CARBOplatin[i] (AUC 5) and 5-Fluorouracil 1000mg/m^2/day Therapy – 28 day cycle

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
Adjuvant chemotherapy following chemoradiation treatment in patients with locally advanced stage III or IV nasopharyngeal carcinoma where CISplatin is contraindicated or not tolerated	C11	00552a	Hospital

**If the reimbursement status is not defined [ii], the indication has yet to be assessed through the formal HSE reimbursement process.*

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

CARBOplatin is administered on Day 1 and 5-Fluorouracil is administered on days 1-4 of a 28 day cycle for up to 3 cycles until disease progression or unacceptable toxicity develops.

Adjuvant treatment should begin 4 weeks after completion of **NCCP Regimen 00417: CARBOplatin (AUC 2) Weekly with Radiotherapy (RT)**

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	CARBOplatin	AUC 5	IV infusion	500ml glucose 5% over 2 hours	1-3
2	1-4	[a]5-Flourouracil	1,000 mg/m^2/day	IV infusion	1000ml 0.9% NaCl over 22 hours	1-3
[a]Alternatively 5-Flourouracil may be administered at 2000mg/m^2 over 48 hours on day 1 and day 2 and then repeated on day 3 and day 4 for a total dose of 4000mg/m^2 over 96 hours						

CARBOplatin dose:

The dose in mg of CARBOplatin to be administered is calculated as follows:

(mg) = target AUC (mg/ml x min) x (GFR ml/min +25)

- **Measured GFR** (e.g. nuclear renogram) is preferred whenever feasible
- **Estimation of GFR (eGFR)** can be done by using the Wright formula or using the Cockroft and Gault formula to measure creatinine clearance.
- The GFR used to calculate the AUC dosing should not exceed 125ml/min.
- For obese and anorexic patients the formulae may not give accurate results and measured GFR is recommended. Where obesity or overweight is likely to lead to an overestimate of GFR and isotope GFR is not available the use of the adjusted ideal body weight for Cockroft and Gault may be considered (5).

WRIGHT FORMULA

There are two versions of the formula depending on how serum creatinine values are obtained, by the kinetic Jaffe method or the enzymatic method. The formula can be further adapted if covariant creatine kinase (CK) values are available (not shown).

1. *SCr measured using enzymatic assay.*

$$\text{GFR (ml/min)} = \frac{(6230 - 32.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.23 \times \text{Sex})}{\text{SCr (µmol/min)}}$$

2. *SCr measured using Jaffe assay*

$$\text{GFR (ml/min)} = \frac{(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \textit{Sex})}{\text{SCr (µmol/min)}}$$

Key: Sex = 1 if female, 0 if male; Age in years; BSA= DuBois BSA

COCKCROFT-GAULT FORMULA

$$\text{GFR (ml/min)} = \frac{S \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

S= 1.04 for females and 1.23 for males

ELIGIBILTY:

- Indications as above following recovery from **NCCP Regimen 00417: CARBOplatin (AUC 2) Weekly with Radiotherapy (RT)**

EXCLUSIONS:

- Hypersensitivity to *CARBOplatin, 5-Flourouracil or any of the excipients
  *If it is felt that the patient may have a major clinical benefit from carboplatin, it may in exceptional circumstances be feasible to rechallenge a patient with a prior mild hypersensitivity reaction e.g using a desensitisation protocol, but only with immunology advice, premedication as advised, and a desensitisation protocol under carefully controlled conditions with resuscitation facilities available and medical and/or ITU/ HDU supervision (6).
- Fluorouracil should not be given to patients who are known to be homozygotic for dihydropyrimidine dehydrogenase (DPD) or with known complete absence of DPD activity

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Audiology and creatinine clearance if clinically indicated

Regular tests:

- FBC, renal and liver profile prior to each cycle

Disease monitoring:
Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

Haematological:

Table 1: Dose modification for haematological toxicity

ANC (x10^9/L)		Platelets (x10^9/L)	Recommended Dose
≥1.0	and	≥100	100% dose
0.5-0.99	or	50-99	Delay treatment until recovery
<0.5	or	<50	Delay treatment until recovery and consider reducing CARBOplatin and fluorouracil by 25% for subsequent cycles
Febrile neutropenia			

Renal and Hepatic Impairment:

Table 2: Recommended dose modification in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment			
CARBOplatin	*See below	No dose modification required			
5-Fluorouracil	Consider dose reduction in severe renal impairment only	**Bilirubin**		**AST**	**Dose**
		<85		<180	100%
		>85	or	>180	Contra-indicated
		Clinical decision. Moderate hepatic impairment; reduce initial dose by 1/3. Severe hepatic impairment, reduce initial dose by 1/2.			

*Renal dysfunction and CARBOplatin:

- Patients with creatinine clearance values of < 60ml/min are at greater risk to develop myelosuppression.
- In case of GFR ≤ 20ml/min CARBOplatin should not be administered at all.
- If Cockroft & Gault or Wright formula are used, the dose should be adjusted per cycle based on a serum creatinine obtained within 48 hrs of drug administration.
- If isotope GFR is used, the dose should remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine is higher than this, consideration should be given to remeasuring the GFR or to recalculating using Cockroft &Gault or Wright formulae taking care this does result in a dose reduction

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: High **(Refer to local policy).**

PREMEDICATIONS: No specific recommendations

OTHER SUPPORTIVE CARE: No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

CARBOplatin

- **Hypersensitivity:** Reactions to CARBOplatin may develop in patients who have been previously exposed to platinum therapy. However allergic reactions have been observed upon initial exposure to CARBOplatin.
- **Neurotoxicity and ototoxicity**: Neurological evaluation and an assessment of hearing should be performed on a regular basis, especially in patients receiving high dose CARBOplatin. Neurotoxicity, such as parasthesia, decreased deep tendon reflexes, and ototoxicity are more likely seen in patients previously treated with cisplatin, other platinum treatments and other ototoxic agents. Frequency of neurologic toxicity is also increased in patients older than 65 years

5-Fluorouracil

- **Myocardial ischaemia and angina:** Cardiotoxicity is a serious complication during treatment with fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with fluorouracil, should be carefully monitored during therapy.
- **Dihydropyrimidine dehydrogenase (DPD) deficiency:** Rare, life-threatening toxicities such as stomatitis, mucositis, neutropenia, neurotoxicity and diarrhoea have been reported following administration of fluoropyrimidines (e.g. fluorouracil and capecitabine). Severe unexplained toxicities require investigation prior to continuing with treatment.

DRUG INTERACTIONS:

- Avoid concurrent use of CARBOplatin with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Marked elevations of prothrombin time and INR have been reported in patients stabilized on warfarin therapy following initiation of fluorouracil regimes.
- Concurrent administration of fluorouracil and phenytoin may result in increased serum levels of phenytoin
- Caution should be taken when using fluorouracil in conjunction with medications which may affect dihydropyrimidine dehydrogenase activity.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

CARBOplatin - L01XA02
5-flourouracil - L01BC02

REFERENCES:

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2. Langendijk, J. A., C. R. Leemans, J. Buter, et al. 2004. "The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: a meta-analysis of the published literature." J.Clin Oncol. 22(22):4604-461
3. Ouyang, P. Y., Xie, C. & Mao, Y. P. et al. 2013 "Significant efficacies of neoadjuvant and adjuvant chemotherapy for nasopharyngeal carcinoma by meta-analysis of published literature-based randomized, controlled trials." Ann Oncol 24(8):2136-46.
4. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2012; 30(13):1553-1561.
5. Ekhart C, Rodenhuis S et al. Carboplatin dosing in overweight and obese patients with normal renal function, does weight matter? Cancer Chemother Pharmacol 2009;64:115-122.
6. NCCN Guidelines Version 3.2017 Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer
7. CARBOplatin Summary of Product Characteristics available at https://www.medicines.org.uk/emc/product/3787/smpc Accessed January 2019
8. Fluorouracil 50mg/ml injection Summary of Product Characteristics available at https://www.medicines.org.uk/emc/product/3791/smpc Accessed January 2019

Version	Date	Amendment	Approved By
1	11/02/2019		Prof Maccon Keane
2	12/02/2020	Update of exclusions	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This indication is outside the licensed indications for CARBOplatin in Ireland. Patients should be informed of the unlicensed nature of this indication and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be aware of their responsibility in communicating any relevant information to the patient and also in ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.

[ii] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/