Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nintedanib for treating idiopathic pulmonary fibrosis [ID752]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: UK Clinical Pharmacy Association (UKCPA) Respiratory Group

Are you (tick all that apply):

- ✓ a specialist in the treatment of people with the condition for which NICE is considering this technology?
- ✓ a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

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What is the expected place of the technology in current practice?
How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

There have been a number of recent changes to the diagnostic criteria for IPF and the evidence base underpinning its management.[1] *The previous standard of care with 'triple therapy' (N-acetylcysteine, azathioprine and prednisolone) has been shown to be harmful,*[2] *and N-acetylcysteine alone has not been shown to have a disease modifying effect,*[3] *although it may have a role in symptomatic management of cough as a mucolytic. Prior to this there was considerable variation in practice and although this is likely to have been attenuated by these publications, and the availability of a licensed disease modifying therapy (pirfenidone), there continues to be variability in practice.*[4]

Within the UK there is considerable geographic variation in the availability of specialist Interstitial Lung Disease (ILD) services and in the time taken for patients to be referred and seen by them. This impacts on access to disease modifying therapies, clinical trials and supportive care such as oxygen assessment, pulmonary rehabilitation and specialist nurse support.

Patients with IPF also appear to be disadvantaged in consideration for, and access to, lung transplantation. The advanced age at presentation, and high incidence of co-morbidities cause many to be ineligible. For eligible patients, the rate of listing is low and IPF patients have the highest waiting list mortality of all patients awaiting lung transplantation.[4,5]

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

IPF is a heterogeneous condition with considerable variation in prognosis and rate of disease progression. Risk factors for mortality have been identified but cannot be considered in isolation. Outside of the clinical trial eligibility criteria there is little information, either at baseline or following a period of treatment, on which to estimate or measure the magnitude of treatment benefit for either nintedanib or pirfenidone. Using single physiological measurements such as FVC and applying eligibility criteria against an upper limit, or stopping criteria against rate of change may significantly disadvantage some individuals and deny them treatment which they may benefit from.

The clinical course of IPF is variable, with both slowly progressive and rapidly progressive patient types recognised. Patients may also experience periods of accelerated decline during acute exacerbations of IPF, which are associated with a significant mortality risk. Risk factors for mortality include gender, age, physiology (including lung function parameters and exercise tolerance testing), radiological features and biomarkers[6,7] *and risk stratification systems such as the CPI*[8] *and GAP index*[9] *have been proposed.*

Whilst patients with IPF have been described as mild, moderate and severe, there is a lack of clear criteria to define these. However clinical trials have generally agreed on a FVC threshold of 50–

*55% predicted **and** a DL_{CO} threshold of 35–40% predicted to separate mild-to-moderate patients from those with severe disease.*[10]

Whilst the rate of change in FVC has consistently been shown to be a risk factor for mortality in IPF, with an FVC decline >10% over 24 weeks being a particularly poor prognostic marker,[10] *to our knowledge, there are no validated prognostic systems to predict the rate at which a patient's FVC or DL_{CO} will decline. Therefore it is not possible to demonstrate a clear relationship between any subgroup defined in terms of change in the rate of lung function decline and the risk reduction of clinically meaningful endpoints such as morbidity, mortality or rate of hospital admission*

Pirfenidone and nintedanib have been shown in clinical trials to reduce the rate of lung function decline (estimated using FVC) in IPF, and more recently pirfenidone has been shown to increase progression free survival and reduce mortality in IPF.[11] *It is currently unclear if modifying the rate of change in FVC, or any effects on other surrogate endpoints, translates to improvements in mortality or morbidity associated with IPF.*

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

As outlined in NICE CG163, the diagnosis of IPF requires input from an MDT with appropriate expertise and should follow clinical assessment by a specialist in ILD, to prevent misdiagnosis, which may result in inappropriate treatments being initiated or denied. Treatment initiation should therefore occur in a specialist/tertiary setting.

Depending on local arrangements continuation of treatment may be appropriate in another secondary care setting, or under shared care between a secondary and tertiary care setting in a similar model to that employed in PAH.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

As previously stated, there are considerable geographic variation in the availability and organisation of specialist ILD services and in the time taken to be referred and seen by them, which impacts on the availability of supportive care, disease modifying therapies and referral for lung transplantation assessment.

Nintedanib for IPF has been made available in some centres via a patient access scheme. There is also a cohort of patients continuing on nintedanib in extension arms of the BIBF-1120 studies.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Nothing to add

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Nintedanib and pirfenidone represent the only licensed disease modifying therapies for IPF, and comparison between these two drugs is difficult due to differences between the eligibility criteria (notably around diagnostic methodology) and baseline characteristics between the CAPACITY[14], ASCEND[11] and INPULSIS[15] studies.

There is currently little consensus on which agent to use first line in any group, or whether they should be used sequentially in patients intolerant to treatment or experiencing rapid progression despite treatment with one of these therapies.

The discontinuation rate due to intolerable/unmanageable ADR's appears to be around 15-20% with pirfenidone,[16–18] and there are differences in the nature of the tolerability profile between nintedanib and pirfenidone which may argue for or against one or other agent in some patients. There are currently no validated risk factors for individual toxicities with either agent on which to base treatment decisions.

The main ADR's associated with nintedanib appear to be gastrointestinal with diarrhoea being of sufficient severity to warrant discontinuation in 4.5% of patients.[15] Whilst there is no specific mention of surgical concerns or contraindications in the manufacturer's SPC, there are theoretical concerns that nintedanib may impair wound healing. Consequently, patients likely to have a lung transplant were excluded from clinical trials and the patient access scheme, but it is unclear if nintedanib use would prejudice eligibility for lung transplantation or complicate recovery from the procedure. In the absence of a formal consensus from transplant centres it may be prudent to avoid nintedanib use in patients being actively considered for lung transplantation.

There are also differences in eligibility criteria between the two agents which may be relevant to some individuals. Access to pirfenidone under NICE TA282 is currently limited to patients with an FVC >50% and ≤80% with a stopping criteria of an FVC decline of 10% or more in 1 year. Nintedanib would represent additional choice for patients with IPF. Taking into account patient specific factors and preference it may represent an appropriate first line option in some patients. It may represent an alternative for patients intolerant to pirfenidone or considered to be rapidly progressing despite treatment with pirfenidone. Depending on any criteria applied nintedanib may be an appropriate option for patients who would be considered ineligible for treatment with pirfenidone.

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If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Consistent with the INPULSIS entry criteria and following on from the discussion above treatment should be considered in patients with; an MDT diagnosis of IPF, an FVC ≥50% predicted and a DL_{CO} 30 – 79% predicted.

Treatment should be discontinued if there are unmanageable/intolerable ADR's.

As discussed above a stopping criteria based on just one single physiological parameter (such as the FVC) may be inappropriate.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Significant exclusion criteria included a history of; haemorrhagic CNS event within 12 months of, myocardial infarction with 6 months or unstable angina within 1 month of initiation. Patients with airways obstruction (FEV_1/FVC <0.7), or those receiving therapeutic anticoagulation were also excluded. The study group therefore probably represented a patient group with less co-morbidity than may be encountered in clinical practice.

Patients with an FVC <50% predicted or DL_{CO} <30% were excluded from trials. Patients with this degree of impairment represent a notable population of patients with IPF in clinical practice and have a considerable disease burden and high short term mortality. In this group listing for lung transplant and/or palliation may be the most appropriate approach. There is a real need to address the evidence base for disease modifying therapies in this cohort.

The most clinically relevant endpoints would be; preservation of quality of life, reduction in morbidity and mortality, and a reduction in the incidence of acute exacerbations of IPF. These were addressed in the studies. Statistically significant benefits were shown in INPULSIS-1 but not in INPULSIS-2 or the pooled analysis.

There was a statistically significant difference in the number of patients experiencing an FVC decline >5% at week 52 in both studies. There was a statistically significant difference in the number of patients experiencing an FVC decline >10% in INPULSIS-1 but not in INPULSIS-2 or the pooled analysis.

The statistically significant reduction in rate of FVC decline demonstrated in the studies is consistent with a slowing of disease progression but the magnitude of benefit on clinically meaningful endpoints is unclear.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Nausea, anorexia, diarrhoea and liver function abnormalities appear to be the main treatment related ADRs. Nausea, anorexia and diarrhoea may have a considerable impact on quality of life, even if of relatively low severity. Monitoring for hepatic dysfunction necessitates monthly blood tests for the first three months of treatment and thereafter quarterly blood tests.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Nothing to add

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Nintedanib would be managed by specialist teams in existing clinical settings.
Supply logistics may necessitate investment in pharmacy services to organise supply to a patient group which may be geographically distant from the centre managing supply.

Equality

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NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

We do not believe the current appraisal will present any issues for these groups.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Nothing to add

References

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