Nintedanib Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
Treatment of adult patients with locally advanced, metastatic of stage IIIB or IV, or locally recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy	C34	00372a	Nintedanib-CDS DOCEtaxel – 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.

Nintedanib and DOCEtaxel Therapy

- Nintedanib 200mg is administered twice daily approximately 12 hours apart, on days 2 to 21 of a standard 21 day DOCEtaxel treatment cycle for up to six cycles.
- Nintedanib must not be taken on the same day of DOCEtaxel chemotherapy administration (= day 1)

Nintedanib Monotherapy

- Patients must receive at least 4 cycles of combination therapy with DOCEtaxel before continuing with nintedanib monotherapy.
- Patients may continue therapy with nindetanib after discontinuation of DOCEtaxel for as long as clinical benefit is observed or until unacceptable toxicity develops.
- Nintedanib 200mg is administered twice daily approximately 12 hours apart continuously based on a 28 day cycle

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	DOCEtaxel	75mg/m^2	IV infusion	[1]250ml 0.9% sodium chloride over 60min	Every 21 days for up to 6 cycles
2-21[2]	Nintedanib	200mg twice daily	PO with food at the same time each day[3, 4]	N/A	Every 21 days for up to 6 cycles
Primary prophylaxis with G-CSF should be considered to reduce the risk of neutropenic complications (See Adverse Effects/Regimen Specific Complications)					
[1]75-185mg dose use 250mL infusion bag. For doses > 185mg use 500mL infusion bag **Use non-PVC equipment.**					
[2]For patients continuing on nintedanib therapy cycle length is taken at 28 days and nintedanib is administered twice daily continuously.					
[3]Nintedanib capsules must be taken orally, preferably with food, swallowed whole with water, and must not be chewed or crushed.					
[4]If a dose of nintedanib is missed, administration should resume at the next scheduled time at the recommended dose. The individual daily doses of nintedanib should not be increased beyond the recommended dose to make up for missed doses. The recommended maximum daily dose of 400 mg should not be exceeded.					

ELIGIBILITY:

- Indications as above.
- ECOG status 0-1.
- Life expectancy > 3 months.

EXCLUSIONS:

- Hypersensitivity to nintedanib, peanut or soya, DOCEtaxel or any of the excipients
- More than one prior chemotherapy regimen for advanced and/or metastatic or recurrent NSCLC
- Severe liver impairment
- Baseline neutrophil count < 1.5 x 10^9 cells/L
- Pregnancy or breast feeding

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, liver and renal profile
- Blood pressure

Regular tests:

- FBC, liver and renal profile prior to each treatment cycle and as clinically indicated
- Blood pressure as clinically indicated

*See Adverse Effects/Regimen specific complications for guidelines regarding hepatic dysfunction

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
- Dosing interruption may be required for the management of adverse reactions relating to nintedanib and DOCEtaxel (see Table 4 and 5 below).
    - After recovery nintedanib may be resumed at a reduced dose.
    - Dose adjustments in 100mg steps per day based on individual safety and tolerability are recommended as described in Table 4 and 5.

Haematological:

Table 1: Modification of DOCEtaxel dosing based on haematological parameters

ANC (x10^9/L)	Recommended dose
≥ 1.5	75mg/m^2
0.5 to less than 1.5	Delay treatment until recovery
Febrile neutropenia or <0.5 for more than 1 week	Reduce dose from 75 to 60mg/m^2. Discontinue treatment if continues at lower dose.

Renal and Hepatic Impairment:

Table 2: Dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
DOCEtaxel	No dose reduction necessary		See Table 3 Below	
Nintedanib	**CrCl (mL/min)**	**Dose**	Mild (Child Pugh A)	100% Dose
	>30	100%	Moderate (Child Pugh B) or severe (Child Pugh C)	Not recommended
	<30	Has not been studied		

Table 3: Dose modification of DOCEtaxel in hepatic impairment

Alkaline Phosphatase		AST and/or ALT		Serum Bilirubin	Dose
> 2.5 ULN	and	> 1.5 ULN			75 mg/m^2
> 6 ULN	and /or	> 3.5 ULN (AST and ALT)	and	> ULN	Stop treatment unless strictly indicated and should be discussed with a Consultant.

Table 4: Recommended dose adjustments for nintedanib in case of AST and/or ALT and bilirubin elevations

AST		ALT		Bilirubin	ALKP	Recommended dose modification
>2.5 x ULN **OR** >5 x ULN	and/or and/or	>2.5 x ULN >5 x ULN	and	≥1.5 x ULN		After treatment interruption and recovery of transaminase values to ≤2.5 x ULN in conjunction with bilirubin to normal, dose reduction from 200mg BD to 150mg BD. If a second dose reduction is considered necessary from 150mg BD to 100mg BD.
>3 x ULN	and/or	>3 x ULN	and	≥2 x ULN and	< 2 x ULN	Unless there is an alternative cause established nintedanib should be permanently discontinued.

AST: Aspartate aminotransferase; ALT :Alanine aminotransferase;
ALKP:Alkaline phosphatise; ULN: Upper Limit normal

Management of adverse events

Table 5: Dose modification schedule based on adverse events

Adverse reactions	Recommended dose modification
Nintedanib	
Diarrhoea Grade ≥ 2 for > 7 consecutive days despite anti-diarrhoeal treatment **OR** Grade ≥ 3 despite anti-diarrhoeal treatment	After treatment interruption and recovery to grade 1 or baseline, dose reduction from 200mg BD to 150mg BD and if a second dose reduction is considered necessary from 150mg BD to 100mg BD.
Vomiting Grade ≥ 2 **AND/OR** **Nausea ≥ grade 3 despite anti-emetic treatment**	
Other non-haematological or haematological adverse reactions ≥Grade 3	
DOCEtaxel	
Grade 3 skin reaction	Decrease dose to 60mg/m^2 If the patient continues to experience these reactions at 60 mg/m^2, the treatment should be discontinued
Grade >2 peripheral neuropathy	
Grade 3 or 4 stomatitis	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

DOCEtaxel: Low **(Refer to local policy)**

Nintedanib: Minimal to Low **(Refer to local policy)**

PREMEDICATIONS:

- Dexamethasone 8 mg PO twice daily for 3 days, starting one day prior to each DOCEtaxel administration unless contraindicated. Patient must receive minimum of 3 doses pre-treatment.
- ***Consideration may be given, at the discretion of the prescribing consultant, to the use of a single dose of dexamethasone 20mg IV immediately before chemotherapy where patients have missed taking the oral premedication dexamethasone as recommended by the manufacturer (3,4).***

OTHER SUPPORTIVE CARE:

- Contraception in males and females
- Nintedanib may cause foetal harm in humans. Women of childbearing potential being treated with nindetanib should be advised to avoid becoming pregnant while receiving this treatment and to use adequate contraception during and at least 3 months after the last dose of nindetanib. The efficacy of oral hormonal contraceptives may be compromised by vomiting and/or diarrhoea or other conditions where the absorption may be affected. Women taking oral hormonal contraceptives experiencing these conditions should be advised to use an alternative highly effective contraceptive measure such as a barrier method.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

Nintedanib

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately. Frequent monitoring of complete blood counts should be performed at the beginning of each treatment cycle and around the nadir for patients receiving treatment with nintedanib in combination with DOCEtaxel, and as clinically indicated after the administration of the last combination cycle.
- **Gastrointestinal effects:** Diarrhoea, nausea, and vomiting may occur. Diarrhoea is generally of mild to moderate intensity and occurred within the first 3 months of treatment. Treat with appropriate supportive care (e.g, adequate hydration, antidiarrhoeals, antiemetics); dose reduction and/or treatment interruption may be required. If gastrointestinal effects do not resolve, discontinue treatment. In addition, nintedanib may increase the risk of gastrointestinal perforation; only use in patients at risk of perforation if the benefit outweighs the risk. Nintedanib therapy should only be initiated at least 4 weeks after major surgery. Therapy with nintedanib should be permanently discontinued in patients who develop gastrointestinal perforation.
- **Bleeding:** May increase the risk of bleeding. Non-serious and serious bleeding events, some of which were fatal, have been reported in the post-marketing period, including patients with or without anticoagulant therapy or other drugs that could cause bleeding. In case of bleeding, dose adjustment, interruption or discontinuation should be considered based on clinical judgement.

- **Thromboembolism:** Patients treated with nintedanib have an increased risk of venous thromboembolism including deep vein thrombosis. Patients should be closely monitored for thromboembolic events. Nintedanib should be discontinued in patients with life-threatening venous thromboembolic reactions. An increased frequency of arterial thromboembolic events was observed in patients with idiopathic pulmonary fibrosis (IPF) when treated with nintedanib monotherapy. Patients with a recent history of myocardial infarction or stroke were excluded from LUME–Lung 1 study. Use caution when treating patients with a higher cardiovascular risk including known coronary artery disease. Treatment interruption should be considered in patients who develop signs or symptoms of acute myocardial ischaemia.
- **Aneurysms and artery dissections**: The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating nintedanib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm
- **Hypertension:** Administration of nintedanib may increase blood pressure. Systemic blood pressure should be measured periodically and as clinically indicated.
- **Wound healing complication:** Based on the mechanism of action nintedanib may impair wound healing. No increased frequency of impaired wound healing was observed in the LUME-Lung 1 trial. No dedicated studies investigating the effect of nintedanib on wound healing were performed. Treatment with nintedanib should therefore only be initiated or - in case of perioperative interruption - resumed based on clinical judgement of adequate wound healing.
- **Effect on QT interval:** No QT prolongation was observed for nintedanib in the clinical trial program. As several other tyrosine kinase inhibitors are known to exert an effect on QT, caution should be exercised when administering nintedanib in patients who may develop QTc prolongation.
- **Allergic reaction:** Dietary soya-products are known to cause allergic reactions including severe anaphylaxis in persons with soya allergy. Patients with known allergy to peanut protein carry an enhanced risk for severe reactions to soya preparations.
- S**pecial populations**: Nintedanib exposure increased linearly with patient age, was inversely correlated to weight, and was generally higher in patients of Asian race. This may result in a higher risk of developing liver enzyme elevations. Close monitoring is recommended in patients with several of these risk factors.

DOCEtaxel

- **Neutropenia:** Most frequent adverse reaction. Fever or other evidence of infection must be assessed promptly and treated appropriately. Frequent blood count monitoring should be conducted in all patients treated with DOCEtaxel. DOCEtaxel should be administered when the neutrophil count is > $1.5x10^9$cells/L.
- **Neutropenic Enterocolitis:** A number of cases of neutropenic enterocolitis have been reported in patients treated with DOCEtaxel in France (5). This is a known and rare side effect of DOCEtaxel which may affect up to one in 1,000 people)
- **Hypersensitivity Reactions:** Patients should be observed closely for hypersensitivity reactions especially during the first and second infusions of DOCEtaxel. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of DOCEtaxel, thus facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localized cutaneous reactions do not require interruption of therapy. However, severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of DOCEtaxel and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with DOCEtaxel.

- **Fluid Retention:** Dexamethasone premedication must be given to reduce the incidence and severity of fluid retention with DOCEtaxel. It can also reduce the severity of the hypersensitivity reaction.
- **Extravasation:** DOCEtaxel causes pain and tissue necrosis if extravasated. (Refer to local extravasation guidelines).
- **Hepatic Dysfunction:** DOCEtaxel undergoes hepatic metabolism. Hepatic dysfunction (particularly elevated AST) may lead to increased toxicity and usually requires a dose reduction.

DRUG INTERACTIONS:

- Nintedanib is a substrate of P-gp. If co-administered with nintedanib, potent P-gp inhibitors (e.g. ketoconazole or erythromycin) may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of nintedanib. Management of side effects may require interruption, dose reduction, or discontinuation of therapy with nindetanib.
- Potent P-gp inducers (e.g. rifampicin, carbamazepine, phenytoin, and St. John's Wort) may decrease exposure to nintedanib. Co-administration with nintedanib should be carefully considered.
- The likelihood of drug-drug interactions with nintedanib based on CYP metabolism is considered to be low.
- Risk of drug interactions causing increased concentrations of DOCEtaxel with CYP3A inhibitors. Patients should also be counselled with regard to consumption of grapefruit juice.
- Risk of drug interactions causing decreased concentrations of DOCEtaxel with CYP3A inducers.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	01/02/2017		Dr Linda Coate
2	05/02/2019	Updated with new NCCP template. Standardisation of treatment table Updated Adverse events/Regimen Specific Complications with respect to bleeding as per SmPC	Prof Maccon Keane
3	24/09/2019	Updated baseline and regular testing to include blood pressure Updated Adverse effects/regimen specific complications with respect to aneurysms,artery dissections and hypertension as per SmPC update	Prof Maccon Keane
4	31/03/2021	Reviewed. Updated emetogenic potential. Updated supportive care with respect to contraception as per SmPC.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.