Original Article

Assessing the budget impact of nintedanib for the treatment of idiopathic pulmonary fibrosis in the Greek healthcare setting

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SUMMARY

Idiopathic pulmonary fibrosis (IPF) is a rare, chronic lung disease with a high mortality rate. IPF affects about 5 million people worldwide with median survival being 2-5 years following diagnosis. Until recently, there was no licensed pharmacologic therapy available for IPF and patients were managed by best supportive care, that includes treatment with pirfenidone. In 2015, nintedanib was approved for the treatment of IPF. This study estimates the reimbursement of nintedanib and its budget impact on the National Organization for Health Care Services Provision (EOPPY). The budget impact of reimbursing nintedanib as part of already available treatment options corresponds to a maximum of 0.13% of annual total pharmaceutical expenditure. Therefore, it has a relatively low impact on the budget of EOPPY, while use of nintedanib was associated with a higher number of acute exacerbation events being avoided, thus providing additional cost savings to EOPPY.
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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a rare, chronic, and fatal interstitial lung disease characterized by dyspnoea and gradual impairment of lung function, ultimately, leading to respiratory failure (NICE 2013). IPF is slightly more prevalent in men than in women, with a mean age of presentation at 66 years (NICE 2013). Median survival is 2–5 years following diagnosis (Meltzer & Noble, 2008). IPF affects approximately 5 million people worldwide. In Europe, the estimated prevalence of IPF ranges from 1.25 to 23.4 cases per 100,000 persons (Nalysnyk et al., 2012). In Greece, the incidence of IPF has been estimated at 0.9 new cases per 100,000 persons every year (1994-2005) and the prevalence at 3.4 cases per 100,000 persons (Karakatsani et al., 2009).

The progressive nature of the disease in combination with acute exacerbations have been linked to increased morbidity and hospitalizations, resulting insubstantial healthcare resource utilization. Acute exacerbations events contribute to approximately 50% of all IPF related hospital admissions (Yanni et al., 2016), while hospital mortality rate varies from 20% to 100% (Ley et al., 2014). A recently published US observational study documented 234 IPF related hospitalizations within one year at an average cost of $16,812 per stay (Yanni et al., 2016).

Until recently, there was no licensed pharmacologic therapy available for the treatment of IPF and patients were managed by best supportive care (BSC), that included oxygen therapy, opioids, corticosteroids etc. In addition, a minority of patients benefited from lung transplantation, although this treatment option was limited by the availability of donors (Kistler et al., 2014). In 2011 pirfenidone, an oral antifibrotic agent, was approved for the treatment of IPF by the European Medicines Agency. Later,in 2015, nintedanib, an oral inhibitor of tyrosine kinase receptors, was also approved for the treatment of IPF. Pivotal clinical trials have shown that nintedanib and pirfenidone slow the decline in Forced Vital Capacity (FVC), which is the primary efficacy endpoint (Raghu & Selman, 2015). A recent network meta-analysis showed that nintedanib is statistically superior compared to placebo on acute exacerbation events avoided and lung function decline (Rinciog et al., 2017). Furthermore, nintedanib reduces the rate of acute exacerbations (Richeldi et al., 2016).

Both pirfenidone and nintedanib have been designed at an orphan drug status, due to the rarity of the condition, and have been reimbursed by the National Organization for Health Care Services Provision (EOPYY) in Greece since May 20, 2014 and February 16, 2016, respectively.

This study estimates the impact on the budget of EOPYY of reimbursing nintedanib for patients with IPF in Greece along with pirfenidone and standard of care (BSC). Potential cost savings associated with nintedanib were assessed in terms of acute exacerbations avoided compared to currently available treatments.

METHODS AND DATA

We used an incident-based cohort model (Figure 1) (OECD 2016, Karakatsani et al., 2009), following IPF patients on treatment for 5 years (2018 - 2022). Each year, patients on treatment could experience either an acute exacerbation event, a serious adverse event, discontinue treatment or die. Clinical data on mortality and discontinuation rates, acute exacerbations and adverse events rates were derived from three Phase III randomized clinical trials, namely INPULSIS-I & II, (Richeldi et al., 2014), CAPACITY (Noble et al., 2011) and TOMORROW (Richeldi et al., 2011). Due to lack of clinical data directly comparing the efficacy of nintedanib and pirfenidone, a network meta-analysis (NMA) was conducted to estimate the relative effectiveness of the comparators (Rinciog et al., 2017). Parametric model extrapolation was used to estimate mortality and time to acute exacerbations (Rinciog et al., 2017).Once patients discontinued their treatment, they were deemed to BSC. To estimate the budget impact of reimbursing nintedanib in the Greek market, defined as the new drug scenario, we compared its cost to the reference scenario which is a health care environment without nintedanib, that is treatment with pirfenidone and BSC.

Direct reimbursed costs included in the analysis in euros (2018) were drug acquisition costs, cost of managing acute IPF exacerbations and cost of managing adverse events. Both clinical and cost data considered in the analysis were reviewed and validated by a key opinion leader in pulmonology to reflect clinical practice in Greece. Budget Impact Analysis was performed according to Mauskopf (ISPOR) guidelines.

RESULTS

Our analysis estimated that the total number of patients eligible for treatment for IPF during the study period in Greece would be 1,072, 1,478, 1,733 and 1,859 patients in 2018, 2019, 2020 and 2021 respectively, allowing for model specific mortality and discontinuation rates (Table 1). Table 1 assumes a base case IPF patient population in 2018 of 555 patients, calculated on the basis of an annual incidence of 5 cases per 100,000 persons over a population of 11,090,000 people in Greece (OECD, 2016).

To estimate the budget impact of reimbursing nintedanib in the Greek market, defined as the new drug scenario, we compared its cost to the reference scenario, that is treatment with pirfenidone and BSC.

At a Daily Defined Dose (DDD) of 2,403mg/day with cost of €55.26, pirfenidone is slightly cheaper than nintedanib (€57.70), whereas their annual costs were calculated at €21,369.90 and €22,260.50 respectively. BSC cost was calculated at €1,200.00 per patient per annum and includes the cost of one visit to a GP per month and the cost of monthly oxygen therapy (Greek legislated DRGs 2012-2017). The cost of managing diarrhea was estimated

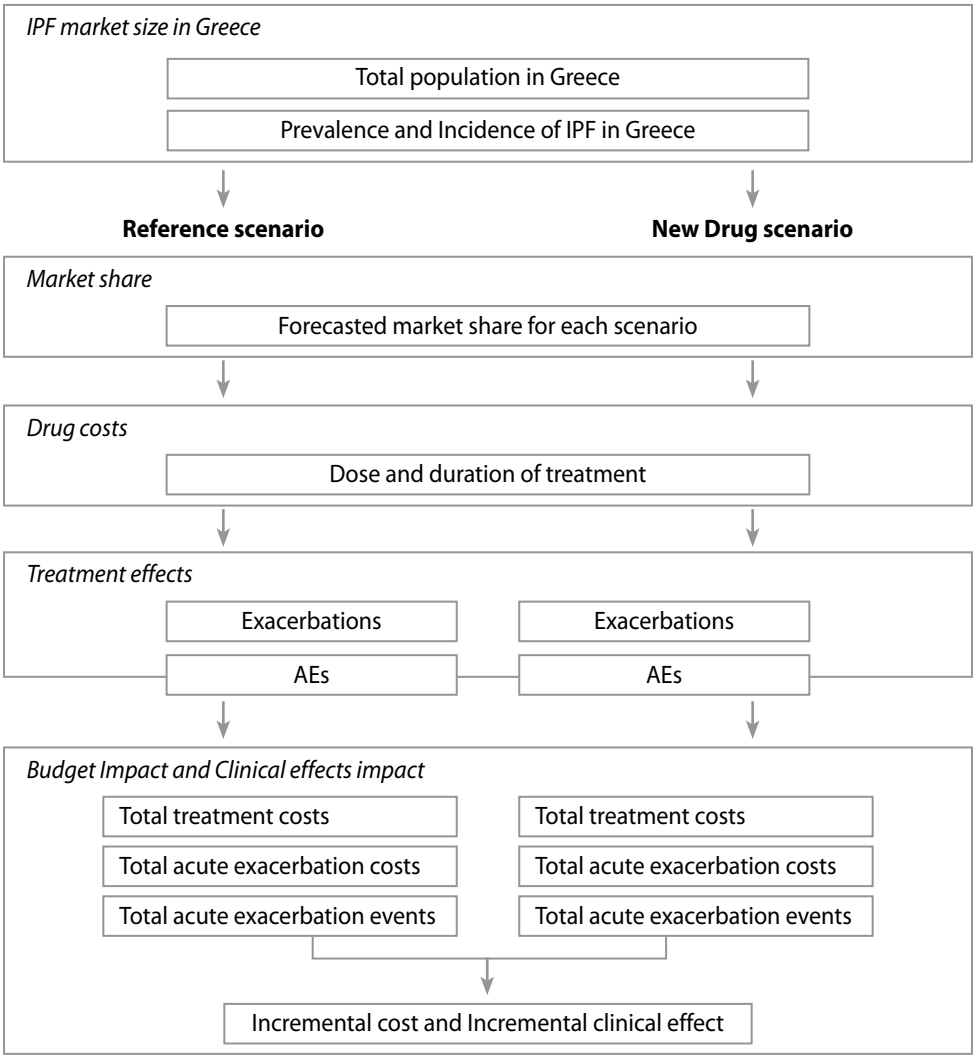

FIGURE 1. Decision model.

TABLE 1. IPF Patient population, 2018 -2022

Years	2018	2019	2020	2021	2022
IPF patient population per year	555	1,072	1,478	1,733	1,859

at €37.50 per patient per annum and is reimbursed by EOPYY for chronic diarrhea only. The cost of managing an acute exacerbation event was calculated on the basis of the diagnosis related group (DRG) code assigned for the management of acute IPF exacerbations by our expert (A24X), which refers to cases of respiratory edema and failure. Cost input data are presented in Table 2.

In order to calculate the impact on the budget of EOPYY across the insured population we estimated current and future market share of available treatment options. As a base case scenario, expert view confirmed that the market share of pirfenidone ranges at 75% and of BSC at 25% for the 2018 starting year of the BIA. This estimate may be modified upon the reimbursement of nintedanib as shown in Figure 2 (Bouros D.).

Market share assumptions for each scenario during the 5-year period were deemed as realistic by expert view despite assuming an increasing uptake for nintedanib, primarily because IPF is an orphan disease with limited available treatment options and nintedanib has a favorable safety and effectiveness profile.

The annual direct cost to EOPYY of reimbursing the two treatments on the basis of the market shares detailed

TABLE 2. Cost inputs supplied by expert and used in the Budget Impact Analysis

Type of costs	Unit costs (€)	Source
Treatment costs		
Pirfenidone	55.26/day	Hospital Price minus 5% based on current legislation and official price list: Price list May 2018 http://www.moh.gov.gr/articles/times-farmakwn/deltia-timwn/5546-deltio-timwn-farmakwn-anthrwpinhs-xrhshs-maioy-2018-11062018 Pricing legislation: ΦΕΚ 445/B/15.02.2017 – Διατάξεις Τιμολόγησης (accessed: October 2018)
Nintedanib	57.70/day	
BSC	100/month	Expert's opinion http://www.moh.gov.gr, http://www.eopyy.gov.gr (accessed: December 2015)
Management of adverse events		
Chronic diarrhea drug	3.29/event	Expert's opinion http://www.moh.gov.gr (accessed: December 2015)
Management of acute exacerbation event costs		
Acute exacerbation event	863/event	Expert's opinion: Code A24X http://www.moh.gov.gr (accessed: December 2015)

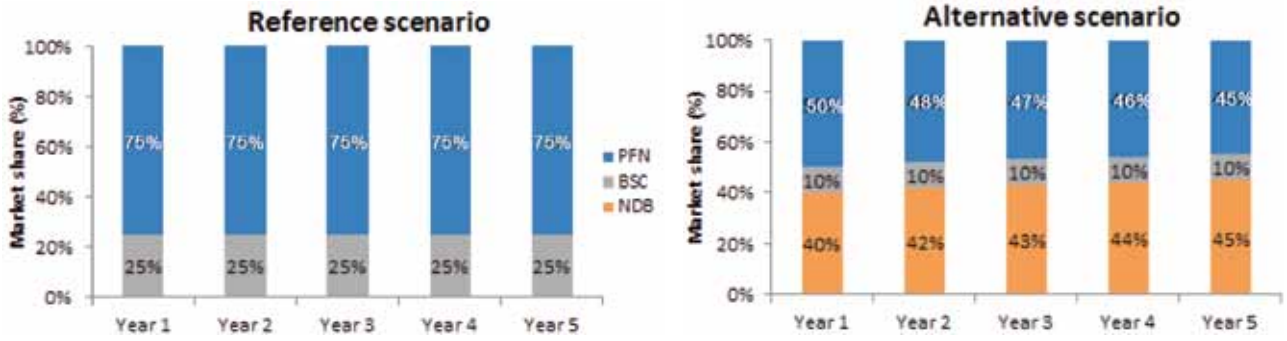

FIGURE 2. Current and new scenario market shares, 2018 -2022.

on Figure 2 is depicted on Table 3.

Table 3 depicts the estimated addition to EOPYY budget of just over €1.5 million in 2018, almost €2.3 million in 2019, €2.6 million in 2020, €2.6 million in 2021 and almost €2.5 million in 2022 when comparing the new scenario (with nintedanib) to the reference scenario (without

TABLE 3. Annual direct budget impact on EOPYY of adding nintedanib to current IPF treatment (current versus new scenario), 2018-2020

		2018	2019	2020	2021	2022
Current scenario	BSC	€ 169.873	€ 317.420	€ 433.659	€ 521.838	€ 588.628
	Nintedanib	€ -	€ -	€ -	€ -	€ -
	Pirfenidone	€ 8.324.693	€ 14.805.840	€ 19.453.637	€ 22.660.487	€ 24.854.822
	Total	€ 8.494.566	€ 15.123.260	€ 19.887.296	€ 23.182.325	€ 25.443.450
New scenario	BSC	€ 67.949	€ 126.968	€ 173.463	€ 208.735	€ 235.451
	Nintedanib	€ 4.414.735	€ 7.673.370	€ 9.869.032	€ 11.342.480	€ 12.368.957
	Pirfenidone	€ 5.549.796	€ 9.648.568	€ 12.463.273	€ 14.279.821	€ 15.397.813
	Total	€ 10.032.480	€ 17.448.906	€ 22.505.769	€ 25.831.036	€ 28.002.222
Impact on EOPYY Budget		€ 1.537.914	€ 2.325.646	€ 2.618.473	€ 2.648.711	€ 2.558.771

nintedanib). This equals an addition of just over 0.08% of total pharmaceutical expenditure for 2018, almost 0.12% in 2019, 0.13% in 2020, 0.13% in 2021 and 0.13% in 2022.

The model also estimated the impact of reimbursing nintedanib on reducing healthcare resource use as a result of preventing acute exacerbation events. According to our results, use of nintedanib was associated with a higher number of acute exacerbation events being avoided compared to the reference scenario (Table 4). More specifically, acute exacerbation events following the introduction of nintedanib were reduced by 18 events over the 5-year study period compared to the reference scenario.

DISCUSSION

IPF is a debilitating chronic disease with a high mortality rate. Nintedanib is a novel treatment option that offers significant clinical benefits to the patients with IPF (Fala, 2015). Management of IPF poses a substantial economic burden on healthcare systems. Resources spent on managing IPF should be yielding optimal return. This is especially critical in countries faced with the persistent challenge of an economic crisis. This is the first study to assess the impact on the budget of EOPYY of reimbursing a new therapy for the treatment of IPF in Greece.

The budget impact of reimbursing nintedanib as part of already available treatment options (pirfenidone and BSC) increasing from approximately €1.5 million in 2018 to €2.5 million in 2022, which corresponds to a maximum of 0.13% of annual total pharmaceutical expenditure. Therefore, reimbursement of nintedanib has a relatively low impact on the budget of EOPYY. Furthermore, the model estimated that a significant number of acute exacerbation events would be averted during the study period when on treatment with the new scenario versus the current scenario, thus providing additional cost savings to the NHS – and EOPYY, which reimburses hospital care for its insured population.

This is the first study that estimates the impact on the budget of EOPYY of reimbursing a new treatment for IPF. Our study findings may underestimate the actual savings of introducing nintedanib for the treatment of IPF, as it only assesses the economic impact of averting one type of adverse event, diarrhea. In addition, other studies (Yanni et al., 2016) have suggested that the majority of patients experiencing acute exacerbation are treated in outpatient settings, an assumption that has been deemed less valid in our setting by our expert and thus excluded from the analysis. The use of a DRG for calculating the cost of an acute exacerbation event may be arbitrary, as it excludes potential comorbidities that would be managed and charged under a different (additional) DRG. In actual fact, evidence suggests that more than 60% of patients with IPF have between 1 and 3 co-morbidities such as arterial hypertension, diastolic dysfunction and diabetes (Kreuter et al., 2016). Such data could not be validated on the basis of a model scenario or through an expert consultation and would require real-life patient data (such as from a disease registry or observational study) to fully capture, correctly assess and report on the impact of comorbidities on overall acute exacerbation cost and the savings to the NHS and social insurance by averting such events.

CONCLUSION

The management of patients with IPF remains a significant challenge in respiratory medicine. Nintedanib is an innovative therapy for the treatment of IPF, the reimbursement of which has a relative low impact on EOPYY budget, whilst saving healthcare resources related to management of acute exacerbation events for the Greek NHS. Data from a real-world patient registry

TABLE 4. Reduction in acute exacerbation events following reimbursement of nintedanib, 2018-2022

	2018	2019	2020	2021	2022
Number of IPF Patients per year, 2018-2022					
Current scenario	555	1,069	1,468	1,712	1,828
New scenario	555	1,071	1,474	1,725	1,847
Acute exacerbation events per year, 2018-2022					
Current scenario	32	61	84	102	116
New scenario	24	47	67	83	96
Acute exacerbation events averted	8	13	17	19	20
Cost of managing acute exacerbation events (averted)	€ (6,904)	€ (11,219)	€ (14,671)	€ (16,397)	€ (17,260)

would allow a more accurate representation of both clinical benefit and resource use associated with either nintedanib or pirfenidone and BSC, and provide evidence based knowledge on the impact of such decision making on the budget of EOPYY.

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DECLARATION OF INTEREST

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

ΠΕΡΙΛΗΨΗ

Εκτίμηση της οικονομικής επίπτωσης της νιντεδανίμπης για τη θεραπεία της ιδιοπαθούς πνευμονικής ίνωσης στο ελληνικό σύστημα υγείας

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Η ιδιοπαθής πνευμονική ίνωση (ΙΠΙ), είναι μια σπάνια, χρόνια ασθένεια των πνευμόνων, με υψηλό δείκτη θνησιμότητας. Η ΙΠΙ επηρεάζει περίπου 5 εκατομμύρια άτομα παγκοσμίως, με τη μέση επιβίωση να κυμαίνεται από 2 έως 5 έτη μετά τη διάγνωση. Μέχρι πρόσφατα δεν υπήρχε διαθέσιμη εγκεκριμένη θεραπεία για την ΙΠΙ και η διαχείριση των ασθενών ήταν κατά βάση υποστηρικτική και περιελάμβανε αγωγή με πιρφενιδόνη. Η μελέτη αυτή εκτιμά την επίπτωση της αποζημίωσης της νιντεδανίμπης, η οποία εγκρίθηκε το 2015 για τη θεραπεία της ΙΠΙ, στον προϋπολογισμό του Εθνικού Οργανισμού Παροχής Υπηρεσιών Υγείας (ΕΟΠΠΥ). Η επίπτωση αυτή αντιστοιχεί κατά μέγιστο σε 0,13% της συνολικής ετήσιας φαρμακευτικής δαπάνης του Οργανισμού και θεωρείται σχετικά χαμηλή, ενώ η χρήση της νιντεδανίμπης έχει συσχετιστεί με μείωση του αριθμού των περιστατικών οξείας παρόξυνσης, εξοικονομώντας πόρους για το σύστημα υγείας.

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Λέξεις - Κλειδιά: *Ιδιοπαθής πνευμονική ίνωση, θεραπεία, αποζημίωση, επίπτωση στον προϋπολογισμό*

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