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Health Technology Assessment: Choices That Must Be Made for Reviewing the Evidence - The Cyprus Perspective

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Abstract

A Health Technology Assessment agency should make a choice whether to review the evidence produced elsewhere or whether evidence is to be produced within the agency and then used to reach a decision. The small size of Cyprus with limited resources should be considered in order to draw the most appropriate conclusion, with regard to the evidence production by the newly established agency. This project analyzes at which point in time Cyprus makes the decision to integrate new high cost medicines into the Formulary of Hospital Drugs, in relation to the time of publication of decisions, taken by the Health Technology Assessment agencies in England and Wales, Scotland and Ireland, for the inclusion of the same medicines and for the same indication, in their national health systems. The review of evidence produced elsewhere would be feasible for Cyprus, as opposition to the production of evidence being undertaken by the new agency, in the case where the other agencies would have already produced evidence before the Cyprus Authority starts reviewing them.

Keywords

Health Technology Assessment, Reviewing of Evidence, Cyprus

1. Introduction

Health Technology Assessment (HTA) is undertaken to inform decisions and it will and should inform a wider vary of choices than simply those for reimbursement at the time of launch. It also can inform early decisions regarding whether or not to pursue development of a technology and later decisions in clinical practice and health service organization regarding how best to adopt a technology and optimize its use [1]. It ought to ensure that challenges in treating patients, evidence production, and technology use are understood and expectations are aligned to form realistic evidence requirements [2, 3]. This implies that HTA moves from merely being a passive assessment to additionally being a vigorous help of dialogue that informs evidence production, evidence-based decision making, and optimum technology use within the health system throughout the life cycle of the technology [4].

A HTA unit reviews the evidence with multiple sources either from within the unit or from external sources elsewhere. The "right" evidence is a determining factor for making the optimal decision for each country for the introduction of a new technology to the national health system [5]. As there are various national HTA models and practices, it becomes obvious that the variety in the approaches employed for the reviewing of evidence in the various HTA bodies across the Member States (MS) is vast and diverse. There are MS where evidence is produced

(collected and analysed) and reviewed within the HTA body and there are MS where the evidence is obtained from external sources outside of the agency, for example the pharmaceutical industry or other HTA agencies in other countries [6]. One of the main choices that must be made pertaining to the assessment by the HTA unit is whether to review the evidence produced elsewhere or whether evidence is to be produced independently and then used to reach a decision.

The implementation of a HTA system in Cyprus aims firstly to integrate cost-effective new technologies to the anticipated health system, secondly, to prevent the adoption of any disputed technologies and, thirdly, to accelerate access to innovative treatments for patients in need [7, 8]. However, in order to draw the most appropriate conclusion, with regard to the evidence production by the newly established agency, or not, the small size of Cyprus with limited financial, physical and human resources should be considered. It is a fact that every country regardless of how big or small, how wealthy or needy, with well equipped HTA unit or not, should respond adequately to the same requirements for the evidence production, since the number of emerging technologies every year is the same for all MS [9].

This study analyzes at which point in time, Cyprus makes the decision to integrate new high cost medicines into the Formulary of Hospital Drugs, in relation to the time of publication of decisions, taken by the HTA agencies in England and Wales, Scotland and Ireland, for the inclusion of the same medicines and for the same indication, in their national health systems. The review of evidence produced elsewhere would be feasible for Cyprus, as opposition to the production of evidence being undertaken by the anticipated HTA agency, in the case where the other HTA agencies would have already produced evidence before the Cyprus Authority starts reviewing them.

2. Material and Methods

2.1. Data Collection

Data were gathered from internal and external sources. Inner sources incorporated secondary data from the Clinical Pharmacy Department of the Pharmaceutical Services of the Ministry of Health and from the electronic version of the Formulary of Hospital Drugs as it is available at the official website of the Pharmaceutical Services of the Ministry of Health Cyprus, for the public sector healthcare professionals. External Data were collected from the following three agencies: 1) National Institute for Health and Care Excellence (NICE), 2) Scottish Medicines Consortium (SMC) and 3) National Centre for Pharmacoeconomics Ireland (NCPE); the Cyprus Authority is currently collecting some information from these agencies for the decision making to integrate new high cost medicines into the Cyprus Health System. The following official websites of NICE, SMC and NCPE have been used for the data collection.

NICE: http://www.nice.org.uk/GuidanceMenu/Conditions-and-diseases

SMC: https://www.scottishmedicines.org.uk/Home

NCPE: http://www.ncpe.ie

2.2. Methodology

They were identified and analyzed 38 new high-cost medicines, with annual budget impact not less than €100,000.00, pertaining to the time of publication of the decision that was taken from the Cyprus Authority, for the inclusion of these drugs for a specific indication (specific therapeutic use), in the Formulary of Hospital Drugs, during the period from July 2017 to August 2018. Table 1 shows the date of decision for the inclusion of the 38 pharmaceutical products in the Formulary of Hospital Drugs, for a specific indication, during the period from July 2017 to August 2018.

Table 1. *Date of decision for the inclusion of 38 high cost pharmaceutical products in the Formulary of Hospital Drugs, for a specific indication, during the period from July 2017 to August 2018.*

a/a	Pharmaceutical Product	Indication	Date of decision
1	Ibrutinib	Chronic Lymphocytic Leukemia	7/2017
2	Vemurafenib - Cobimetinib	As a 1st line treatment in a patient with metastatic melanoma	7/2017
3	Radium 223	To treat symptomatic patients pretreated with docetaxel and only with bone metastases	9/2017
4	Nicolumab	As a 2nd line treatment for treating metastatic kidney cancer	9/2017
5	Erlotinib	As a 1st line treatment for NSCLC (Non Small Cell Lung Cancer) with positive mutations in the EGFR gene based on criteria	12/2017
6	Osimertinib	In patients with NSCLC and a positive T790M mutation in the epidermal EGFR growth factor receptor based on criteria	12/2017
7	Pembrolizumab	As a 1st line treatment in patients with NSCLC and positive PD-L≥50% tumor expression, regardless of tumor histology (squamous / non-squamous)	12/2017
8	Pemetrexed	As maintenance treatment in patients with adenocarcinoma or large cell cancer	12/2017
9	Pembrolizumab	As a 2nd line treatment for cases with squamous non-small cell lung cancer and PD-L≥ 1% based on criteria	12/2017
10	Nivolumab	As a 2nd line treatment for cases with non-squamous, non-small cell lung cancer and PDL <1% based on criteria	12/2017
11	Atezolizumab	As a 2nd line treatment for cases with non-squamous, non-small cell lung cancer and PDL <1% based on criteria	12/2017
12	Kovaltry	For patients with haemophilia A '	2/2018
13	Radium 223	For prostate cancer	2/2018
14	Ventolizumab	As a 3rd line treatment in patients with ulcerative colitis	2/2018
15	Ustekinumab	As a 3rd-line treatment in patients with Crohn's disease	2/2018

a/a	Pharmaceutical Product	Indication	Date of decision
16	Bevacizumab	As an initial treatment for cases with epithelial cervical cancer in combination with chemotherapy	3/2018
17	Nab paclitaxel	For the treatment of patients with pancreatic adenocarcinoma and its administration based on criteria	3/2018
18	Parecoxib	To treat post-operative pain	3/2018
19	Lanreotide	For the treatment of patients with neuroendocrine tumors	3/2018
20	Regorafenib	As a 3rd line treatment for colorectal cancer	4/2018
21	Bevacizumab	As initial treatment in ovarian cancer, ovarian cancer or primary peritoneal cancer	4/2018
22	Trastuzumab emtansine	As monotherapy with a Human Epidermal Growth Factor Receptor 2 (HER2), breast cancer	4/2018
23	Palbociclib	In combination with aromatase inhibitors for the treatment of postmenopausal women with negative HER2 locally advanced or metastatic breast cancer as initial endocrine therapy.	4/2018
24	Ribobiclib	In combination with aromatase inhibitors for the treatment of postmenopausal women with negative HER2 locally advanced or metastatic breast cancer as initial endocrine therapy.	4/2018
25	Trastuzumab (subcutaneous)	In patients with metastatic or early breast cancer	4/2018
26	HPV vaccination	Protects against nine HPV strains (Human Papilloma Virus)	4/2018
27	Glatiramer	For Multiple Sclerosis	8/2018
28	Dimethyl fumarate	1st line treatment for Multiple Sclerosis	8/2018
29	Fampridine	Adjuvant treatment of multiple sclerosis	8/2018
30	Ocrelizumab	3rd line treatment for multiple sclerosis	8/2018
31	Nivolumab	As 2nd or 3rd line treatment for kidney cancer	8/2018
32	Cabozantinib	As 2nd or 3rd line treatment for kidney cancer	8/2018
33	Baricitinib	For Rheumatoid Arthritis	8/2018
34	Tofacitinib	For Rheumatoid Arthritis	8/2018
35	Lenalidomide	For Multiple Myeloma	8/2018
36	Carflilzomide	For Multiple Myeloma	8/2018
37	Pomalidomide	For Multiple Myeloma	8/2018
38	Daratimumab	For Multiple Myeloma	8/2018

Subsequently the time of the publication of the decision of each of the three agencies, NICE, SMC, NCPE, has been recorded, for the inclusion or not of these 38 medicines, for the same indications, in the health systems of England and Wales, Scotland and Ireland, respectively, as listed in Table 2.

Table 2. *Publication date of the decision for the inclusion of the identified 38 high-cost pharmaceutical products, with the same indication, in the health systems of England and Wales, Scotland and Ireland through their agencies.*

a/a	Pharmaceutical Product	Date of decision for the inclusion in the Cyprus National Formulary	Publication date		
			NICE	SMC	NCPE
1	Ibrutinib	7/2017	3/2017	6/2017	8/2016
2	Vemurafenib- Cobimetinib	7/2017	10/2016	9/2016	4/2016
3	Radium 223	9/2017	9/2016	10/2015	12/2015
4	Nivolumab	9/2017	11/2016	6/2017	4/2016
5	Erlotinib	12/2017	4/2014	1/2012	-
6	Osimertinib	12/2017	10/2016	2/2017	8/2018
7	Pembrolizumab	12/2017	7/2017	7/2017	1/2017
8	Pemetrexed	12/2017	8/2016	12/2014	-
9	Pembrolizumab	12/2017	9/2017	1/2017	-
10	Nivolumab	12/2017	1/2017	7/2016	-
11	Atezolizumab	12/2017	5/2018	8/2018	-
12	Kovaltry	2/2018	-	-	-
13	Radium 223	2/2018	9/2016	10/2015	12/2014
14	Ventolizumab	2/2018	6/2015	5/2015	11/2015
15	Ustekinumab	2/2018	7/2017	7/2017	1/2017
16	Bevacizumab	3/2018	5/2013	5/2016	-
17	Nab paclitaxel	3/2018	9/2017	2/2015	3/2014
18	Parecoxib	3/2018	-	-	-
19	Lanreotide	3/2018	8/2018	-	-
20	Regorafenib	4/2018	-	-	-
21	Bevacizumab	4/2018	8/2015	9/2017	-
22	Trastuzumab emtansine	4/2018	7/2017	4/2017	12/2015
23	Palbociclib	4/2018	12/2017	12/2017	7/2017
24	Ribobiclib	4/2018	12/2016	12/2016	5/2016
25	Trastuzumab (subcutaneous pr)	4/2018	3/2013	1/2014	-
26	HPV vaccination (9 str)	4/2018	-	-	-
27	Glatiramer	8/2018	6/2018	12/2015	-
28	Dimethyl fumarate	8/2018	8/2014	4/2014	1/2015
29	Fampridine	8/2018	-	11/2016	-

a/a	Pharmaceutical Product	Date of decision for the inclusion in the Cyprus National Formulary	Publication date		
30	Ocrelizumab	8/2018	8/2018	8/2018	12/2017
31	Nivolumab	8/2018	11/2016	6/2017	10/2016
32	Cabozantinib	8/2018	8/2017	7/2017	7/2017
33	Baricitinib	8/2018	8/2017	9/2017	7/2017
34	Tofacitinib	8/2018	10/2017	2/2018	-
35	Lenalidomide	8/2018	-	-	-
36	Carflilzomide	8/2018	7/2017	2/2017	10/2016
37	Pomalidomide	8/2018	1/2017	2/2014	3/2015
38	Daratimumab	8/2018	3/2018	5/2017	3/2017

3. Results

The results revealed that from the total of 38 pharmaceutical products 31 (81.6%) have been analyzed from at least one of the three agencies and the relevant decision have been published, before Cyprus took any decision for the inclusion or not of the same medicines and for the same indications in the Formulary of Hospital Drugs. The time of publication of decisions taken by these three HTA agencies varies from one to 71 months before Cyprus took any decision. From these 31 pharmaceutical products 17 (54.8%), were analyzed by all three agencies NICE, SMC and NCPE and subsequently their decisions have been published before the Cyprus Authority took any decision for the inclusion or not of these medicines in the Formulary of Hospital Drugs.

From the total of 38 pharmaceutical products 5 (12.8%), have not been analyzed from any HTA agency before the Cyprus Authority took any decision for the inclusion of these medicines or not in the Formulary of Hospital Drugs.

From the total of 38 pharmaceutical produces only 2 (5.26%), have been analyzed from the Cyprus Authority before any other HTA agency took any decision for the inclusion or not of these medicines in their health systems.

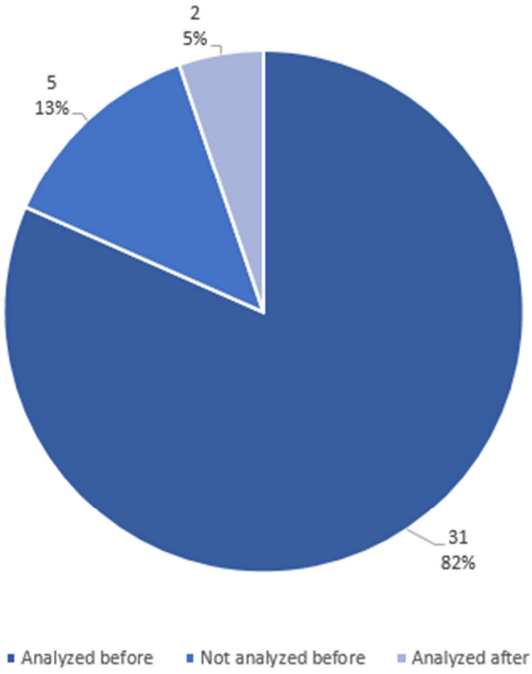

Figure 1. *Distribution of high cost medicnes according to the time of publication of the decision from the three external agencies and Cyprus.*

Figure 1 shows the distribution of the high cost medicines according to the time of publication of the decision.

4. Discussion

This study analyses at which point in time, Cyprus makes the decision to integrate new high cost medicines into the Formulary of Hospital Drugs during the period from July 2017 to August 2018, in relation to the time of publication of decisions taken by NICE, SMC and NCPE for the inclusion or not of the same medicines and for the same indication, in the health systems of England and Wales, Scotland and Ireland respectively.

It can be seen, that for the majority of the above 38 new high cost medicines, the decisions taken by the HTA agencies, NICE, SMC and NCPE, for their inclusion in the health systems of England and Wales, Scotland and Ireland respectively, have been published before the Cyprus Authority took any decision for the inclusion of these medicines, or not, in the Formulary of Hospital Drugs.

The SMC does not review evidence on clinical effectiveness and does not undertake economic evaluations independently but instead makes use of 'ready-made' information provided by the pharmaceutical industry [10, 11]. This is also the case with the NICE for the Single Technology Appraisals which covers a single technology for a single indication, where the Evidence Review Group reviews the evidence synthesis submitted by industry. This review may also include comparative studies with alternative therapies used in the clinic [11]. However, in the case of Multiple Technology Appraisals which covers more than one technology or one technology for more than one indication, the NICE undertakes an independent review of clinical effectiveness. For the economic evaluation, the NICE does not produce the evidence itself but sub contracts this activity to other independent bodies, for example, university teams [12, 13]. The NCPE assess evidence, submitted by the industry and independent systematic reviews, for comparative effectiveness and cost effectiveness of high cost medicines in Ireland. It is obligatory for the industry to submit evidence as part of the technology assessment [14].

The HTA outcome has the same characteristic of public goods, that is both non-rivalry and non-excludable. This means that a HTA agency could produce and review evidence and this evidence could then be further utilized by others, without any limitations [7]. At the same time, owing to the

transparency of the efforts, all the agencies enjoy the benefits which arise from the use of a single HTA evaluation and its accompanying outcome [15, 8]. It is not the final decisions based on HTAs that have characteristic of the public goods but the evidence and the exploration of the evidence assessment for decision making that is non-rival and non-excludable. Consequently, Cyprus could use the "readymade" information of evidence from various HTA agencies or from industry as an input to decision-making, avoiding the need to undertake any resource intensive HTA evaluations.

The difference between the reviewing evidence produced elsewhere as an input to the decision making and the undertaking the collection and analysis of data and then used to make the decision is huge [3]. The main advantage of the evidence gathering process, is that is less costly, is faster and does not require specialized personnel. Nevertheless, there are several drawbacks as the evidence produced by another HTA body may not be aligned and applicable with the Cyprus reality. Furthermore the gathering of the information from various agencies may cause heterogeneity, within the data sets and even with the decisions, and this entails a burden for the final decision process [16]. Finally, the mere collection of "ready-made" information from other HTA bodies may discourage staff from being creative and further develop their skills.

5. Conclusion

The challenge of this study was whether the publications of the HTA decisions in England and Wales, Scotland and Ireland for the inclusion of high-cost innovative drugs in their health systems, taken earlier in time than of the time of decisions taken by the Cyprus Authority to introduce the same medicines and for the same indication in the Formulary of Hospital Drugs. If this is the case, Cyprus and the new HTA agency should take advantage of the "ready-made" information to accelerate the access of the right medicines to the system.

This case study supports the view that Cyprus could review evidence from other HTA agencies without having to produce them and align them with the Cyprus reality. Therefore, the small size of Cyprus with limited financial, physical and human resources should be considered. Cyprus as a small country, without a well defined health system, with limited experience and limited access to useful and essential data sources, due to the absence of an integrated national health system, seems to be unable to meet the requirements for effective gathering of evidence. Moreover, the anticipated HTA agency should respond appropriately and in the best possible way to provide information, from which to draw conclusions for the inclusion or not of new technology in the upcoming health system. It seems that by reviewing evidence from other HTA agencies, Cyprus could integrate cost-effective new technologies to the anticipated health system and to accelerate access to innovative treatments for patients in need, as the whole process will require less time, less budget and fewer skilled personnel. In addition to the above, the new HTA unit would complement the "ready-made" reviews with the submission of the industry which ccould be required to contain an analysis of both clinical and cost effectiveness.

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