# RED GUIDANCE FOR NINTEDANIB FOR PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS AND PROGRESSIVE FIBROSING – INTERSTITIAL LUNG DISEASES

## 1. Background

Nintedanib is a tyrosine kinase inhibitor used for the treatment of both Idiopathic Pulmonary Fibrosis (IPF) and Progressive fibrosing interstitial lung diseases (PF-ILD). Nintedanib has been shown to slow the rate of progression in IPF and PF-ILD.

It is recommended that nintedanib is added to patients' records as per local SOPs.

## 2. Indication

All patients who are to be considered for nintedanib must be discussed at the Hull ILD MDT. It can then recommend as an option for treating idiopathic pulmonary fibrosis in line with the criteria as set out in NICE Technology Appraisal 379. e.g. if:

- The patient has a forced vital capacity (FVC) between 50% and 80% predicted, and
- The manufacturer provides nintedanib with the discount agreed in the patient access scheme.

Or, PF –ILD in line with the criteria as set out in NICE Technology Appraisal 747. Eg if:

a) Fibrotic CT pattern of ILD extent ≥ 10%
b) Case must be discussed at regional ILD service ILD MDT and have a PF-ILD diagnosis

There must be evidence of disease progression at any point in the preceding 24 months despite standard therapy (where appropriate) e.g. a decent trial of immunosuppression therapy.

Disease progression is outlined in INBUILD study as:

1. Relative FVC decline of ≥ 10% of predicted
2. Relative FVC decline of 5% - <10% of predicted and worsening respiratory symptoms
3. Relative FVC decline of 5% - <10% of predicted and increased extent of fibrosis on HRCT
4. Worsening respiratory symptoms and increased extent of fibrosis on HRCT

## 3. Dose/Duration

The recommended dose of nintedanib is 150 mg twice daily (administered approximately 12 hours apart). Patient who cannot tolerate this dose may be reduced to 100 mg twice daily. If a patient does not tolerate 100 mg twice daily, treatment with nintedanib should be discontinued. If a dose is missed, administration should resume at the next scheduled time at the recommended dose. If a dose is missed the patient should not take an additional dose. The recommended maximum daily dose of 300 mg should not be exceeded.

Dose adjustments

Dose adjustments may be required due to adverse reactions. Adjustments will usually be managed or discussed with the specialist centre and may involve dose reduction or temporary interruption until the adverse reaction has resolved. Treatment may be resumed at either 150mg or 100mg twice daily.

In case of interruptions due to aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations > 3x upper limit of normal , once transaminases have returned to baseline values, treatment with nintedanib may be reintroduced at a reduced dose (100 mg twice daily) which subsequently may be increased to the full dose (150 mg twice daily). Adjustment of the dose in patients with mild to moderate renal impairment is not required. The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (CrCL<30 ml/min) and it is a clinical decision whether or not to use the drug in this patient group. (Note: less than 1% of a single dose of nintedanib is excreted via the kidneys). Further information can be found in the Summary of Product Characteristics - Nintedanib

## 4. Contraindications

- Hypersensitivity to nintedanib or its excipients
- Hypersensitivity to peanut or soya
- Moderate to severe hepatic impairment (Child Pugh B or C)
- Myocardial infarction in previous 6 months
- Unstable angina in last month Increased bleeding risk e.g. haemorrhagic CNS event in last 12 months, haemoptysis, haematuria, gastrointestinal bleed, injury or surgery in last 3 months
- Thrombotic event in last 12 months or inherited predisposition to thrombosis
- Pregnancy
- Breastfeeding

Further information can be found in the Summary of Product Characteristics – Nintedanib

## 5. Adverse effects

Very common side effects (may affect more than 1 in 10 people):

- Diarrhoea (62.4% of patients but only 3.3% reported severe diarrhoea)
- Nausea
- Liver enzyme elevation (reversible on dose reduction/discontinuation) – see also individual liver function tests below
- Abdominal pain

Uncommon side effects (may affect up to 1 in 100 people):

- Hypertension
- Hyperbilirubinaemia
- Alkaline phosphatase (ALKP) increased

Further information can be found in the Summary of Product Characteristics - Nintedanib

| Adverse effects | Action for GP |
|---|---|
| Diarrhoea | Prescribe Loperamide |
| Nausea | Prescribe anti emetic |
| Liver enzyme elevation | Report to specialist centre |
| Abdominal pain | Report to specialist centre |

Diarrhoea, nausea, and vomiting are the most common adverse effects associated with nintedanib therapy. The GP or local hospital may recommend supportive treatment e.g., hydration, antidiarrheal agents, and/or antiemetic's to manage symptoms.

If patient has any manifestations of hepatotoxicity (e.g., jaundice, unusually dark or "tea-coloured" urine, right upper quadrant pain, bleeding or bruising more easily than normal, lethargy) discontinue nintedanib, perform liver function blood tests and contact specialist hospital.

**Monitoring of Hepatic Function (ALT/ AST/Alk Phos / Bilirubin):**

Initially at monthly intervals for at least 3 months by specialist hospital team and if stable every 3 months thereafter by local hospitals (NLAG/York) and relay results back to Hull. There is no responsibility for GPs to perform phlebotomy or monitor blood results).

- If the **AST or ALT is more than 3 times upper limit of normal (and less than 5 times ULN)** after starting nintedanib then:

  Contact the Hospital Specialists for advice

- If the **AST or ALT is less than or equal to 5 times ULN together with hyperbilirubinaemia and symptoms** then:

  Discontinue treatment and contact the specialist hospital who will manage.

- If the **AST or ALT is more than 5 times ULN** then:

  Discontinue treatment and contact the specialist hospital who will manage.

## 6. Drug interactions

Nintedanib is a substrate of P-glycoprotein (P-gp).

- Strong inhibitors of P-gp (e.g. ciclosporin, erythromycin, ketoconazole) may increase exposure to nintedanib with associated dose related side effects. Close monitoring is recommended.

- Strong inducers of P-gp (e.g. rifampicin, carbamazepine, phenytoin and St John's Wort) may decrease exposure to nintedanib. Avoid concomitant use wherever possible.

Not all inducers and inhibitors are mentioned by name. When in doubt, GPs are advised to seek the advice of the hospital pharmacist or medicines information service. Since the effect of nintedanib on the metabolism and efficacy of hormonal contraceptives has not been investigated, barrier methods should be applied as a second form of contraception, to avoid pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant while receiving nintedanib and for 3 months after stopping.

Nintedanib may increase the risk of bleeding - patients receiving full-dose anticoagulation therapy should be monitored closely for bleeding.

Cigarette smoking reduces exposure to nintedanib by approximately 21%. Dosage adjustments are not required in smokers however patients should be encouraged to stop smoking prior to initiation of nintedanib and to avoid smoking during therapy.

• Avoid concomitant use with: Strong inducers of P-gp which can decrease nintedanib exposure (list not exhaustive):

Primidone, rifampicin, carbamazepine, phenytoin, St John's Wort, fosphenytoin, phenobarbital

• Use with caution: Strong inhibitors of P-gp which can increase nintedanib exposure. Close monitoring is recommended (list not exhaustive):

Amiodorane, ketoconazole, azithromycin, opinavir, atazanavir, quinidine, boceprevir, ritonavir, ciclosporin, saquinavir, clarithromycin, telaprevir, danuravir, telithromycin, erythromycin, verapamil, itraconazole, voriconazole

Further information can be found in the Summary of Product Characteristics - Nintedanib.

| The following drugs are known or suspected interactions: | |
|---|---|
| Interacting Drug | Advice |
| Primidone | Avoid |
| Rifamicin | Avoid |
| Carbamazepine | Avoid |
| Phenytoin | Avoid |
| St. John's Wart | Avoid |
| Phenobarbitol | Avoid |
| Fosphenytoin | Avoid |

## 7. Pregnancy and Lactation

Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered to a pregnant woman. There are no data on the use of OFEV during pregnancy. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2% to 4% and miscarriage in clinically recognized pregnancies is 15% to 20%.

There is no information on the presence of nintedanib in human milk, the effects on the breast-fed infant or the effects on milk production. Nintedanib and/or its metabolites are present in the milk of lactating rats. Because of the potential for serious adverse reactions in nursing infants from OFEV, we advise women that breastfeeding is not recommended during treatment with OFEV.

## 8. Information for patient

The Patient has the following responsibilities whilst taking Nintedanib

- Attend appointments for the scheduled blood tests to be taken.

- Report to the specialist hospital specialist nurse if they do not have a clear understanding of their treatment.

- Patients must not exceed the recommended dose. - Patients must attend their scheduled clinic appointments.

- Must inform other clinical staff that they are receiving treatment and inform clinicians of existing or contemplated concomitant therapy, including prescription and over the counter drugs and dietary or herbal supplements.

- Report any adverse effects to the local or specialist hospital specialist nurse or doctor (in particular immediately reporting any manifestations of hepatotoxicity e.g., jaundice, unusually dark or “tea-coloured” urine, right upper quadrant pain, bleeding or bruising more easily than normal, lethargy).

- Report to the specialist hospital specialist nurse or doctor if they become pregnant

pil.7705.pdf (medicines.org.uk)

# RED GUIDANCE

Humber Area Prescribing Committee

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| Document and version control | **This information is not inclusive of all prescribing information and potential adverse effects. Please refer to the SPC (data sheet) or BNF for further prescribing information.** | | |
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| 1 | Mark Major | Specialist Nurse (HUTH) | Adapted from HERPC guidance |