

Lung Pathway Group – Nintedanib (Vargatef) in advanced Non-Small Cell Lung Cancer (NSCLC)

Indication: In combination with docetaxel in locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology that has progressed after first-line chemotherapy. Nintedanib is then continued as monotherapy.

Patients much receive at least 4 cycles of combination therapy with docetaxel before continuing with nintedanib monotherapy.

Eligible for patients able to tolerate and comply with oral dosage forms.

Regimen details: In combination with docetaxel:

Nintedanib	200mg	PO	Twice daily	Days 2-21
Docetaxel	60-75mg/m ²	IV	Day 1	

Refer to separate docetaxel protocol for details of dosing and monitoring.

Followed by nintedanib monotherapy after completing at least 4 cycles in combination with docetaxel:

Nintedanib	200mg	PO	Twice daily continuously
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Administration: Nintedanib is available as 100mg and 150mg soft capsules. Swallow whole with water, 12 hours apart. Take with food.

Frequency: Combination Therapy:
Every 21 days for 4-6 cycles in combination with docetaxel. Not to be taken on the day of docetaxel administration

Monotherapy:

Dosing is continuous, until disease progression or unacceptable toxicity. For purposes of resupply one cycle is 28 days.

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Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla and Rebecca Johl 21/01/2016
Prepared by: Melanie Dalby	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jatinder Harchowal 21/01/2016
Second check by: Lisa Yuen 09/12/15	Date prepared: December 2015 Review Date: December 2017
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Pre-medication:	Not routinely required.																	
Anti- emetics:	Minimal emetogenicity Follow local anti-emetic policy																	
Supportive medication:	Diarrhoea can be managed with loperamide. Mouthcare as per local policy. Various approaches may be considered to deal with skin reactions including rash, acne type reactions, erythema/ pruritus, dryness or blistering (topical emollients, cleansers or possibly anti-infective creams). Urea containing creams may be beneficial to treat dry skin. Support use of non-deodorant, non-fragrance products. Consider products with anti-itch additions in pruritus, and exfoliating products in hyperkeratosis. Anti-dandruff shampoo may help in management of itchy scalp. Analgesia may help but a 1-2 week dose interruption may be necessary for painful and severe symptoms. Rashes usually resolve rapidly upon cessation of treatment.																	
Extravasation:	Not applicable																	
Regular investigations:	<p>Prior to Cycle 1:</p> <table border="0"> <tr> <td>FBC</td> <td>Day 1 (within 14 days)</td> </tr> <tr> <td>LFTs (incl. AST, ALT, ALP)</td> <td>Day 1 (within 14 days)</td> </tr> <tr> <td>U&Es</td> <td>Day 1 (within 14 days)</td> </tr> <tr> <td>Imaging</td> <td>Baseline</td> </tr> </table> <p>Prior to Day 1 (all cycles):</p> <table border="0"> <tr> <td>FBC</td> <td>Day 1 (within 72 hours)*</td> </tr> <tr> <td>LFTs (incl. AST, ALT, ALP)</td> <td>Day 1 (within 72 hours)*</td> </tr> <tr> <td>U&Es</td> <td>Day 1 (within 72 hours)*</td> </tr> <tr> <td>Imaging</td> <td>3 months</td> </tr> </table>		FBC	Day 1 (within 14 days)	LFTs (incl. AST, ALT, ALP)	Day 1 (within 14 days)	U&Es	Day 1 (within 14 days)	Imaging	Baseline	FBC	Day 1 (within 72 hours)*	LFTs (incl. AST, ALT, ALP)	Day 1 (within 72 hours)*	U&Es	Day 1 (within 72 hours)*	Imaging	3 months
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Refer to separate protocol for further investigations that may be required for docetaxel.

*Note: When nintedanib is given as monotherapy bloods should be taken monthly. Resupply of nintedanib monotherapy does not require blood monitoring parameters to be available on the day. The medical team will set up treatment pathways to ensure continuous trend monitoring and timely clinical review when needed.

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Toxicities: Diarrhoea, nausea, vomiting, fatigue, elevation of liver enzymes, increased risk of venous thromboembolism, mucositis, rash, increased risk of haemorrhage, increased risk of GI perforation.

DOSE MODIFICATIONS

Haematological Toxicity

Neutrophils		Platelets	Dose
≥ 1.0	&	≥ 50	Continue treatment
< 1.0	Or	< 50	After a treatment interruption and recovery to grade 1 or baseline, dose reduction from 200 mg twice daily to 150 mg twice daily and - if a 2 nd dose reduction is considered necessary - from 150 mg twice daily to 100 mg twice daily.

Non-haematological Toxicities

Renal Impairment

No dose adjustment is recommended for patients with mild (creatinine clearance 60 to 90 mL/min) and moderate renal impairment (CrCl 30 to 60 mL/min).

Studies have excluded patients with calculated CrCl <30ml/min. Discuss the management of the treatment for such patients with the consultant.

Hepatic Impairment

No adjustment of the starting dose is needed for patients with mild hepatic impairment based on clinical data (Child Pugh A). The safety, efficacy, and pharmacokinetics of nintedanib have not been investigated in patients with moderate (Child Pugh B) OR SEVERE (Child Pugh C) hepatic impairment. Therefore, treatment of these patients with nintedanib is not recommended.

AST / ALT		Bilirubin		ALP	Dose
≤ 2.5 x ULN	&	< 1.5 x ULN			Continue treatment
> 2.5 x ULN	&	≥ 1.5 x ULN			Withhold treatment until recovery of transaminase-values to ≤ 2.5 x ULN in conjunction with bilirubin to normal, dose reduce from 200 mg twice daily to 150 mg twice daily and - if a 2 nd dose reduction is required - from 150 mg twice daily to 100 mg twice daily
> 5x ULN					
> 3 x ULN	&	≥ 2 x ULN	&	< 2 x ULN	Unless there is an alternative cause established,

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				nintedanib should be permanently discontinued
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Dose modifications for other toxicities as appropriate

For the management of adverse reactions treatment with nintedanib should be temporarily interrupted until the specific adverse reaction has resolved to levels that allow continuation of therapy. Nintedanib treatment may then be resumed at a reduced dose. Dose adjustments of 100mg per dose per day based on individual safety and tolerability are recommended. If the adverse reaction continues to persist then treatment with nintedanib should be permanently discontinued.

CTCAE Adverse reaction	Dose Modification Algorithms
Diarrhoea \geq grade 2 for more than 7 consecutive days despite anti-diarrhoeal treatment OR Diarrhoea \geq grade 3 despite anti-diarrhoeal treatment	After treatment interruption and recovery to grade 1 or baseline, dose reduction from 200 mg twice daily to 150 mg twice daily and - if a 2 nd dose reduction is considered necessary - from 150 mg twice daily to 100 mg twice daily.
Vomiting \geq grade 2 AND/OR Nausea \geq grade 3 despite anti-emetic treatment	

Venous 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.

Impaired wound healing

Based on the mechanism of action nintedanib may impair wound healing. Treatment with nintedanib should therefore only be initiated or - in case of perioperative interruption - resumed based on clinical judgement of adequate wound healing.

Gastrointestinal Perforation

Based on the mechanism of action patients treated with nintedanib may have an increased risk of gastrointestinal perforations. Particular caution should be exercised when treating patients with

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previous abdominal surgery or a recent history of a hollow organ perforation. Nintedanib should therefore only be initiated at least 4 weeks after major surgery. Therapy with nintedanib should be permanently discontinued in patients who develop gastrointestinal perforation.

Allergic Reaction

Capsules contain Soya. There is a risk of severe anaphylaxis if given to patients with a soya and/or peanut allergy.

Location of regimen: Outpatient setting.
delivery

Comments: To be supplied to the patient for oral self-administration.
Ensure that the patient has an information pack and the treatment plan.
Always supply the brand Vargatef.

Drug interactions: Nintedanib is a substrate of P-glycoprotein (P-gp). Co-administration with the potent P-gp inhibitors ketoconazole and erythromycin may increase exposure to nintedanib. Patients should be monitored for tolerability and side effects managed by treatment interruption, dose reduction or discontinuation of nintedanib. Potent P-gp inducers (e.g. rifampicin, carbamazepine, phenytoin and St. John’s Wort) may decrease exposure to nintedanib. Co-administration should be carefully considered.

References: Boehringer Ingelheim. (2014) Summary of product characteristics: Vargatef (nintedanib). Available at www.medicines.org.uk [accessed 14/10/2015]
NICE Technology Appraisal Guidance TA347 (2015)
Reck. M, et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small cell lung cancer (LUME-LUNG 1): a phase 3, double-blind, randomised controlled trial. (2014) The Lancet. Volume 15, No. 2, p143–155.
NHS England Specialised Services Circular 1537

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