nab-PACLitaxel and Gemcitabine Therapy– 28 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
nab-PACLitaxel in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas.	C25	00256a	nab-PACLitaxel : ODMS (where Karnofsky Performance Score (KPS) = 70-80) Gemcitabine : Hospital

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.

nab-PACLitaxel is administered on days 1, 8 and 15 of each 28-day cycle until disease progression or unacceptable toxicity develops. Gemcitabine is administered immediately after completion of nab-PACLitaxel administration on Days 1, 8 and 15 of each 28-day cycle.

Facilities to treat anaphylaxis MUST be present when nab-PACLitaxel is administered

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1, 8 and 15	nab-PACLitaxel	125mg/m^2	IV infusion	over 30mins	Repeat every 28 days
2	1, 8 and 15	Gemcitabine	1000 mg/m^2	IV infusion	250ml 0.9% sodium chloride over 30mins	Repeat every 28 days
The use of medical devices containing silicone oil as a lubricant (i.e. syringes and IV bags) to reconstitute and administer nab-PACLitaxel may result in the formation of proteinaceous strands. Administer nab-PACLItaxel using an infusion set incorporating a 15 µm filter to avoid administration of these strands. Use of a 15 µm filter removes strands and does not change the physical or chemical properties of the reconstituted product. If strands are present and a filter is not available, the product must be discarded.						

ELIGIBILITY:

- Indications as above
- Histologic/Cytologic proof of pancreatic adenocarcinoma
- ECOG status 0-2
- Life expectancy > 3 months
- Adequate haematological, hepatic and renal function (ANC ≥ 1.5 x10^9/L, Hb ≥ 9g/dl and bilirubin levels ≤ ULN)

CAUTION:

Use with caution in patients with

- Biliary stents: increased risk of biliary sepsis
- CNS metastases-safety not established

EXCLUSIONS:

- Hypersensitivity to nab-PACLitaxel, albumin, gemcitabine or to any of the excipients
- Pregnancy
- Lactation
- Severe hepatic impairment
- Baseline Neutrophil Counts < 1.5 x 10^9/L
- Grade ≥ 2 sensory or motor neuropathy

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Glucose
- Assessment of cardiac function, e.g. ECHO/MUGA scan if significant cardiac history

Regular tests:

- FBC and renal profile prior to treatment
- Liver profile monthly
- Cardiac function if clinically indicated

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.

Table 1: Dose level reductions for patients with pancreatic adenocarcinoma

Dose Level	nab-PACLitaxel **Dose (mg/m²)**	**Gemcitabine Dose (mg/m²)**
Full Dose	125	1000
1st Dose Level Reduction	100 (20%)	800 (20%)
2nd Dose Level Reduction	75 (40%)	600 (40%)
If additional dose reduction required	Discontinue treatment	Discontinue treatment

Haematological:

Table 2: Dose modifications for neutropenia and/or thrombocytopenia at the start of a cycle or within a cycle for patients with pancreatic adenocarcinoma.

Cycle	ANC ($x10^9$/L)		Platelets ($x10^9$/L)	nab-PACLitaxel	Gemcitabine
Day 1	< 1.5	OR	<100	Delay doses until recovery	
Day 8	≥ 0.5 but < 1	OR	≥ 50 but < 75	Reduce doses by 1 dose level	
Day 8	< 0.5	OR	< 50	Withhold doses	
Day 15: If Day 8 doses were given without modifications:					
Day 15	≥ 0.5 but < 1	OR	≥ 50 but < 75	Treat with Day 8 dose level and follow with WBC Growth Factors **OR** Reduce doses by 1 dose level from Day 8 doses	
	< 0.5	OR	< 50	Withhold doses	
Day 15: If Day 8 doses were reduced:					
Day 15	≥ 1	AND	≥ 75	Return to the Day 1 dose levels and follow with WBC Growth Factors **OR** Treat with same doses as Day 8	
	≥ 0.5 but < 1	OR	≥ 50 but <75	Treat with Day 8 dose level and follow with WBC Growth Factors **OR** Reduce doses by 1 dose level from Day 8 doses	
	< 0.5	OR	<50	Withhold doses	
Day 15: If Day 8 doses were withheld:					
Day 15	≥ 1	AND	≥ 75	Return to Day 1 dose levels and follow with WBC Growth Factors **OR** Reduce doses by 1 dose level from Day 1 doses	
	≥ 0.5 but < 1	OR	≥ 50 but < 75	Reduce 1 dose level and follow with WBC Growth Factors **OR** Reduce doses by 2 dose levels from Day 1 doses	
	< 0.5	OR	<50	Withhold doses	

Renal and Hepatic Impairment:

Table 3: Dose modification of nab-PACLitaxel and gemcitabine in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
nab-PACLitaxel	**CrCl (ml/min)**	**Dose**	**Bilirubin**		**AST**	**Dose**
	≥30 to <90	No dose adjustment necessary	>1.5 x ULN	**and**	≤10 x ULN	Not recommended
	<30	Insufficient data available to make recommendation	>5 x ULN	**or**	>10 x ULN	Insufficient data to permit dosage recommendations
Gemcitabine	30-50	Reduce gemcitabine by 20%	If bilirubin > 27 micromol/L, initiate treatment with dose of 800 mg/m^2.			
	<30	Reduce gemcitabine by 40%				

Management of adverse events:

Table 4: Dose Modifications for Adverse Events

Adverse reactions	Recommended dose modification	
	nab-PACLitaxel Dose	**Gemcitabine Dose**
Grade ≥3 Febrile neutropenia	Withhold doses until fever resolves and ANC ≥ 1.5; resume at next lower dose level[a]	
Grade ≥3 Peripheral neuropathy	Withhold dose until improves to ≤ Grade 1; Resume at next lower dose level[a].	Treat with same dose.
Grade 2 or 3 Cutaneous toxicity	Reduce to next lower dose level[a]; discontinue treatment if adverse reaction persists.	
Grade 3 Mucositis or diarrhoea	Withhold doses until improves to ≤ Grade 1; resume at next lower dose level[a].	
Pneumonitis	Discontinue treatment	
Haemolytic Uremic Syndrome (HUS)	Discontinue treatment	

[a] See Table 1 for dose level reductions

SUPPORTIVE CARE:

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

PREMEDICATIONS: None usually required.

OTHER SUPPORTIVE CARE:

Myalgias and arthralgias may occur with PACLitaxel. Analgesic cover should be considered.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

nab-PACLitaxel is an albumin-bound nanoparticle formulation of PACLitaxel, which may have substantially different pharmacological properties compared to other formulations of PACLitaxel. It should not be substituted for or with other PACLitaxel formulations.

- **Hypersensitivity:** Rare occurrences of severe hypersensitivity reactions have been reported. If a hypersensitivity reaction occurs, the medicinal product should be discontinued immediately, symptomatic treatment should be initiated, and the patient should not be rechallenged with PACLitaxel.
- **Extravasation**: PACLitaxel causes pain and tissue necrosis if extravasated (**Refer to local policy**).
- **Neutropenia:** Bone marrow suppression (primarily neutropenia) occurs frequently with nab-PACLitaxel Neutropenia is dose-dependent and a dose-limiting toxicity. Frequent monitoring of blood cell counts should be performed during nab-PACLitaxel therapy. Patients should not be retreated with subsequent cycles of nab-PACLitaxel until neutrophils recover to >1.5 x 10^9/L and platelets recover to >100 x 10^9/L (see Table 2).
- **Peripheral neuropathy:** Sensory neuropathy occurs frequently with nab-PACLitaxel, although development of severe symptoms is less common. For combination use of nab-PACLitaxel and gemcitabine, if grade 3 or higher peripheral neuropathy develops, withhold nab-PACLitaxel; continue treatment with gemcitabine at the same dose. Resume nab-PACLitaxel at reduced dose when peripheral neuropathy improves to Grade 0 or 1 (see Table 4).
- **Hepatic Dysfunction:** Because the toxicity of PACLitaxel can be increased with hepatic impairment, administration of nab-PACLitaxel in patients with hepatic impairment should be performed with caution. Patients with hepatic impairment may be at increased risk of toxicity, particularly from myelosuppression, and such patients should be closely monitored for development of profound myelosuppression. nab-PACLitaxel is not recommended in patients that have total bilirubin > 5 x ULN or AST > 10 x ULN. In addition, nab-PACLitaxel is not recommended in patients with metastatic adenocarcinoma of the pancreas that have moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN and AST ≤ 10 x ULN)
- **Cardiotoxicity:** Rare reports of congestive heart failure and left ventricular dysfunction have been observed among individuals receiving nab-PACLitaxel. Most of the individuals were previously exposed to cardiotoxic medicinal products such as anthracyclines, or had underlying cardiac history.
- **Renal dysfunction:** Irreversible renal failure associated with haemolytic uremic syndrome (HUS) has occurred rarely in patients on gemcitabine therapy. Treatment is discontinued if HUS develops.
- **Pneumonitis:** Even though the incidence is low, patients should be closely monitored for signs and symptoms of pneumonitis. During the conduct of a trial in metastatic pancreatic cancer, a higher rate of pneumonitis events was observed in patients receiving nab-PACLitaxel in combination with gemcitabine. Treatment is discontinued if pneumonitis develops.

DRUG INTERACTIONS:

- Risk of drug interactions causing increased concentrations of paclitaxel with CYP3A inhibitors. Patients should also be counselled with regard to consumption of grapefruit juice.
- Risk of drug interactions causing decreased concentrations of PACLitaxel with CYP3A inducers.
    - CYP 2C8 inhibitors, e.g. PAZOPanib, lapatanib, gemfibrozil, montelukast, tretinoin, ethinyloestradiol, testosterone – increased toxicity possible with nab-PACLitaxel

- Close monitoring advised with the use of digoxin, antiplatelet agents and NSAIDs and vaccines
- Increased anti-coagulant risk with warfarin and gemcitabine. INR requires regular monitoring
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	15/02/2016		Dr Derek Power, Prof Maccon Keane
2	10/02/2018	Updated with new NCCP regimen template. Updated emetogenic status and dosing in renal and hepatic impairment.	Prof Maccon Keane
3	26/02/2020	Reviewed.	Prof Maccon Keane
4	24/02/2022	Brand name Abraxane® removed. ATC codes removed. Updated reference section.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.