Shared Care Guideline – GP monitoring bloods only (no prescribing required)

Nintedanib for idiopathic pulmonary fibrosis

Executive Summary

- Nintedanib is recommended as an option for treating idiopathic pulmonary fibrosis only if the person has a forced vital capacity (FVC) between 50% and 80% predicted
- It should be discontinued if there is evidence of disease progression (a decline in per cent predicted FVC of 10% or more within any 12-month period)
- Patients liver function should be monitored as below
- Patients should be educated on how to take nintedanib and potential side effects
- Nintedanib has a number of potential drug interactions that prescribers should be aware of.
- Hospital specialist teams will be responsible for nintedanib prescribing and supply.
- The responsibilities of the hospital specialist, GP and patient for this Shared Care Guideline can be found within this document in section 11.

Sharing of care depends on communication between the specialist, GP and the patient or their parent/carer. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. The doctor/healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use. Further information about the general responsibilities of the hospital specialist and GP can be found here

1. Scope

Prescribing and monitoring by hospital specialist consultants and monitoring by General Practitioners

2. Aim

To outline the details of prescription and the responsibilities for each person caring for the patient taking nintedanib.

3. 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 Cambridge ILD MDT. It is then recommended 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.

4. 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

5. 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 by 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

6. Adverse Effects

The summary of product characteristics lists the following adverse reactions for nintedanib as the most commonly reported (10% or higher): nausea, diarrhoea, abdominal pain and deranged liver function test results. Bleeding complications such as epistaxis and haemorrhage have also been reported. Nintedanib is in the black triangle scheme and all adverse drug reactions should be reported via the Yellow Card Scheme.

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
• Abdominal pain
• Liver enzyme elevation (reversible on dose reduction/discontinuation) – see also individual liver function tests below
Common side effects (may affect up to 1 in 10 people):
• Weight loss +/- decreased appetite
• Vomiting
• Epistaxis
• Increased liver transferases (ALT, AST, GGT)
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

7. Cautions

- Mild hepatic impairment
- Concomitant anticoagulation

8. 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

9. 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).**

amiodarone	ketoconazole
azithromycin	lopinavir
atazanavir	quinidine
boceprevir	ritonavir
ciclosporin	saquinavir
clarithromycin	telaprevir
darunavir	telithromycin
erythromycin	verapamil
itraconazole	voriconazole

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

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

- GP to inform Hospital Specialists as per contacts below if patient is suffering from any side effects.
- Diarrhoea, nausea, and vomiting are the most common adverse effects associated with nintedanib therapy. The GP or specialist may recommend supportive treatment e.g., hydration, antidiarrheal agents, and/or antiemetics to manage symptoms.
- If patient has any manifestations of hepatotoxicity (e.g., jaundice, unusually dark or "tea-colored" urine, right upper quadrant pain, bleeding or bruising more easily than normal,

lethargy) discontinue nintedanib, perform liver function blood tests and contact Hospital Specialists.

- **GP monitoring of Hepatic Function (ALT/ AST/Alk Phos / Bilirubin):**

  (At monthly intervals for 6 months and if stable every 3 months thereafter)

  - 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 Hospital Specialists who will manage.

  - If the **AST or ALT is more than 5 times ULN** then:
    - Discontinue treatment and contact the Hospital Specialists who will manage.

11. Shared Care Responsibilities

a. Hospital specialist:

- Diagnosis of ILD in line NICE TAG282, Clinical Guideline 163 and Specialist Service Specifications
- Perform baseline blood tests
- Send a letter to the GP requesting shared care for the patient.
- Educate the patient on how to take the medicine and what to do if they feel unwell.
- Prescribe Nintedanib
- Provide the patient with a blood monitoring booklet for recording results of liver function blood tests
- Arrange for delivery of the medicine
- Review the patient in clinic and via telephone calls
- Provide the patient with contact information should they require.
- Inform the GP after each clinic attendance 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 when requested.
- Report adverse effects to the Yellow Card Scheme

b. General Practitioner:

- Provide confirmation of whether agreed to participate in shared care within 14 days of receipt of the request for shared care.
- Take blood to monitor liver function at monthly intervals for 6 months and if stable every 3 months thereafter as per Section 10.
- Communicate results to the patients to be recorded in the 'Blood Monitoring Booklet'
- Ensure no interacting medication is prescribed without liaising with the specialist team first.
- Report any adverse events to the hospital specialist as outlined in sections 6 & 10, where appropriate
- Request advice from the hospital specialist when necessary.
- To ensure drug interactions & potential adverse effects of nintedanib are considered during consultations within primary care GP's should include details of nintedanib in the hospital only/3rd

party prescriber section of the repeat medication template on their GP clinical system. (CCG medicines management team can provide details of how to do this for both SystemOne & EMIS web- if this process is unfamiliar).

c. Patient or parent/carer:

- Hold responsibility for their 'Blood monitoring Booklet' – to record their blood test results and bring to each clinic appointment.
- Make appointments for the scheduled blood tests to be taken.
- Report to the hospital specialist or GP if they do not have a clear understanding of their treatment.
- Patients must not exceed the recommended dose.
- Patients must attend their scheduled clinic and blood test appointments (where relevant).
- 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 hospital specialist or GP (in particular immediately reporting any manifestations of hepatotoxicity e.g., jaundice, unusually dark or "tea-colored" urine, right upper quadrant pain, bleeding or bruising more easily than normal, lethargy).
- Report to the hospital specialist or GP if they become pregnant

12. Contact numbers for advice and support

Cambridge University Hospital Trust – Addenbrooke's Hospital		
Specialist	**Post**	**Telephone**
Professor Chilvers	Consultant	01223 762007
Caroline Owen	Respiratory Nurse Specialist	07872048641
Medicines Information		01223 217502/217478

Papworth Hospital NHS Foundation Trust		
Specialist	**Post**	**Telephone**
Dr Helen Parfrey	ILD Consultant	01480 364521
Dr Muhunthan Thillai	ILD Consultant	01480 364530
Dr Nicky Simler	ILD Consultant	01480 364530
ILD CNS	Specialist Nurse	01480 364184
Duncan Grady	Thoracic Directorate Pharmacist	01480 830541 pager 845
Medicines Information		01480 364179
Medicines Helpline (patients)		01480 364739

13. Equality and Diversity Statement

This document complies with the Cambridge University Hospital Trust service Equality and Diversity statement.

14. Disclaimer

It is your responsibility to check that this printed out copy is the most recent issue of this document.

15. Document Management

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The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Product Characteristics
https://www.medicines.org.uk/emc/medicine/30110