

Nintedanib and pirfenidone: 24 month predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

February 2020

Abstract

Purpose

To compare the predicted and actual utilisation of nintedanib and pirfenidone for the treatment of idiopathic pulmonary fibrosis (IPF) since PBS listing.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

- Nintedanib: 1 May 2017
- Pirfenidone: 1 July 2017

Data Source / methodology

PBS prescription data for nintedanib and pirfenidone dispensed from 1 May 2017 to 30 September 2019 were extracted from the Department of Human Services (DHS) Supplied Prescriptions database.

Key Findings

- In total, 31,860 prescriptions have been supplied to 2,975 patients for the treatment of IPF.
- In the third quarter of 2019, there were 2,620 (56%) prescriptions of nintedanib dispensed compared with 2,084 (44%) of pirfenidone. Nintedanib was supplied to 1,007 (54%) patients, 833 (45%) were supplied pirfenidone, and 25 (1%) were supplied both nintedanib and pirfenidone.
- Of the nintedanib prescriptions supplied since PBS listing, 4,559 (27%) of 16,717 were for the 100 mg capsule. The median time of a dose reduction for nintedanib was estimated from the data to be 318 days.
- The number of patients treated for IPF estimated by the sponsor of nintedanib was underestimated in the first two years of listing. The number of prescriptions was overestimated in year 1 and similar to the estimated number in year 2.
- The number of patients treated for IPF and the number of supplied prescriptions estimated by the sponsor of pirfenidone were overestimated in the first two years of listing.

Purpose of analysis

To compare the predicted and actual utilisation of nintedanib and pirfenidone for the treatment of idiopathic pulmonary fibrosis (IPF) since PBS listing, as requested by DUSC at its October 2019 meeting.

Background

Clinical situation

IPF is a condition that causes lung tissue to become thickened and scarred over time.^{1,2} IPF causes a progressive decline in lung function, which increasingly restricts routine physical activity due to breathlessness.³ The prevalence of IPF increases with age, most patients are aged over 50 years at diagnosis and the disease affects a higher proportion of males than females.⁴ Prior to the listing of nintedanib and pirfenidone, the median survival for this disease was considered to be three to five years.³

Both medicines were approved to improve patient outcomes by slowing the progression of IPF.

Pharmacology

Nintedanib is classed as an antineoplastic agent (L01XE31), and pirfenidone is classed as an immunosuppressant (L04AX05).

Therapeutic Goods Administration (TGA) approved indications

Nintedanib is TGA approved and PBS listed for the treatment of IPF. Nintedanib is also TGA approved in combination with docetaxel for the treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after failure of first line chemotherapy.

Pirfenidone is TGA approved and PBS listed for the treatment of IPF.

¹ Ofev (nintedanib). Australian Approved Consumer Medicine Information. Sydney: Boehringer Ingelheim Pty Limited. Updated July 2018. Available from <<https://www.ebs.tga.gov.au>>

² Esibriet (pirfenidone). Australian Approved Consumer Medicine Information. Sydney: Roche Products Pty Limited. Updated 23 January 2018. Available from <<https://www.ebs.tga.gov.au>>

³ Ofev (nintedanib). PBAC Public Summary Document, November 2016, p7. Available from <<http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-11/files/nintedanib-psd-november-2016.pdf>>

⁴ Olson AL, Gifford AH, Inase N, Fernández Pérez ER, Suda T. The epidemiology of idiopathic pulmonary fibrosis and interstitial lung diseases at risk of progressive-fibrosing phenotype. Eur Respir Rev 2018; 27: 180077. Doi:10.1183/16000617.0077-2018.

Dosage and administration

Table 1: Dosage and administration of nintedanib and pirfenidone

Brand name and sponsor	Product	Dose and frequency of administration
Ofev®, Boehringer Ingelheim Pty Ltd	Nintedanib 100 mg capsule Nintedanib 150 mg capsule	Nintedanib capsules should be taken orally, preferably with food, swallowed whole with water, and should not be chewed or crushed. The recommended dose of nintedanib for IPF is 150 mg twice daily administered approximately 12 hours apart. The recommended maximum daily dose of 300 mg should not be exceeded. Side effects can be managed through dose reduction and temporary interruption of therapy. Treatment may be resumed at the full dose (150 mg twice daily) or a reduced dose (100 mg twice daily).
Esbriet®, Roche Products Pty Ltd	Pirfenidone 267 mg capsule Pirfenidone 801 mg capsule	Upon initiating treatment, the dose should be titrated to the recommended daily dose of nine capsules per day over a 14 day period as follows: <ul style="list-style-type: none"> Days 1 to 7: one capsule, three times a day (801 mg/day) Days 8 to 14: two capsules, three times a day (1602 mg/day) Day 15 onward: three capsules, three times a day (2403 mg/day) The recommended daily dose of pirfenidone for patients with IPF is three 267 mg capsules three times a day with food for a total of 2403 mg/day. Patients who miss 14 consecutive days or more of pirfenidone treatment should re-initiate therapy by undergoing the initial two week titration regimen up to the recommended daily dose.

Source: Nintedanib Product Information,⁵ Pirfenidone Product Information,⁶ Accessed 1 November 2019

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from the TGA (Product Information) and the TGA (Consumer Medicines Information).

⁵ Ofev (nintedanib). Australian Approved Product Information. North Ryde: Boehringer Ingelheim Pty Limited. Approved day 1 September 2015, updated 6 March 2019. Available from < <https://www.tga.gov.au/product-information-pi>.>

⁶ Esbriet (pirfenidone). Australian Approved Product Information. Sydney: Roche Products Pty Limited. Approved 29 February 2016, updated 13 July 2018. Available from < <https://www.tga.gov.au/product-information-pi>.>

PBS listing details (as at November 2019)

Table 2: PBS listing of nintedanib and pirfenidone

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
11100F	nintedanib 100 mg capsule, 60	1	5	\$1753.03	Ofev®, Boehringer Ingelheim Pty Ltd
11106M	nintedanib 150 mg capsule, 60	1	5	\$3389.72	
11136D	pirfenidone 267 mg capsule, 270	1	5	\$3067.12	Esbriet®, Roche Products Pty Ltd
11406H	pirfenidone 267 mg capsule, 90	3	5	\$3067.12	
11410M	pirfenidone 801 mg capsule, 90	1	5	\$3067.12	

Source: the PBS website. Special Pricing Arrangements apply.

Restriction

Nintedanib and pirfenidone are PBS listed as Authority Required listings for IPF. Applications for authorisation to initial treatment must be made in writing. Applications for authorisation to change or re-commence treatment, and for continuing treatment, may be made by telephone.

The PBS listing states:

The condition must be diagnosed through a multidisciplinary team, and

Patient must have chest high resolution computed tomography (HRCT) consistent with diagnosis of idiopathic pulmonary fibrosis within the previous 12 months, and

Patient must have a forced vital capacity (FVC) greater than or equal to 50% predicted for age, gender and height, and

Patient must have a forced expiratory volume in 1 second to forced vital capacity ratio (FEV1/FVC) greater than 0.7, and

Patient must have diffusing capacity of the lungs for carbon monoxide (DLCO) corrected for haemoglobin equal to or greater than 30%, and

Patient must not have interstitial lung disease due to other known causes including domestic and occupational environmental exposures, connective tissue disease, or drug toxicity, and

The treatment must be the sole PBS subsidised treatment for this condition.

The patient must be treated by a respiratory physician or specialist physician, or in consultation with a respiratory physician or specialist physician.

For details of the current PBS listings, refer to the PBS website.

Date of listing on PBS

- Nintedanib: 1 May 2017
- Pirfenidone: 1 July 2017

Current PBS listing details are available from the PBS website.

Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

Nintedanib

Nintedanib March 2015 PBAC meeting

At its March 2015 meeting the PBAC rejected a submission for the listing of nintedanib for the treatment of IPF on the basis of an uncertain estimate of comparative effectiveness, as measured by the effect on clinically relevant outcomes, including acute IPF exacerbations and overall survival, and a resulting very high and uncertain estimate of cost effectiveness.

There was limited epidemiological evidence to reliably determine the prevalence of IPF in Australia. Epidemiological studies located by the submission reported prevalence rates that varied from 1.25/100,000 to 27.9/100,000. While an average prevalence rate was applied in the financial estimates, this was likely to be underestimated given the inclusion of non-population based studies in the analysis. In addition, the uptake rate applied by the submission was highly conservative. No other specific IPF therapies were readily available in the Australian market. The accuracy of the estimated net costs may have been further compromised by the prevalence only approach used in the financial model, which applied an average prevalence rate per year. Without an incident population, the financial model was unable to estimate the number of new IPF patients that would enter the PBS population each year or consider the expected treatment duration over the 5 year estimates.

This submission was considered by DUSC. DUSC considered that the submission had underestimated the likely utilisation and budget impact resulting from the proposed listing of nintedanib for IPF due to the following:

- The prevalence of IPF and the rate of uptake of nintedanib were likely to be higher than proposed. Limiting the analysis to population based studies resulted in an average prevalence of 14.4 per 100,000.
- The submission applied an “Accuracy of diagnosis” rate of 87% to the estimated prevalent IPF population. DUSC considered that this reduction was not necessary as the studies used to estimate prevalence only included diagnosed patients.
- Given that IPF is a progressive and ultimately fatal disease, with no other specific therapies available in Australia, DUSC considered that uptake in the eligible population would be substantial.

DUSC recommended a revised uptake rate of 60% in Year 1 increasing to 100% in Year 5. DUSC considered that the net cost to the PBS for listing nintedanib could be approximately triple the submission Year 1 estimates and approximately double the submission Year 5 estimates.

In addition, the ESC noted that estimates of use and financial implications were based on uncertain incidence and prevalence of IPF in Australia. The ESC considered that incidence and prevalence of IPF to date may be underestimated given the absence of an effective treatment and the limited use of the major diagnostic test, HRCT chest scanning. The ESC noted that Raghu et al (2014) analysed a 5% random sample of US Medicare beneficiaries (age >65) from 2000 to 2011 and found a stable incidence rate of 93.7 per 100,000 person years and increasing prevalence from 202 per 100,000 in 2001 to 494 per 100,000 in 2011, with median survival increasing from 3.3 years to 4.0 from 2001 to 2007. The Pre-PBAC Response accepted that the prevalence rate of 14.4/100,000 suggested by DUSC was reasonable.

The Pre-PBAC Response presented revised financial estimates incorporating this revised prevalence rate and diagnosis and uptake rates and methodology recommended by DUSC to account for the proposed RSA.

For further details refer to the Public Summary Document from the March 2015 PBAC meeting.

Nintedanib November 2015 PBAC meeting

The PBAC deferred the decision to recommend nintedanib for PBS listing for IPF subject to a revised base case ICER of approximately \$60,000/QALY, re-specified to incorporate a continuation rule and a price reduction which does not take into account any consequence of the proposed RSA.

This submission was not considered by DUSC. The re-submission updated the estimated extent of use and financial implications associated with the requested listing for nintedanib, with the estimated eligible patient pool calculated using parameters consistent with the DUSC advice (IPF prevalence = 14.4/100,000, diagnosis rate for IPF = 100%). Adverse events (diarrhoea, nausea, vomiting) and liver monitoring costs were also included in the updated estimates.

For further details, refer to the Public Summary Document from the November 2015 PBAC meeting.

Nintedanib November 2016 PBAC meeting

At its November 2016 meeting the PBAC recommended the listing of nintedanib for the treatment of idiopathic pulmonary fibrosis (IPF).

The resubmission was considered by DUSC. The resubmission updated the estimated extent of use and financial implications associated with the requested listing for nintedanib. At Year 5, the submission estimated that the number of patients treated with nintedanib

(adjusted for the continuation rule) would be less than 10,000 and the net cost to the PBS would be \$10 – 20 million per year.

The one major change in the approach to estimating financial implications was the incorporation of the continuation rule: those who experienced a decline in FVC%Pred of 10 percentage points or more in the past 12 months were discontinued from PBS subsidised treatment. The resubmission relied on the annual probability of failing to meet the continuation rule calculated for the economic evaluation for Years 2-5, and assumed that this probability would be half this in Year 1.

DUSC considered the estimates presented in the resubmission to be underestimated. The main issues were:

- As the number of Australian IPF patients was derived from prevalence estimates consistent with the restriction, rather than population prevalence, DUSC considered that it was unnecessary to further reduce the population based on FVC. Therefore, DUSC considered the eligible patient pool was slightly underestimated.
- DUSC confirmed its opinion that the proposed uptake rates in the resubmission were underestimated (nintedanib March 2015 PSD, paragraph 6.38). Given that IPF is fatal and there are limited treatment options, and nintedanib is an oral therapy, DUSC considered it reasonable that uptake may reach 100% within the first five years of listing. However, DUSC considered that tolerability in practice might be lower than in the clinical trials, meaning patients may not persist with therapy.
- DUSC noted that the resubmission financial model did not consider that patients may discontinue and recommence treatment.
- DUSC considered that a compliance rate of 96.4% seemed high for a medicine where 44% of people experience diarrhoea to the extent that it requires treatment for 158 days.

For further details refer to the Public Summary Document from the November 2016 PBAC meeting.

Pirfenidone

Pirfenidone November 2015 PBAC meeting

At its November 2015 meeting the PBAC decided not to recommend pirfenidone for PBS listing for IPF on the basis of unacceptably high and uncertain cost-effectiveness.

The submission relied on a systematic review of IPF incidence rates (Hutchinson 2015), which reported a range of 3-9/100,000 for Europe and North America. The crude average was applied in the base case of the estimates. While this incidence rate appeared to be comparable to epidemiological studies with larger datasets (n>2000: Navaratnam 2011, Kornum 2008), a study by Raghu 2014 using a narrow and broad case definition of IPF reported a 2011 incidence rate of 31.1 and 43.0/100,000 in patients aged ≥65 years, respectively. Given that the estimates from Raghu 2014 were only applicable to patients

aged 65 years or older, there was potential that the incident population could be greater than that predicted by the submission.

Of further consequence to the reliability of the estimates was the calculation of the prevalent population at year 1, which only included incident patients from the preceding year of PBS listing. As reported in Strand 2014, the median survival for the IPF population was estimated at 4.4 years and 10 year survival was approximately 15%. Given that the expected duration of survival was well beyond 1 year, it would have been more appropriate if the submission applied a broader approach to the calculation of the prevalent population at year 1.

For further details, refer to the Public Summary Document from the November 2015 PBAC meeting.

Pirfenidone March 2016 PBAC meeting

At its March 2016 meeting the PBAC did not recommend the PBS listing of pirfenidone for the treatment of IPF on the basis of unacceptably high cost effectiveness, in the context of total cost and uncertain utilisation.

The PBAC recalled its key concerns in November 2015 regarding the derivation of the pirfenidone treated population (potentially higher IPF incidence rate; limiting calculation of prevalent population to IPF patients in the year prior to listing) and hospitalisations were likely to result in underestimated net costs to the government. The evaluation also noted additional factors (application of ABS population projections; potential duplication of deaths in the pirfenidone treatment continuation rates) that were likely to further contribute to this underestimate. The PBAC considered that the minor resubmission did not sufficiently address these issues, and noted the potential for the absence of a stopping rule to increase the utilisation estimates.

For further details, refer to the Public Summary Document from the March 2016 PBAC meeting.

Pirfenidone November 2016 PBAC meeting

At its November 2016 meeting the PBAC deferred making a recommendation for pirfenidone.

This resubmission was considered by DUSC. The resubmission followed the same general approach to estimating use as the previous submissions, with the following change: instead of patients treated per year, the resubmission calculated pirfenidone treatment quarters and divided the number of treatment quarters by four to estimate the number of patient treatment years in each year of listing. DUSC considered that the approach to the financial estimates was complex and not fully transparent, as the independent contribution of deaths and discontinuations to the retention rate could not be determined. While DUSC identified some issues in the derivation of the patient estimates in relation to the application of treatment discontinuations, DUSC noted that the patient treatment years in the resubmission did not greatly differ from the estimated number of patients treated in the March 2016 submission.

DUSC considered the number of eligible patients in the submission may have been underestimated. However, DUSC considered the number of treated patients in the later years may have been overestimated. Despite methodological issues, overall the number of full patient years on treatment may have been a reasonable estimate. The main issues were:

- The estimated number of incident patients relied on a narrow definition of IPF, thus the eligible proportion of 66% may have been underestimated.
- The estimated number of patients treated relied on application of the same retention rate to the prevalent pool as for incident patients, which may have overestimated the number of continuing patients.

Subsequent to the deferral, the sponsor provided the PBAC with the following information:

- a cost-minimisation analysis on the basis that the effective price for pirfenidone be no higher than the effective price for nintedanib at equi-effective doses;
- proposed equi-effective daily doses of 2,104.6 mg pirfenidone and 281.1 mg nintedanib;
- a comparison of prescribing, administration, safety and toxicity management profiles between pirfenidone and nintedanib; and
- in principle agreement to join the risk sharing arrangement negotiated for nintedanib and to accept a common financial cap for both products.

The PBAC recommended the listing of pirfenidone for the treatment of IPF on a cost-minimisation basis to nintedanib.

For further details refer to the Public Summary Document from the November 2016 PBAC meeting.

Pirfenidone March 2018 PBAC meeting

At its March 2018 meeting the PBAC recommended the Authority Required listing for a new tablet form at the same strength as the currently listed capsule, as well as a higher strength, of pirfenidone for the treatment of IPF.

For further details refer to the Public Summary Document from the March 2018 PBAC meeting.

Methods

PBS prescription data for nintedanib and pirfenidone dispensed from 1 May 2017 to 30 September 2019 were extracted from the DHS PBS prescription database. These data were used to determine the number of prescriptions supplied, the number of incident and prevalent treated patients and to analyse patient demographics such as age and sex.

A medicine sequence analysis was completed in the full dataset to investigate the number of patients who were supplied both nintedanib and pirfenidone. Using a smaller cohort of patients who only received nintedanib, further analyses were completed to assess the proportion of use of the 100 mg dose of nintedanib, and the duration of dose reductions.

Length of treatment was analysed to compare to the duration of dose reductions. In both these analyses, patients were assumed to be continuing (censored) if they were supplied a prescription within 3 times the median time to resupply the medicines (31 days).

Data manipulation was undertaken using SAS.

As this analysis used date of supply prescription data, there may be small differences compared with publicly available Department of Human Services (DHS) Medicare date of processing data.⁷

Results

Analysis of drug utilisation

Overall utilisation

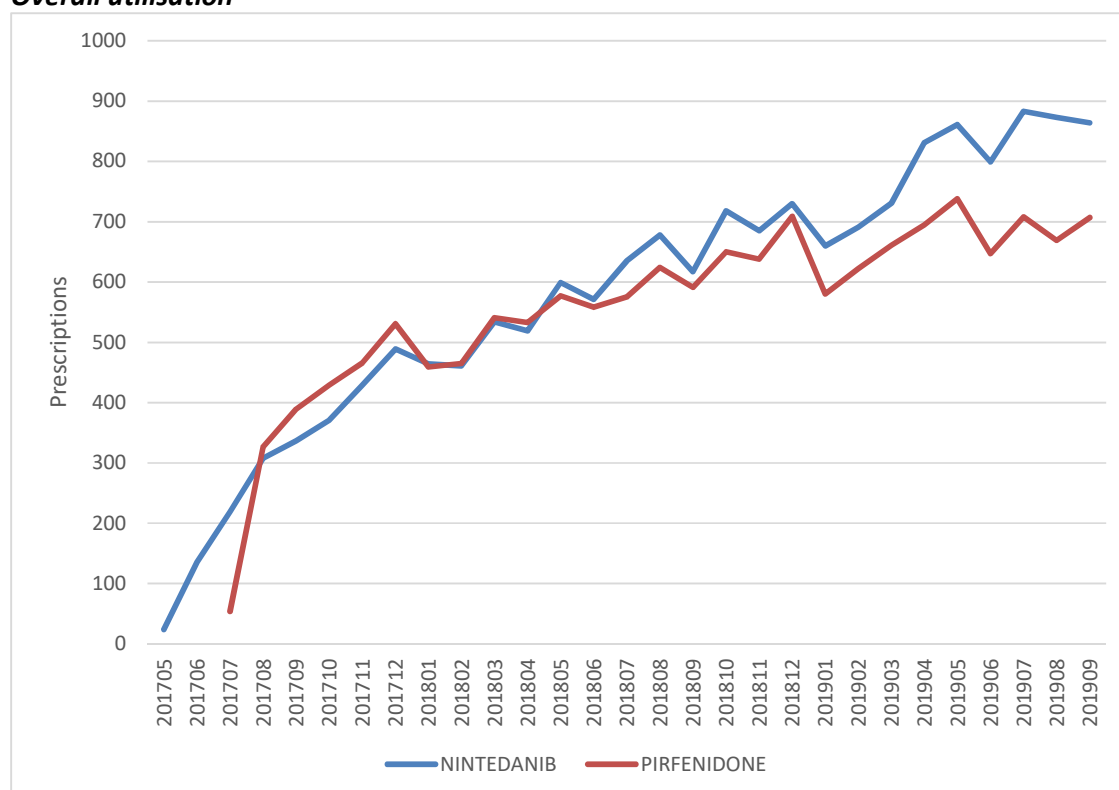


Figure 1: Number of prescriptions by medicine

After a steep increase in the number of supplied prescriptions during 2017, the rate of growth has slowed although the number of prescriptions supplied per month is continuing

⁷ PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>.

to grow. The proportion of use of the two medicines was similar until the end of 2018. The number of nintedanib prescriptions supplied each month now appears to be consistently higher than the number of pirfenidone prescriptions. Between July and September 2019 there were 2,620 (56%) prescriptions of nintedanib dispensed compared with 2,084 (44%) of pirfenidone.

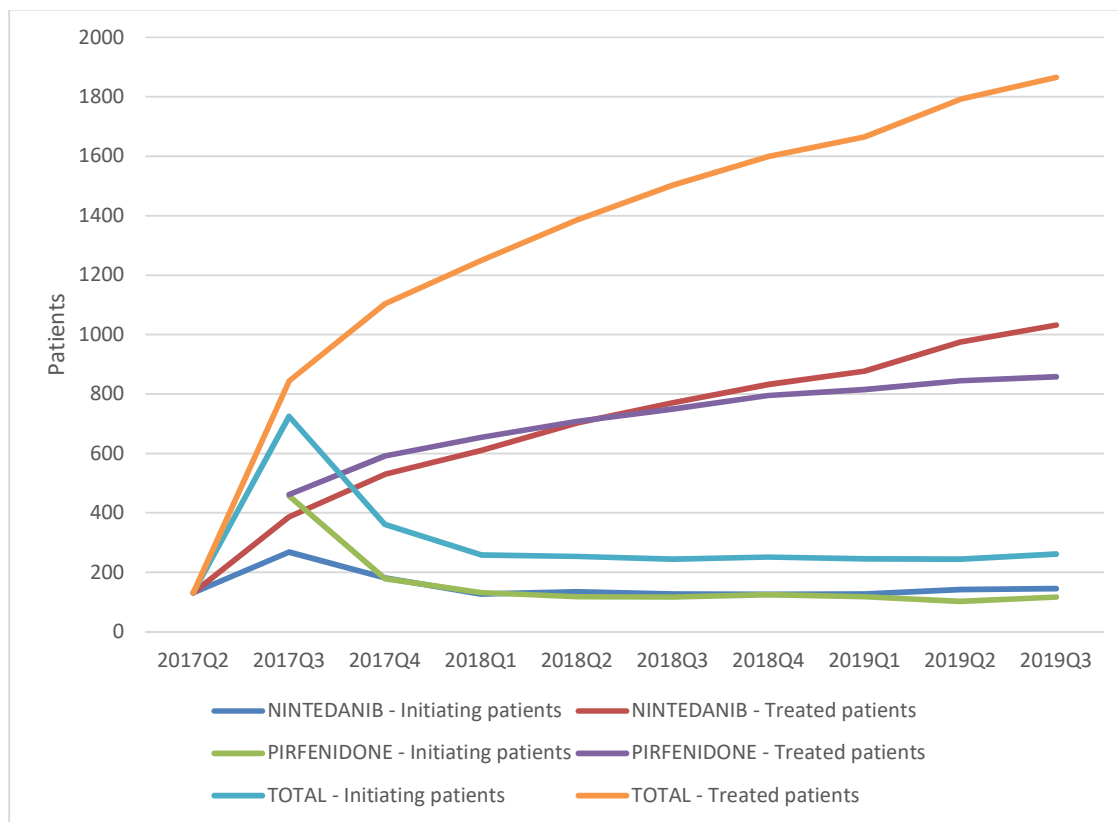


Figure 2: Initiating and treated patients by medicine

A total of 2,975 patients have initiated treatment with nintedanib or pirfenidone since PBS listing. In 2018, 1,007 patients initiated PBS treatment with either nintedanib or pirfenidone, and 2,048 patients were supplied at least one prescription. The number of patients supplied the two medicines was similar until the end of 2018. Between July and September 2019 there were 1,007 (54%) supplied nintedanib, 833 (45%) supplied pirfenidone, and 25 (1%) supplied both nintedanib and pirfenidone.

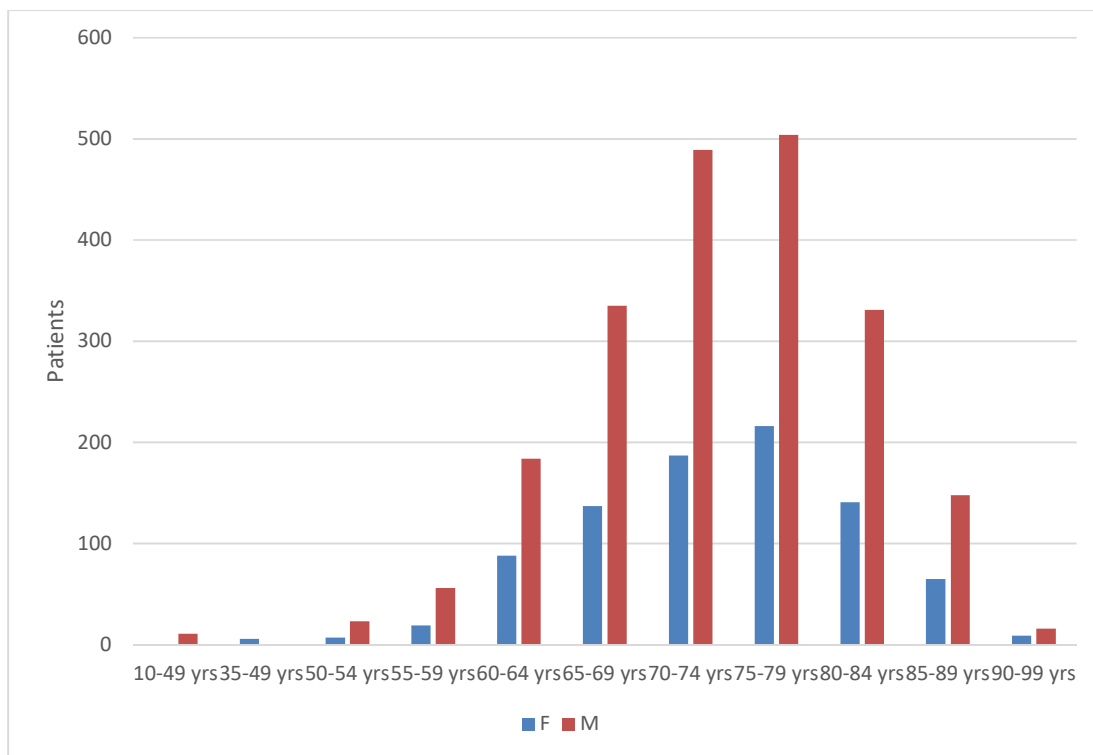


Figure 3: Number of initiating patients by age and sex

Across all age groups, males accounted for approximately 70% of initiating patients. The group with the highest proportion of initiating patients was 75-79 years old in males, females and overall.

Table 3: Medicine sequence

Sequence	Patient count	Proportion
NINTEDANIB	1,305	43.9%
PIRFENIDONE	1,244	41.8%
PIRFENIDONE>NINTEDANIB	197	6.6%
NINTEDANIB>PIRFENIDONE	179	6.0%
NINTEDANIB>PIRFENIDONE>NINTEDANIB	21	0.7%
PIRFENIDONE>NINTEDANIB>PIRFENIDONE	10	0.3%
THREE OR MORE SWITCHES	19	0.6%
TOTAL	2,975	

Overall, 86% of patients who initiated on either nintedanib or pirfenidone have not been supplied the other medicine.

Dose analysis of nintedanib

Of the nintedanib prescriptions supplied since PBS listing, 4,559 (27%) of 16,717 were for the 100 mg capsule. This is a little higher than the estimated proportion of 24%.

The 1,305 patients who were only supplied nintedanib were further investigated to understand the duration of dose reductions. Of the 1,305 patients, 241 (18%) were supplied the 100 mg strength after being supplied the 150 mg strength, and 1,064 (82%) were not. A further breakdown can be found in Table 4. The estimated mean time of dose reductions using a Kaplan Meier analysis was 0.76 years (278 days) with a standard error of 0.032. The median was estimated as 0.87 years (318 days) with a lower limit of 0.58 years and an upper limit of 1.05 years.

In comparison, the mean length of treatment for patients only treated with nintedanib was estimated to be 1.51 years with a standard error of 0.025, and the median could not be estimated. For all patients treated with either nintedanib or pirfenidone the mean length of treatment was estimated to be 1.47 years. The median was estimated to be 1.88 years with a lower limit of 1.67 years and an upper limit of 2.17 years. However, it should be noted that in the analyses of dose reduction time and time on treatment, more than 60% of patients were censored as they had not stopped treatment.

Table 4: Number of nintedanib patients with dose reductions and censoring

	Continuing (censored)	Stopped treatment	Subtotal
No dose reduction	693	371	1,064
Dose reduction	161	57	218
Dose reduction and subsequent increase		<6	23
Total			1,305

Approach taken to estimate utilisation - nintedanib

Nintedanib was given a positive recommendation by the PBAC at its November 2016 meeting. The predicted versus actual analysis of nintedanib compares the predicted use in the final agreed estimates, adjusted to listing years (May to April), to the actual number of patients and prescriptions for nintedanib and pirfenidone.

The submission used an epidemiological approach to estimate the number of treated patients. The final agreed estimates were similar to the estimates presented in the November 2016 submission.

Analysis of actual versus predicted utilisation - nintedanib

Table 5: Actual versus predicted utilisation of nintedanib

Nintedanib listing years		Year 1	Year 2	Year 3
		May 2017 - April 2018	May 2018 - April 2019	May 2019 - September 2019
Treated patients	Predicted	903	1,318	1,686
	Actual	1,551	2,221	2,026
	Difference	+72%	+68%	+20%
Prescriptions	Predicted	10,593	15,459	19,770
	Actual	8,485	15,626	7,749
	Difference	-20%	+1%	-61%

Note: Year 3 predicted numbers are for the full year, actual numbers are five months of data

The difference in predicted and actual cost (not presented) was the same (less than 1% different) in each year as the difference in the number of supplied prescriptions. Overall, the number of patients treated for IPF estimated in the November 2016 submission was underestimated, and the number of prescriptions was overestimated in year 1 and similar to the estimated number in year 2. The numbers presented in year 3 include only five months of the listing year.

Of the nintedanib prescriptions supplied since PBS listing, 4,559 (27%) of 16,717 were for the 100 mg capsule. This is a little higher than the estimated proportion of 24%.

Approach taken to estimate utilisation - pirfenidone

Pirfenidone was cost minimised to nintedanib following its positive recommendation at the November 2016 meeting. The predicted versus actual analysis of pirfenidone compares the predicted use in the pirfenidone November 2016 submission, adjusted to listing years (July to June), to the actual number of patients and prescriptions for nintedanib and pirfenidone.

The November 2016 submission was considered by DUSC. DUSC considered the number of eligible patients in the submission may have been underestimated. However, DUSC considered the number of treated patients in the later years may have been overestimated.

Analysis of actual versus predicted utilisation - pirfenidone

Table 6: Actual versus predicted utilisation of pirfenidone

Pirfenidone listing years		Year 1	Year 2	Year 3
		July 2017 - June 2018	July 2018 - June 2019	July 2019 - September 2019
Treated patients	Predicted	████	████	████
	Actual	1,722	2,306	1,865
	Difference	████	████	████
Prescriptions	Predicted	████	████	████
	Actual	10,630	16,366	4,704
	Difference	████	████	████

Note: Year 3 predicted numbers are for the full year, actual numbers are three months of data

The difference in predicted and actual cost (not presented) was similar (less than 10% different) in each year to the difference in the number of supplied prescriptions. Overall, the number of treated patients and prescriptions estimated in the November 2016 submission were overestimated. The numbers presented in year 3 include only three months of the listing year.

Discussion

Although nintedanib listed two months earlier than pirfenidone, the use of these medicines was similar until the end of 2018. However, the analysis of prescriptions by medicine showed that nintedanib now has a higher market share than pirfenidone, of 56% in the third quarter of 2019.

At the time of the first PBAC consideration of nintedanib, it was noted that there was limited epidemiological evidence to reliably determine the prevalence of IPF in Australia. In the first submission for nintedanib in March 2015, epidemiological studies located by the submission reported prevalence rates that varied from 1.25/100,000 to 27.9/100,000. In 2018 there were 2,048 patients treated for IPF. Using the estimated Australian population in 2018 of 25 million⁸ this suggests 8.2/100,000 patients were treated for IPF. In the first submission for pirfenidone in November 2015, the submission relied on a systematic review of IPF incidence rates (Hutchinson 2015), which reported a range of 3-9/100,000 for Europe and North America. In 2018, 1,007 patients initiated PBS treatment for IPF. Using the estimated Australian population in 2018 of 25 million⁸ this suggests 4/100,000 Australians initiated treatment for IPF.

Studies from overseas, such as those reviewed in Olson et al.⁴, report that the prevalence of IPF increases with age. Most patients are aged over 50 years at diagnosis and the disease affects a higher proportion of males than females. These findings match the pattern of Australian patients supplied medicines for the treatment of IPF. Of the 2,972 patients who have initiated IPF treatment, 0.6% were younger than 50 years. Approximately 70% of initiating patients were male, and the group with the highest proportion of initiating patients was 75-79 years old in males, females and overall.

The analysis of switching showed that 86% of patients who initiated on either nintedanib or pirfenidone have not been supplied the other medicine. This proportion may decrease over time as patients are treated for longer.

The analyses of time of dose reductions and length of treatment showed that more than 60% of patients had not stopped treatment at the end of the dataset. This is reasonable as the report used less than three years of data for both medicines, and prior to the listing median survival was expected to be three to five years.

At the time of its consideration of the November 2016 nintedanib submission, DUSC considered the estimates presented in the resubmission to be underestimated. The predicted versus actual review of the nintedanib November 2016 estimates showed that the number of patients treated for IPF in the first two years of listing were underestimated. The number of prescriptions was overestimated in year 1 and similar to the estimated number in year 2.

⁸ Australian Bureau of Statistics, 2019, Australian Demographic Statistics, Table 59. Estimated Resident Population By Single Year Of Age, Australia', time series spreadsheet, cat. no. 3101.0, viewed 17/12/2019, <<https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3101.0Mar%202019?OpenDocument>>

At the time of its consideration of the November 2016 pirfenidone submission, DUSC considered the number of eligible patients in the submission may have been underestimated. However, DUSC considered the number of treated patients in the later years may have been overestimated. The predicted versus actual review of the pirfenidone November 2016 estimates showed that the number of treated patients and prescriptions in the first two years of listing were overestimated.

Of the nintedanib prescriptions supplied since PBS listing, 4,559 (27%) of 16,717 were for the 100 mg capsule. This is a little higher than the estimated proportion of 24%.

Actions undertaken by the DUSC Secretariat

The report was provided to the sponsors of nintedanib and pirfenidone for comment.

DUSC consideration

DUSC noted the report showed that males accounted for approximately 70% of initiating patients and that the group with the highest proportion of initiating patients was 75-79 years old. DUSC commented that the age and gender of patients being treated for IPF matches the reported epidemiology of the disease.

DUSC noted that it appears nintedanib is becoming the preferred treatment for IPF, with 56% of the prescriptions for IPF being for nintedanib in the most recent three months of the extracted data. DUSC noted the report showed that most patients (85%) have not switched from the product they were initiated on. DUSC commented this may partly be due to prescriber preference.

DUSC noted that when PBAC recommended nintedanib, it was interested to know how many patients had dose reductions or interruptions. DUSC commented there are likely dose reductions and interruptions not able to be captured in utilisation analyses, for example, if someone stops or reduces their dose for a week.

DUSC noted that 27% of nintedanib prescriptions were for the 100 mg capsule, and that this is a little higher than the estimated proportion of 24%. DUSC commented that trials often include younger patients than those treated once the medicine is PBS listed. DUSC commented that older patients may need to be treated with a lower dose due to tolerability, although there is a lack of evidence if a sub-trial dose has the same clinical effect. DUSC commented that consumer input may have helped to understand why lower doses are being used.

DUSC noted the number of patients treated for IPF estimated by the sponsor of nintedanib was underestimated in the first two years of listing. The number of prescriptions was overestimated in year 1 and similar to the estimated number in year 2. The number of patients treated for IPF and the number of supplied prescriptions estimated by the sponsor of pirfenidone were overestimated in the first two years of listing. Sponsor feedback questioned whether the financial caps should be increased to account for the availability of

both therapies. DUSC noted that IPF was hard to distinguish from other conditions and it could not be determined if patients were using these medicines for a number of other conditions outside of the PBS restrictions.

DUSC actions

DUSC requested that the report be provided to the PBAC for consideration.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsors' comments

Roche Products Pty Ltd: The sponsor has no comment.

Boehringer Ingelheim Pty Ltd: The sponsor has no comment.

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical

Benefits Advisory Committee. The context for that information may have changed since publication.

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