiation	187 months (95% CI 160 to infinity)	-	-	
Siefker-Radtke 2009 (prospective)[1]	18	IA/EP plus cystectomy	58 months (CI 58 months to not achieved)	78%	-	
Siefker-Radtke 2004 (retrospective)[5]	46	Upfront cystectomy -v- preoperative chemotherapy including EP, IA, methotrexate/cisplatin	36-v-78% (cystectomy alone -v- neoadjuvant chemotherapy)	-	-	
Bex 2005[2]	17	TUR+platinum-based chemotherapy and local RT (56-70Gy).	12 months (range 4 months to 84 months)	-	-	
Lohrisch 1999[6]	10	EP followed by local RT	2 year 70%	-	-	4
Choong 2005[7]	3	1 patient had neoadjuvant, 2 adjuvant chemotherapy (not specified- most likely EP)	2 patients alive at the end of the study. OS of other not known	-	-	
Mukesh 2008[8]	6/11 had chemotherapy for limited disease	3 carboplatin/etoposide pre cystectomy and RT (1 pt died after chemotherapy), 2 CAV, 1 ACE	33 months (range 6-60 months). 3 alive at time of article publication	-	-	

Author/Year	No. of patients	Treatment	Overall survival	Response Rate	Cancer specific free survival	s
Quek 2005[9]	20/25 small cell bladder	14 chemotherapy (13 adjuvant 1 preoperative). cisplatin/etoposide/doxorubicin	30% - 2 years 10% - 5 years	-	-	
Asmis 2004[10]	8/12 limited bladder cancer	1 neoadjuvant cisplatin etoposide, rest sequential chemotherapy and radiation therapy with either carboplatin/etoposide or EP	19.8 months, 5 alive at 31.2 months	-	-	

This table had been expanded from Macedo et al 2011[11]

IA= ifosfamide & doxorubicin; EP= etoposide & cisplatin; MVAC= methotrexate, vinblastine, doxorubicin & cisplatin; IEP= ifosfamide, etoposide & cisplatin; CAV= cyclophosphamide, doxorubicin & vincristine; ACE= doxorubicin, cyclophosphamide & etoposide

Toxicity

Based on the meta-analysis of the cisplatin-based regimens compared with carboplatin-based regimens in small cell lung cancer, statistically significantly more haematological toxicities (anaemia, thrombocytopenia, leucopenia) were observed in patients treated with carboplatin. Other toxicities (nausea, neurotoxicity, nephrotoxicity) were significantly more common in patients treated with cisplatin.[12]

Table 3. Toxicity

Toxicity	Patients With Toxicity Information	Any Grade						Severe Toxicity (grade ≥ 3)					
		Cisplatin (%)	Carboplatin (%)	Exact OR	95% CI	P*	P† for Homogeneity	Cisplatin (%)	Carboplatin (%)	Exact OR	95% CI	P*	P† for Homogeneity
Leucopenia	655	74	77	1.22	0.81 to 1.88	.357	< .001	34	34	0.96	0.67 to 1.37	.863	< .001
Neutropenia	458	86	90	1.53	0.81 to 2.92	.177	.397	64	73	1.74	1.07 to 2.83	.021	.999
Anemia	512	84	89	1.72	0.99 to 3.03	.049	.046	16	25	1.73	1.12 to 2.89	.011	< .001
Platelets	512	39	71	3.36	2.83 to 6.34	< .001	< .001	14	42	3.78	2.86 to 7.19	< .001	< .001
Nausea/vomiting	655	72	63	0.66	0.47 to 0.93	.013	.012	6	3	0.49	0.21 to 1.11	.066	.999
Stomatitis	655	25	21	0.78	0.52 to 1.17	.239	.065	1	< 1	0.24	0.01 to 3.32	.320	.999
Diarrhea	458	19	22	1.23	0.76 to 2.00	.415	.999	2	2	0.99	0.18 to 5.40	.999	.999
Constipation	239	39	51	1.58	0.92 to 2.73	.091	.999	3	5	1.51	0.35 to 7.48	.749	.999
Neurotoxicity	416	19	7	0.29	0.14 to 0.58	< .001	.243	1	< 1	0.35	0.01 to 7.27	.569	.999
Renal toxicity	415	25	10	0.34	0.19 to 0.61	< .001	.787	1.5	5	0.28	0.01 to 3.78	.351	.540
Toxic deaths	655	—	—	—		—	—	1.9	1.5	0.80	0.19 to 3.18	.769	.101

Abbreviation: OR, odds ratio.
*Exact text stratified by trial.
†Exact test for homogeneity of odds ratios.

References

1. Siefker-Radtke, A. O., A. M. Kamat, H. B. Grossman, et al. 2009. "Phase II clinical trial of neoadjuvant alternating doublet chemotherapy with ifosfamide/doxorubicin and etoposide/cisplatin in small-cell urothelial cancer." J Clin Oncol 27(16):2592-2597.

2. Bex, A., J. A. Nieuwenhuijzen, M. Kerst, et al. 2005. "Small cell carcinoma of bladder: a single-center prospective study of 25 cases treated in analogy to small cell lung cancer." Urology 65(2):295-299.

3. Meijer, R. P., W. Meinhardt, H. G. van der Poel, et al. 2013. "Local control rate and prognosis after sequential chemoradiation for small cell carcinoma of the bladder." Int J Urol 20(8):778-784.

4. Lynch, S. P., Y. Shen, A. Kamat, et al. 2013. "Neoadjuvant chemotherapy in small cell urothelial cancer improves pathologic downstaging and long-term outcomes: results from a retrospective study at the MD Anderson Cancer Center." Eur Urol 64(2):307-313.

5. Siefker-Radtke, A. O., C. P. Dinney, N. A. Abrahams, et al. 2004. "Evidence supporting preoperative chemotherapy for small

cell carcinoma of the bladder: a retrospective review of the M. D. Anderson cancer experience." J Urol 172(2):481-484.

6 Lohrisch, C., N. Murray, T. Pickles, et al. 1999. "Small cell carcinoma of the bladder: long term outcome with integrated chemoradiation." Cancer 86(11):2346-2352.

7 Choong, N. W., J. F. Quevedo and J. S. Kaur. 2005. "Small cell carcinoma of the urinary bladder. The Mayo Clinic experience." Cancer 103(6):1172-1178.

8 Mukesh, M., N. Cook, A. E. Hollingdale, et al. 2009. "Small cell carcinoma of the urinary bladder: a 15-year retrospective review of treatment and survival in the Anglian Cancer Network." BJU Int 103(6):747-752.

9 Quek, M. L., P. W. Nichols, J. Yamzon, et al. 2005. "Radical cystectomy for primary neuroendocrine tumors of the bladder: the university of southern california experience." J Urol 174(1):93-96.

10 Asmis, T. R., M. N. Reaume, S. Dahrouge, et al. 2006. "Genitourinary small cell carcinoma: a retrospective review of treatment and survival patterns at The Ottawa Hospital Regional Cancer Center." BJU Int 97(4):711-715.

11 Macedo, L. T., J. Ribeiro, G. Curigliano, et al. 2011. "Multidisciplinary approach in the treatment of patients with small cell bladder carcinoma." Eur J Surg Oncol 37(7):558-562.

12 Rossi, A., M. Di Maio, P. Chiodini, et al. 2012. "Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data." J Clin Oncol 30(14):1692-1698.

History

Version 6

Date	Summary of changes
10/09/2020	Patient information title updated- 'small cell' added. Version number changed to V.6.

Version 5

Date	Summary of changes
04/05/2020	Treatment schedule cycle title changed to 'cycle 1 to 4'. Patient information updated to include 'You will have 4 to 6 cycles'. Day 1 approximate treatment time changed to 2.5 hours. Version number changed to V.5.
30/06/2020	Protocol reviewed electronically by Medical Oncology Reference Committee. No changes. Review 5 years.

Version 4

Date	Summary of changes
27/03/2015	New protocol discussed at Medical Oncology Reference Committee meeting.
11/05/2015	Approved and published on eviQ.
31/03/2017	Protocol discussed and decided to have a 5 year review period. Next due for review in 2020.
31/05/2017	Transferred to new eviQ website. Version number changed to V.2. Antiemetic change: A NK1 receptor antagonist and a $5HT_3$ receptor antagonist in combination with dexamethasone has been added as available on the PBS for primary prophylaxis of carboplatin induced nausea and vomiting.
10/05/2018	Haematological dose modifications updated as per consensus of the expert clinician group. Version number changed to V.3.
17/01/2019	Carboplatin AUC ≥ 4 changed from highly to moderately emetogenic as per MASCC/ESMO and ASCO guidelines and medical oncology reference committee consensus. Dexamethasone day 4 dose removed. NK1 receptor antagonist unchanged. Treatment detail and clinical information updated to reflect the change. Version number changed to V.4

First approved: 11 May 2015
Last reviewed: 30 June 2020
Review due: 30 June 2025

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/1021
17 Jun 2023

Patient information - Bladder/urinary tract small cell cancer - Carboplatin and etoposide

Patient's name:

Your treatment

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

Carboplatin and etoposide

This treatment cycle is repeated every 21 days. You will have 4 to 6 cycles. Your doctor will advise you of the number of treatments you will have.

Day	Treatment	How it is given	How long it takes
1	**Carboplatin** (*carb-o-PLAT-in*) **Etoposide** (*e-TOE-poe-side*)	By a drip into a vein	About 2.5 hours
2 and 3	**Etoposide**	By a drip into a vein	About 1.5 hours

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 38°C or higher • chills, sweats, shivers or shakes • shortness of breath • uncontrolled vomiting or diarrhoea • pain, tingling or discomfort in your chest or arms • 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.

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)	

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.

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.**
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.**
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.**
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.
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.**

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.**
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

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

Bladder and urinary tract cancer information

- Australian Government Bladder and Bowel – bladderbowel.gov.au
- Australian Government Department of Health & Ageing Stoma appliance scheme – health.gov.au/internet/main/publishing.nsf/Content/Stoma+Appliance+Scheme-1
- BEAT Bladder Cancer Australia Inc. – beatbladdercanceraustralia.org.au/
- Continence Foundation of Australia – continence.org.au
- National Continence Program – health.gov.au/initiatives-and-programs/national-continence-program-ncp
- National Public Toilet map – toiletmap.gov.au
- Recovering after Pelvic Radiation Therapy: A guide for women – Recovering after Pelvic Radiation Therapy: A guide for women

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: 11 May 2015
Last reviewed: 30 June 2020
Review due: 30 June 2025

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/1021
17 Jun 2023