Review of TA379; Nintedanib for treating idiopathic pulmonary fibrosis and TA504; Pirfenidone for treating idiopathic pulmonary fibrosis

TA379 was published in January 2016 and scheduled to be considered for review in 2020.

TA504 was published in February 2018, as an update of TA282. It is scheduled to be considered for review in 2021.

1. Decision

A part-review of TA379 and TA504 should be planned into the appraisal work programme.

2. Rationale

The existing recommendations are optimised for a narrower population than covered by the marketing authorisations. Stakeholders have indicated that only recommending the use of these treatments to when a person has a forced vital capacity (FVC) between 50% and 80% predicted does not reflect current clinical practice, and that there may be new information to warrant an update of the guidance.

We did not identify any compelling new published clinical evidence, and the companies have confirmed that they are not aware of any new evidence that would change the existing recommendations. However, the threshold for treatment currently in the guidance is not supported by clinicians in the UK, who consider the UK to be an outlier internationally for treating idiopathic pulmonary fibrosis. Also, the companies may be able to offer an improved value proposition which may mean that the treatments become cost-effective for patients who are not currently covered by TA379 and TA504.

It is therefore decided that TA504 and TA379 be partially updated to consider the patient population not currently recommended to receive treatment in the existing guidance. This review would be subject to charging.

3. Summary of new evidence and implications for review

Has there been any change to the price of the technology(ies) since the guidance was published?

There are no changes to the list prices of nintedanib and pirfenidone since the publication of TA379 and TA504. The companies confirmed that they both have existing patient access schemes (simple discount).

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

There are no existing or proposed changes to the marketing authorisations for nintedanib and pirfenidone that would affect the existing guidance.

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

The marketing authorisations for nintedanib and pirfenidone are broader than the population for whom they are recommended in the guidance. Nintedanib has a marketing authorisation for idiopathic pulmonary fibrosis. Pirfenidone has a marketing authorisation for mild and moderate idiopathic pulmonary fibrosis. Both are recommended for treating idiopathic pulmonary fibrosis in people with a forced vital capacity (FVC) between 50% and 80% predicted. The treatment is stopped if there is evidence of disease progression (an absolute decline of 10% or more in predicted FVC within any 12-month period).

Pirfenidone was first appraised by NICE in 2013 to establish cost effectiveness compared with best supportive care (NICE appraisal for pirfenidone for treating idiopathic pulmonary fibrosis TA282) and reviewed in 2018 (NICE appraisal for pirfenidone for treating idiopathic pulmonary fibrosis TA504). The review included new evidence relating to people with a FVC above 80% predicted and considered removing the stopping rule, that is, to no longer stop pirfenidone after an absolute decline of 10% or more in predicted FVC within any 12-month period. None of the studies were designed to determine the effectiveness of pirfenidone in people with FVC above 80% predicted, or to compare this group with those with an FVC between 50% and 80% predicted. However, based on the presented evidence, the committee agreed to accept that pirfenidone has the same relative effectiveness in people with an FVC above 80% predicted and in people with an FVC of 80% predicted or less. But because of uncertainty in the cost effectiveness estimates the committee concluded that pirfenidone only remained cost effective for people with idiopathic pulmonary fibrosis with an FVC between 50% and 80% predicted when the stopping rule was applied.

There is no new RCT evidence for pirfenidone for treating mild to moderate idiopathic pulmonary fibrosis. Our literature search identified a real-world study from the UK that included people with FVC above 80% who received pirfenidone on a compassionate scheme. The results from this study support the effectiveness of pirfenidone in this subgroup. However, this is unlikely to reduce the uncertainty in the cost effectiveness estimates enough to affect the previous recommendation for pirfenidone compared with best supportive care in this subgroup. There was no evidence that could be considered for a decision on the stopping rule. We identified limited evidence for treating more severe disease, that is, an FVC below 50% with pirfenidone. This included post-hoc analysis of data from ASCEND, CAPACITY and RECAP as well as real-world data. Clinical experts stated that drug treatment may

not be appropriate for more severe disease. Also, this is not included in pirfenidone's marketing authorisation in the UK.

Ninetanib was appraised by NICE in 2016 to establish its cost effectiveness compared with pirfenidone for treating idiopathic pulmonary fibrosis in people who have a FVC between 50% and 80% and with best supportive care in in people who have a FVC above 80% predicted. Clinical experts stated that drug treatment may not be appropriate for more severe disease (a percent predicted FVC of less than 50%). The clinical effectiveness of nintedanib was similar to pirfenidone based on the results of the network meta-analysis. Nintedanib was cost effective compared with pirfenidone. Because pirfenidone is a comparator for a subgroup (people with a percent predicted FVC of between 50% and 80%), nintedanib was cost effective only for this group. Ninetanib was not cost effective when compared with best supportive care. The cost effectiveness estimate was sensitive to survival rates. There is no new RCT evidence for ninetanib for treating mild to moderate idiopathic pulmonary fibrosis. Our literature search identified real-world studies from the UK that included people with FVC above 80% who received ninetanib on a compassionate scheme. The results support the effectiveness of ninetanib in this subgroup. However, this is unlikely to substantially reduce the ICER which was considerably above £30,000 per QALY gained when ninetanib was compared with best supportive care in this subgroup. We identified post-hoc analyses of the INPULSE trial that stratified overall survival by the absolute decline in predicted FVC that is people with a decline of less than 10% and people with a decline of 10% or more. Mortality was higher in patients with FVC decline ≥10% predicted than <10% predicted but this was similar of whether patients received placebo or ninetanib. Therefore, the results of these analyses are unlikely to change the recommendations on the stopping rule. We identified real-world evidence for treating more severe disease that is an FVC below 50% with ninetanib. Although included in the marketing authorisation, clinical experts stated that drug treatment may not be appropriate for more severe disease.

Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?

See Appendix C for a list of related NICE guidance.

Additional comments

The search strategies from the original ERG reports were adapted for the Cochrane Library, Medline, Medline In-Process and Embase. References from September 2014 to November 2020 were reviewed for TA379 and from April 2015 to November 2020 for TA504. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

4. Equality issues

During consultation on TA504 consultees raised a potential equality issue. They stated that restricting treatment based on percent predicted FVC could discriminate against minority ethnic people, older people and disabled people. The committee discussed this issue with the clinical experts. It recognised the limitations of FVC but understood that, in clinical practice, other patient characteristics would be taken into account when interpreting percent predicted FVC. It concluded that its recommendations did not discriminate against any groups of people protected by the Equality Act. No equality issues were raised during the development and consultation of TA379.

Proposal paper sign off

Jenniffer Prescott – Programme Director, Technology Appraisals

11 May 2021

Contributors to this paper

Information Specialist: Paul Levay

Technical Analyst: Verena Wolfram

Project Manager: Charlotte Downing

Programme Manager: Andrew Kenyon

Associate Director: Nicole Elliott

Appendix A – Information from existing guidance

1. Original remit

TA379

To appraise the clinical and cost effectiveness of nintedanib within its licensed indication for treating idiopathic pulmonary fibrosis.

TA504

To appraise the clinical and cost effectiveness of pirfenidone within its marketing authorisation for treating idiopathic pulmonary fibrosis.

2. Current guidance

TA379

1.1 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% of predicted
- the company provides nintedanib with the discount agreed in the patient access scheme and
- treatment is stopped if disease progresses (a confirmed decline in percent predicted FVC of 10% or more) in any 12-month period.

1.2 People whose treatment with nintedanib is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

TA504

1.1 Pirfenidone is recommended as an option for treating idiopathic pulmonary fibrosis in adults only if:

- the person has a forced vital capacity (FVC) between 50% and 80% predicted
- the company provides pirfenidone with the discount agreed in the patient access scheme and
- treatment is stopped if there is evidence of disease progression (an absolute decline of 10% or more in predicted FVC within any 12-month period).

1.2 This recommendation is not intended to affect treatment with pirfenidone that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

3. Research recommendations from original guidance

N/A

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE's work programme.	Yes
The decision to review the guidance should be deferred.	NICE will reconsider whether a review is necessary at the specified date.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance will remain unchanged until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance remains relevant and an update is not needed.	The guidance will remain unchanged, in its current form, unless or until NICE becomes aware of substantive information which would make it reconsider.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Options	Consequence	Selected – 'Yes/No'
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

Appendix C – Other relevant information

Relevant Institute work

Published

COVID-19 rapid guideline: interstitial lung disease (2020) NICE guideline 177

Idiopathic pulmonary fibrosis in adults: diagnosis and management (2013) NICE guideline CG163. Surveillance decision: no update necessary (May 2017)

Idiopathic pulmonary fibrosis in adults (2015) NICE quality standard 79

In development

Nintedanib for treating progressive fibrosing interstitial lung disease [ID1599] NICE technology appraisal guidance. Publication expected September 2021.

Details of changes to the marketing authorisation for the technology

Marketing authorisation and price considered in original appraisal

TA379

Nintedanib has a marketing authorisation in the UK 'in adults for the treatment of idiopathic pulmonary fibrosis'.

The list price of nintedanib is £2151.10 for 60 capsules.

TA504

Pirfenidone has a marketing authorisation in the UK for treating mild to moderate idiopathic pulmonary fibrosis in adults.

The list price of pirfenidone is £501.92 for 63 capsules.

Proposed marketing authorisation (for this appraisal) and current price

No changes

Source: BNF (5 October 2020)

Registered and unpublished trials

Trial name and registration number	Details
Nintedanib Twice Daily vs Placebo in Patients Diagnosed With Idiopathic Pulmonary Fibrosis NCT01979952	Purpose: 6 month multi-centre, prospective, randomized, placebo controlled, double blind clinical trial followed by conversion of each arm to active nintedanib for an additional 6 months comparing the effect of nintedanib 150mg bis in die (BID twice daily) on the progression of IPF Phase 3 Status: complete Enrolment: 113 Start date: November 2013 Expected completion date: October 2016 Results: available in registry
Pragmatic Management of Progressive Disease in Idiopathic Pulmonary Fibrosis: a Randomized Trial NCT03939520	Purpose: evaluate the efficacy and tolerance of the combination pirfenidone and nintedanib as compared to a "switch monotherapy": i.e. switching from the current to the other of the two existing drugs prescribed as monotherapy, in patients who present chronic worsening IPF Phase 4 Status: recruiting Enrolment: 210 Start date: June 2020 Expected completion date: December 2022
Can a patient assistance program reduce the proportion of people with idiopathic pulmonary fibrosis (IPF) who stop taking pirfenidone? ISRCTN15587630	Purpose: to investigate whether a patient assistance program designed for people with IPF who are being prescribed pirfenidone can increase the effect of the drug on their symptoms and improve their quality of life. The patient assistance program will include information on IPF and pirfenidone, as well as information on how to recognise and prevent side effects of treatment. Status: ongoing Enrolment: 189 Start date: January 2019 Expected completion date: July 2022

Additional information

American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), Latin American Thoracic Society (ALAT) (2018) Diagnosis of Idiopathic Pulmonary Fibrosis An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), Latin American Thoracic Society (ALAT) (2015) An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis An Update of the 2011 Clinical Practice Guideline

British Thoracic Society (2019) BTS ILD registry annual report 2019

British Thoracic Society (June 2020) Restoring Lung Function testing for management of ILD

References

Abe, Mitsuhiro, Tsushima, Kenji, Sakayori, Masashi et al. (2018) Utility of nintedanib for severe idiopathic pulmonary fibrosis: a single-center retrospective study. Drug design, development and therapy 12: 3369-3375

Barczi, Eniko, Starobinski, Livia, Kolonics-Farkas, Abigel et al. (2019) Long-Term Effects and Adverse Events of Nintedanib Therapy in Idiopathic Pulmonary Fibrosis Patients with Functionally Advanced Disease. Advances in therapy 36(5): 1221-1232

Chung, M.P., Park, M.S., Oh, I.J. et al. (2020) Safety and Efficacy of Pirfenidone in Advanced Idiopathic Pulmonary Fibrosis: A Nationwide Post-Marketing Surveillance Study in Korean Patients. Advances in Therapy 37(5): 2303-2316

Costabel, U., Albera, C., Glassberg, M.K. et al. (2019) Effect of pirfenidone in patients with more advanced idiopathic pulmonary fibrosis. Respiratory Research 20(1): 55

Harari, Sergio, Caminati, Antonella, Poletti, Venerino et al. (2018) A Real-Life Multicenter National Study on Nintedanib in Severe Idiopathic Pulmonary Fibrosis. Respiration; international review of thoracic diseases 95(6): 433-440

Kolb, Martin, Richeldi, Luca, Behr, Jurgen et al. (2017) Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume. Thorax 72(4): 340-346

Nakamura, M., Okamoto, M., Fujimoto, K. et al. (2019) A retrospective study of the tolerability of nintedanib for severe idiopathic pulmonary fibrosis in the real world. Annals of Translational Medicine 7(12): atm20190533

Nathan, S.D., Costabel, U., Albera, C. et al. (2019) Pirfenidone in patients with idiopathic pulmonary fibrosis and more advanced lung function impairment. Respiratory Medicine 153: 44-51

Nathan, Steven D, Albera, Carlo, Bradford, Williamson Z et al. (2016) Effect of continued treatment with pirfenidone following clinically meaningful declines in forced vital capacity: analysis of data from three phase 3 trials in patients with idiopathic pulmonary fibrosis. Thorax 71(5): 429-35

Noor, S.; Nawaz, S.; Chaudhuri, N. (2020) Real-World Study Analysing Progression and Survival of Patients with Idiopathic Pulmonary Fibrosis with Preserved Lung Function on Antifibrotic Treatment. Advances in Therapy

Richeldi, L., Crestani, B., Azuma, A. et al. (2019) Outcomes following decline in forced vital capacity in patients with idiopathic pulmonary fibrosis: Results from the INPULSIS and INPULSIS-ON trials of nintedanib. Respiratory Medicine 156: 20-25

Senoo, Satoru, Miyahara, Nobuaki, Taniguchi, Akihiko et al. (2020) Nintedanib can be used safely and effectively for idiopathic pulmonary fibrosis with predicted forced vital capacity <= 50%: A multi-center retrospective analysis. PloS one 15(8): e0236935

Toellner, H., Hughes, G., Beswick, W. et al. (2017) Early clinical experiences with nintedanib in three UK tertiary interstitial lung disease centres. Clinical and Translational Medicine 6(1): 41

Yoon, Hee-Young; Kim, Dong Soon; Song, Jin Woo (2019) Efficacy and Safety of Pirfenidone in Advanced Idiopathic Pulmonary Fibrosis. Respiration; international review of thoracic diseases 97(3): 242-251

