IS IT POSSIBLE TO ACCELERATE THE ACCESS OF PATIENTS WITH RARE DISEASES TO NEW THERAPY – THE CASE WITH IPF MEDICINES

Elka Boncheva[1,2], Tatyana Benisheva[1,2], Daniela Cherneva[1,2]

[1]Medical University - Sofia, Bulgaria, Faculty of Public Health,
[2]Bulgarian Association for Drug Information www.badibg.org

OBJECTIVES

Health technology assessment (HTA) as multidisciplinary process of evaluation of the social, economic, organizational and ethical issues of a health technology is used within the decision-making processes concerning reimbursement of new molecules. It is also applied for orphan drugs in Germany, France, UK and Bulgaria. Two orphan molecules (at the time of HTA assessment) Pirfenidone and Nintedanib - indicated for treatment of Idiopathic Pulmonary Fibrosis (IPF) have been HTA assessed and reimbursed in all four countries.

METHODS

1. Documentary method - Review and comparative analysis of the HTA recommendations of Pirfenidone and Nintedanib in Bulgaria - NCPHA, United Kingdom - NICE, France - HAS, and Germany - IQWIG.
2. Analytical method - clinical evidence, comparators and pharmaco-economic parameters were evaluated and reimbursement status in the selected countries was analyzed.

OVERVIEW

HTA of medicines is used within the decision making processes for reimbursement of new molecules which is also applied for orphan drugs. At the time of introducing of HTA in Bulgaria in 2015 a negative HTA opinion/statement issued in Germany, France and UK was a barrier for starting the HTA assessment. As of April, 2019 the positive HTA opinion from Germany, France, UK or Sweden is required for new molecules to receive reimbursement. This requirement is also valid for orphan drugs used for the treatment of rare diseases. On-time patients' access to treatment of rare diseases depends on requirements and time for evaluation by the health authorities.

RESULTS

- In all 4 surveyed countries (100%) Pirfenidone and Nintedanib have positive HTA assessment (Table 3).
- In 90% of the countries the products are 100% reimbursed except France where the reimbursement is 30% (Table 2).
- In 50% countries (UK and Germany) treatment with Pirfenidone is compared with best supportive care only. In UK and Bulgaria for Nintedanib the best supportive care and Pirfenidone have been used as relevant comparators (Table 3).
- The added benefit has been evaluated based on the same clinical studies in all 4 (100%) countries (Table 3).
- Only in Germany according to the local legislation, an added benefit of orphan drugs was deemed as proven by the granted EU marketing authorisation (Table 3).
- Identical recommendation of all HTA Bodies are listed for the two products (Table 3).
- Patients have access to the treatment within 1 to 5 years after granting the marketing authorisation by European Commission (Tables 1 and 2).

Table 1. Pirfenidone and Nintedanib – general information

	Pirfenidone	Nintedanib
Marketing Authorisation Holder	Roche Registration GmbH, Germany	Boehringer Ingelheim International GmbH, Germany
Indication	Indicated in adults for the treatment of mild to moderate IPF	Indicated in adults for the treatment of IPF
Marketing Authorisation granted on	28 Feb 2011	15 Jan 2015
Related orphan designation	Orphan market exclusivity for "Treatment of IPF"	Orphan market exclusivity for "Treatment of IPF"
Orphan designation from	16 Nov 2004	26 Apr 2013
10 years Orphan market exclusivity started on	02 Mar 2011	19 Jan 2015
Market exclusivity expire on	02 Mar 2021	25 May 2020*

*Withdrawn from the Community register of designated orphan medicinal products on request of the marketing authorisation holder at the time of the granting of a change to the terms of the marketing authorisation.

CONCLUSIONS

1. The results of the review show that patient access to treatment options depends on the Marketing Authorisation Holder despite products' Orphan designation.
2. In all of the reviewed countries (100%) treatment of IPF with Pirfenidone and Nintedanib is paid by the local health fund.
3. The data analysis and recommendations can be used for reassessment the need from clinical review within the HTA process for orphan drugs in each EU country –
4. The patient access to orphan medicines would be shorter, if there was a mutual recognition of the HTA-clinical benefit evaluation among the EU countries.
5. The results supports the proposals for a new EU HTA regulation – reducing duplication of work for health authorities and industries.
6. In terms of faster patients' access to treatment of rare diseases exceptions from HTA requirements for reimbursement of new molecules could be applied and proposed as update of the BG legislation.

References

1. Union Register of medicinal products for human use. https://ec.europa.eu/health/documents/community-register/html/index_en.htm (access date 01/08/2020)
2. Ordinance № 9 from 1 December 2015 for the conditions and rules of the HTA assessment, SG no. 97 from 11December 2015 https://dv.parliament.bg/DVWeb/showMaterialDV.jsp?idMat=99208 (access date 10/09/2020)
3. Ordinance on the Terms, Rules and Procedure for Regulation and Registration of Prices for Medicinal Products, SG no. 40 from 30 April 2013, last changes and amend. SG no. 19 from 6 March 2020 https://www.ncpr.bg/images/Naredbi/2020/10.03.2020/%D0%9D%D0%90%D0%A0%D0%95%D0%94%D0%91%D0%90_%D0%97%D0%90_%D0%A3%D0%A1%D0%9B%D0%9E%D0%92%D0%98%D0%AF%D0%A2%D0%90_%D0%9F%D0%A0%D0%90%D0%92%D0%98%D0%9B%D0%90%D0%A2%D0%90_%D0%98_%D0%A0%D0%95%D0%94%D0%90_%D0%97%D0%90_%D0%A0%D0%95%D0%93%D0%A3%D0%9B%D0%98%D0%A0%D0%90_compressed.pdf (access date 10/09/2020)

Table 2. Time of HTA evaluation for Pirfenidone and Nintedanib

	Pirfenidone	Nintedanib
Bulgaria		
decision from	19 July 2017	13 December 2016
reimbursement	100 %	100 %
available on	http://www.ncphp.government.bg/index.php?option=com_content&view=article&id=1840&catid=369&Itemid=638&lang=bg	http://www.ncphp.government.bg/index.php?option=com_content&view=article&id=1743&catid=369&Itemid=638&lang=bg
UK		
decision from	24 April 2013/ 06 February 2018 updated	27 January 2016
reimbursement	100 %	100 %
available on	https://www.nice.org.uk/guidance/ta504	https://www.nice.org.uk/guidance/ta379
France		
decision from	18 February 2015	20 May 2015
reimbursement	30 %	30 %
available on	https://www.has-sante.fr/portail/jcms/c_2023166/fr/esbriet-pirfenidone-immunosuppresseur	https://www.has-sante.fr/portail/jcms/c_2038122/fr/ofev-nintedanib-inhibiteur-des-tyrosines-kinases
Germany		
decision from	15 March 2012	03 September 2015/ 17 October 2019 reassessment
reimbursement	100 %	100 %
available on	https://www.iqwig.de/en/projects-results/projects/drug-assessment/a11-18-pirfenidone-benefit-assessment-according-to-35a-social-code-book-v-dossier-assessment.1426.html	https://www.iqwig.de/en/projects-results/projects/health-economic/g15-03-nintedanib-assessment-according-to-35a-para-1-sentence-10-social-code-book-v-dossier-assessment.6640.html https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/2019/a19-64-nintedanib-idiopathische-lungenfibrose-addendum-zum-auftrag-a19-36.12511.html

Table 3. HTA recommendation for Pirfenidone and Nintedanib

	Pirfenidone	Nintedanib
Bulgaria		
comparators	Nintedanib	Pirfenidone and best supportive care
clinical trials	Data from ASCEND, CAPACITY (1&2)	Data from INPULSIS, CAPACITY, ASCEND
recommendation	The product can be submitted for reimbursement but under certain conditions, namely compliance with the NICE criteria for inclusion and continuation of drug treatment in patients with IPF.	
UK		
comparators	The committee therefore agreed it was more appropriate to compare pirfenidone with best supportive care and it did not consider the comparison with nintedanib further.	Nintedanib had different comparators (either pirfenidone or best supportive care) for different subgroups according to percent predicted FVC.
clinical trials	Phase III trials (CAPACITY 1 and 2, ASCEND and SP3) and other observational data	Phase III trials INPULSIS 1 and 2 and a phase IIb dose-ranging trial TOMORROW
recommendation	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 drug 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).	
France		
comparators	Two strategies are compared: treatment with pirfenidone and management without drug treatment outside exacerbation period (supportive treatment).	In the treatment of mild to moderate IPF, pirfenidone is the relevant comparator. There is no comparator in the treatment of severe IPF.
clinical trials	Data from ASCEND, CAPACITY (1&2), RECAP	Data from INPULSIS 1 and 2, TOMORROW 1 and 2, also supplemented by their respective follow-up studies
recommendation	The Commission is in favor of maintaining the inclusion in the list of reimbursable specialties for the insured persons and on the list of approved specialties for community use at MDA dosages in patients with confirmed clinical, radiological and / or histopathological diagnosis of IPF disease, who do not consume tobacco and with the criteria respiratory function: FVC ≥ 50% and DLco ≥ 30%.	
Germany		
comparators	The assessment was based on the comparison of pirfenidone combined with best supportive care (pirfenidone/BSC) with treatment consisting of best supportive care alone (placebo/BSC)	The Pirfenidone has been used as comparator at the time of first assessment. Appropriate comparator therapy for the reassessment: Pirfenidone (only for patients with mild to moderate idiopathic pulmonary fibrosis according to marketing authorisation) or best supportive care.
clinical trials	data from CAPACITY (1&2)	data from INPULSIS (1&2)
recommendation	In accordance with § 35a (para. 1, sentence 10) Social Code Book V, the added medical benefit of orphan drugs is deemed as proven by the fact that they have been approved. Reassessment of an orphan drug after exceeding the € 50 million limit required.	
	The extent of the added benefit is classed as "no proven added benefit".	The extent of the added benefit is classed as "little added benefit". After the reassessment: Hint for a considerable additional benefit compared with best supportive care.