Information Guideline for Local Hospitals and GPs. Nintedanib for idiopathic pulmonary fibrosis

1. Introduction

Nintedanib is a tyrosine kinase inhibitor used for the treatment of Idiopathic Pulmonary Fibrosis.

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.

Treatment should be discontinued if there is evidence of disease progression, defined as a decline in predicted FVC of 10% or more within any 12 month period or if the patient is unable to tolerate nintedanib due to side effects.

Nintedanib is a Red drug and will be prescribed and supplied by the specialist team.

2. Abbreviations

ILD – Interstitial Lung Disease
FVC – forced vital capacity
IPF – Idiopathic Pulmonary Fibrosis
MDT – multi-disciplinary team
GP – General Practitioner
CNS – central nervous system
ULN – upper limit of normal

3. Dose and Administration

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. 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

5. Cautions

- Mild hepatic impairment
- Concomitant anticoagulation

6. 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

7. 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.

8. Monitoring Standards & Actions to take in the event of abnormal test results/symptoms

Local hospital (NLAG/York) and GPs to inform specialist hospital as per contacts below if patient is suffering from any side effects and that the local hospital/GP is unable to manage those side effects.

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.

9. Responsibilities

a. Specialist Hospital:

- Diagnosis of ILD in line with NICE TAG282, Clinical Guideline 163 and Specialist Service Specifications.
- Perform baseline blood tests.
- See patient monthly for the first 6 months, perform blood tests and issue Nintedanib
- Send a letter to the local hospital or GP to communicate diagnosis and treatment.
- Educate the patient on how to take the medicine and what to do if they feel unwell.
- Prescribe Nintedanib and arrange for delivery of the medicine via home delivery company.
- Review the patient in clinic every 12 months after patient returns to local hospital for review and via telephone calls as required
- Provide the patient with contact information should they require help or advice.
- Inform the GP and local hospital after each clinic attendance and if there is any change to treatment or monitoring.
- Inform GP of patients who do not attend clinic appointments.
- To provide any advice to the patient/carer/GP and local hospital when requested.
- Report adverse effects to the Yellow Card Scheme
- To continue blood monitoring if local hospital/GP can't provide monitoring (not signed up to enhanced contract).

b. Local Hospitals and GPs (if signed up to enhanced contract):

- Ensure Nintedanib is added to the patient's SCR in the hospital only/3rd party prescriber section (CCG medicines management team can provide details of how to do this for both SystemOne & EMIS web- if this process is unfamiliar).

- Local hospital (NLAG/York) to review patient and take blood to monitor liver function at 3 monthly intervals as per Section 7 and relay results back to Hull. (No responsibility for GP to perform phlebotomy or review results)
- Inform the specialist hospital in writing if unable to comply with monitoring requirements.
- Ensure no interacting medication is prescribed without liaising with the specialist hospital team first.
- Report any adverse events to the specialist hospital as outlined in sections 6 & 10, where appropriate
- Request advice from the specialist hospital when necessary.
- To ensure drug interactions & potential adverse effects of nintedanib are considered during consultations

c. Patient or parent/carer:

- 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

10. Contact numbers for advice and support

Dr Simon Hart Secretary 01482 624067

Specialist Nurse Mark Major and Amanda Bell 01482 622409