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Compassionate drug uses and saving for the national health system: the case study of Fondazione Policlinico Gemelli

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Abstract. – OBJECTIVE: Compassionate Drug Use (CDU) allows patients with a specific disease and no further treatment option to access unauthorized treatments. In this study, we analyzed the requests of CDU approved by the Ethics Committee of Fondazione Policlinico Gemelli in the period January 1, 2018-June 30, 2021. We also estimated the economic impact of CUs.

MATERIALS AND METHODS: CDU requests were analyzed by year, by frequency and by regulatory status of the medicines requested. If an ex-factory price was available at the cutoff date of June 30, 2021, we estimated what would have been the costs for the National Health System (NHS) if the price was already negotiated at the time of CDU request.

RESULTS: In the study period, 463 CDU requests were processed by the Ethics Committee. The number of requests increase linearly from 45 in 2018 to an estimated number of 260 in 2021. The requests included 68 medicines or combinations of medicines; 16 products out of 68 accounted for 75% of all requests. For 7 of these 16 highly requested treatments, accounting for 110 requests out of 463, it was possible to estimate the costs of therapies according to their ex-factory prices. If these products were to be purchased by the NHS, the estimated cost was € 5.472.225.

CONCLUSIONS: The access to unauthorized drugs through CDUs is undergoing a huge increase in the last few years. Such increase meets the ethical need to provide patients with the most recent, often innovative, therapeutic options.

Key Words:
Compassionate drug use, Early access program, National health system, Price negotiation.

Introduction

Compassionate Drug Use (CDU) is one of the ways through which patients with a specific disease and no further treatment option can access unauthorized treatments. Other pathways are: *i*) the access to drugs authorized for use abroad; *ii*) the access to drugs authorized for therapeutic indications different from the intended one (off-label), and *iii*) the access to unauthorized drugs through the participation in clinical trials (CT). At variance with CTs, where drugs are investigated to demonstrate their efficacy and safety, the aim of CDUs is exquisitely ethical, although the data generated by CDUs are usually considered as real word evidence and might have relevance in price negotiation. Compassionate drug use can be managed in different ways: the drug may be released for individual use, or the patient may be included into specific Early Access Programs or Expanded Access Programs (EAPs); in any case, the Company producing the drug scrutinizes the CDU request for approval and covers the cost of treatment[1].

In the European Community (EC), the Regulation n. 726/2004 of the European Parliament sets the rules for managing CDUs within the EC, allowing the access to medicines that are under clinical development, or to medicines that completed the development and applied for a marketing authorization (MA)[2,3]. In 2017 the Italian Ministry of Health released an Act that implements the European regulation; such Decree unifies and established the rules to manage all the

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above-described types of access to unauthorized drugs[4]. Concerning CDUs in particular, the evidence required to authorize a treatment span from medicines that applied for a MA in Italy down to drugs with only phase-2 evidence of efficacy, or even phase-1 in the case of rare diseases. Article 4, paragraph 1 of the above Act establishes that the local Ethic Committee (EC) is in charge to evaluate and approve CDU requests[4].

There is few information available on the economic aspects of CDUs. Recently, Jommi et al[5] reported a study carried out analyzing 11 CDU programs managed by Roche in Italy in the period 2016-2020. In advance to their investigation, these authors conducted a search in the literature and found no specific study dedicated to the economic impact of CDUs. In their study, Jommi et al[5] addressed two main issues, one concerning the savings for the National Health System (NHS), in terms of costs avoided because of CDU programs (costs for Standard-of-Care, diagnostics, adverse events, etc), the other on the incremental costs related to CDU programs.

In the present work, we describe and analyze the requests of CDU evaluated and approved by the EC of *Fondazione Policlinico Gemelli* (FPG) in the period January 1, 2018-June 30, 2021. *Policlinico Gemelli* is the largest academic and research hospital in Italy and is located in the area of Rome.

The requests were analyzed by year, by frequency and by type of medicines (regarding their approval status in Europe and in Italy). When possible, an economic analysis was carried out, addressing the question: what would have been the cost of CDU treatment for the NHS, if the price of the drug had already been negotiated and the drug was available on the market? The costs of CDUs (that are covered by the Companies instead of the NHS, since the price has not been negotiated) represent a sort of 'virtual saving', which is directly related to the timing of price negotiation in Italy. From the perspective of NHS payer, such indirect savings should be fully considered, along with other CDU-related forms of saving analyzed by Jommi et al[5].

Materials and Methods

The dataset used in this study was obtained from the Technical Secretariat of the Ethic Committee. All requests of CDU processed by the EC in the period January 1, 2018-June 30, 2021, were included in the analysis. Each CDU request was recorded in the dataset by 1) the name of medicine; 2) the anonymized name of patient(s); 3) the disease/intended indication; 4) the applying physician; 5) the company holding the medicine, and 6) the start date of assessment procedure. The actual number of requests did not correspond to the number of patients, because in many cases a single request included more than one patient. To avoid misunderstanding, in this work the term 'CDU request' will be used to refer to any single patient.

Data were analyzed: *i*) by chronological order, starting from the first request received per each drug; *ii*) by year, allowing to show for how long any single medicine was dispensed through CDU; *iii*) per number of requests for each medicine or combination of medicines. Thereafter, the analysis was restricted to a smaller number of products bearing a higher frequency of requests, overall representing 75% of all requests.

For each of the drugs belonging to this subset of highly requested products, we reported 1) the approved indications in EU at the cutoff date of June 30, 2021, obtained from the last-released version of the Summary of Product Characteristics (SmPC), as well as 2) the reimbursement state for each indication in Italy at the same date, obtained by consulting the relevant Official Journal (*Gazzetta Ufficiale,* GU). For each drug, we reported: a) the number and date of executive decision (*determina*) by AIFA (*Agenzia Italiana del Farmaco* or Italian Medicines Agency); b) the date of publication in the GU, and the issue number; c) the ex-factory price, i.e., the official price negotiated between AIFA and the Company. The reimbursement state is highly relevant for dispensing drugs via CDU in Italy. As a matter of fact, if the price negotiation process has not been completed, the drug is not available, and it is considered as not authorized. This is an interpretation that allows dispensing drugs by CDU in compliance with the EU regulation, even if a product possesses a MA valid throughout EU, and even if it has been classified as Cnn (*classe C non negoziata*, meaning that the product has a temporarily free price, waiting for a negotiated price) in Italy.

The ex-factory price was then used to calculate the virtual costs of CDU therapies. For each analyzed product, such cost was obtained by multiplying the ex-factory cost per Unit (vial, tablet, hard capsule, etc) per the total number of Units delivered by the *Farmacia Prodotti Sperimentali* of FPG.

All statistics used in this study are descriptive, except the time-dependent increase in the number of CDU requests, which required a linear regres-

sion analysis carried out with a Prism™ v.6 computer program (GraphPad, San Diego CA, USA).

Results

The total number of CDU processed by the EC of FPG in the period January 1, 2018-June 30, 2021, was 463. Table I shows that the EC received and processed 45 requests in 2018, 121 requests in 2019, 167 requests in 2020 and 131 requests in the period January 1, 2021-June 30, 2021. If the same trend will be maintained in the second half of 2021, about 260 requests are expected within this year. Thus, it can be estimated that the number of requests during the whole period of investigation increased in a linear manner ($r^2 = 0.983$), with an average increase of 69 requests per year (Figure 1).

In Table I the requests are shown per year, and the medicines are listed in chronological order. The requests involved 63 products (including one CAR-T cell therapy) and 5 combinations of 2 products, to a total of 68 different treatments. For each product or association, most of the requests were clustered in 1-year (42 requests) or 2-year periods (19 requests), with only 5 and 2 drugs associated to requests spanning for 3 and 4 years, respectively (Table I).

In Table II, the medicines are sorted by decreasing number, starting from niraparib, which was requested 91 times within the period under scrutiny. The first 16 products and combinations of products had 8 or more requests, to a total of 345 requests out of 463. The remaining 52 products or combinations had 7 (2 products), 6 (1 product), 5 (2 products), 4 (3 products), 3 (9 products), 2 (14 products) or a single (21 products) request. The subsequent analysis of the data has been restricted to the first 16 products listed in Table II, which represent 74.55% of all requests.

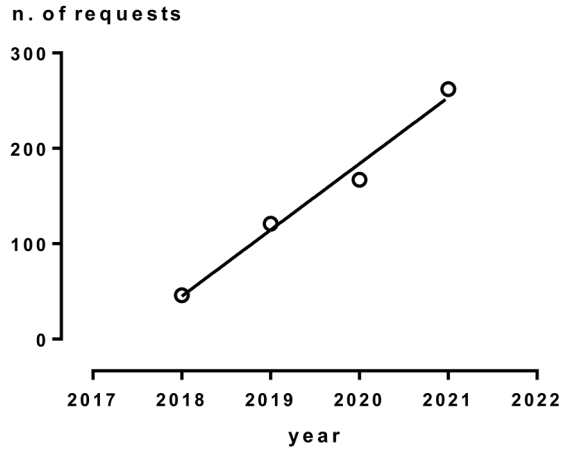

Figure 1. The number of CDU requests increased in a linear manner during the period January 1, 2018 – June 30, 2021.

Table III shows the first 16 medicines or combinations, each of which has been associated to the approved indications at the data cutoff date of June 30, 2021, along with the reimbursement state for each indication in Italy at the same date. If price negotiation per each indication was concluded, the ex-factory price is reported; otherwise, the indication is referred to as 'not reimbursed'. The indications according to which CDU were requested are highlighted in gray.

By crossing the information obtained from each individual CDU request (which included the intended indication/disease) with that reported in Table III, three possible categories of CDU requests emerge:

1) Requests of medicines having one or more indications approved by EMA/EC, but no indication negotiated and reimbursed by the NHS. Under this condition, two cases may occur in our study:
   a. first, the indication has been approved by EMA/EC; thereafter, a number of CDU has been requested for a certain period of time, and subsequently a price has been negotiated by the NHS, so that an ex-factory price is available at the cutoff date of June 30, 2021 (e.g., this is the case of ocrelizumab or vaborbactam meropenem);
   b. second, the indication has been approved by EMA/EC; thereafter, a number of CDU has been requested for a certain period of time, but a price has not been negotiated yet at the cutoff date of June 30, 2021, so that an ex-factory price is not available (e.g., this is the case of lorlatinib, fenfluramine, risdiplam or trastuzumab deruxtecan);
2) Requests of medicines having one or more indications approved by EMA/EC, some of which – but not others – were negotiated and reimbursed by the NHS at the cutoff date of June 30, 2021. This is the case, for example, of trastuzumab emtansine, durvalumab or encorafenib;
3) Requests of medicines having no indications approved by EMA/EC at the cutoff date of June 30, 2021. This category is far less frequent in our sample; only one product out of the first 16 can be classified into this group, namely upadacitinib, which has been requested for patients with atopic dermatitis (an

Table I. CDU requests are reported per year of request. From top to bottom, the medicines were included in the list per chronological order of the first request. The total number of requests per year and per drug are also shown.

	2018	2019	2020	2021 Jan. 1st – June 30	Total
Ocrelizumab	18				18
Niraparib	8		53	30	91
Nintedanib	3				3
Midostaurine	1				1
Inotuzumab Ozogamicin	1				1
Blinatumomab	2	1			3
Begelomab	2	1	4		7
Teduglutide	1				1
Crenolanib	2				2
Olaparib	1	31	4	1	37
Eculizumab	2		2		4
Dabrafenib/Trametinib	2	8	1		11
Lorlatinib	1	2	6	2	11
Quizartinib	1	2			3
Inotersen		5	1		6
Epidiolex		2	1		3
Patisiran		2			2
Nivolumab		11			11
Daunorubicin Citarabine		5			5
Devimistat		1			1
Cabozantinib		1	1		2
Nivolumab /Ipilimumab		16			16
Caplacizumab		1			1
Axicabtagene Ciloleucel		2			2
Neratinib		4	3		7
Fenfluramine		7	4		11
Cemiplimab		8	5	1	14
Siponimod		4	1		5
Trastuzumab Emtansine		3	12	13	28
Encorafenib/Binimetinib		2			2
Rucaparib		1			1
Atezolizumab/Nab Paclitaxel		1	1		2
Encorafenib			12	9	21
Darolutamide			1		1
Polatuzumab Vetodin			2		2
Venetoclax			1		1
Alpelisib			2		2
Lurbinectedine			1		1
Selumetinib			2		2
Durvalumab			9	7	16
Atezolizumab			1		1
Belantamab Mafodotin			2	1	3
Risdiplam			14	2	16
Vaborbactam Meropenem			1	7	8
Esketamine			3		3
Pemigatinib			1		1
Upadacitinib			8	10	18
Avapritinib			2	1	3

Table Continued

Table I. ***(Continued).*** CDU requests are reported per year of request. From top to bottom, the medicines were included in the list per chronological order of the first request. The total number of requests per year and per drug are also shown.

	2018	2019	2020	2021 Jan. 1st – June 30	Total
Sapanisertib			1		1
Daratumumab			2		2
Cefiderocol			1		1
Ustekinumab			1	3	4
Trametinib			1		1
Tepotinib				1	1
Burosumab				1	1
Pembrolizumab				4	4
Dostarlimab				2	2
Afatinib				1	1
Avelumab				2	2
Trastuzumab Deruxtecan				19	19
Amifampridine				1	1
Alentuzumab				1	1
Tafamidis				1	1
Poziotinib				1	1
Talazoparib				1	1
Osimertinib				2	2
Ribociclib				2	2
Golodirsen				3	3
	45	121	167	131	463

indication currently under phase-3 clinical development, but not approved in Europe). Even more rare (they should be better defined as sporadic) are the cases of CDU requests based on phase-2 evidence of efficacy or less.

It also happens that a single medicine can be classified into both categories 1 and 2. For example, niraparib had a first wave of 8 CDU requests in 2018, following EMA/EC approval of the initial indication. Then, the indication was negotiated and approved by the NHS in September 2018, and the drug became available on the Italian market. Subsequently, a second indication has been approved by EMA/EC, but the latter has not been negotiated yet at the cutoff date of June 30, 2021. Following the approval of the second indication, a second wave of CDU requests ensued, far larger than the first one (Table I). Thus, niraparib should be classified into category 1a for the first wave of CDU requests, as well as into category 2 for the second one.

The following part of the study deals with an esteem of the savings in pharmaceutical spending associated to CDUs. In the ideal scenario of new agents having the price negotiated in Italy upon EMA/EC approval, the cost of most therapies currently provided through CDU would have been covered by the NHS. Thus, we calculated the costs of CDU therapies according to the ex-factory price that has been negotiated by AIFA at some stage after EMA/EC approval.

In some cases (e.g., for requests of 1b type, or in the case of combination therapies) no estimate is possible since no ex-factory price was available.

In the case that an ex-factory price became available after a number of CDU were granted (e.g., the type-1a requests), such price was applied to the products delivered by CU. In this group we included ocrelizumab, vaborbactam meropenem and nivolumab (referring specifically to the indication 'Adjuvant treatment of melanoma'). Niraparib was also included, limited to the first wave of CDU requests following the approval of the first indication (i.e., the first 8 requests, in 2018). The results from this sub-group are shown in Table IV, upper panel.

A second series of esteems was carried out on type-2 requests, including trastuzumab emtansine, durvalumab and encorafenib. In this sub-group, the ex-factory price negotiated on the first-approved indication was used, but it should

Table II. Compassionate Drug Use requests are sorted per frequency of request. The 16 most requested products or associations, accounting for 75% of all requests, are highlighted in gray.

Medicinal product	Requests	Total	Medicinal product	Requests	Total
Niraparib	91	91	Atezolizumab/Nab Paclitaxel	2	418
Olaparib	37	128	Avelumab	2	420
Trastuzumab Emtansine	28	156	Cabozantinib	2	422
Encorafenib	21	177	Crenolanib	2	424
Trastuzumab Deruxtecan	19	196	Daratumumab	2	426
Ocrelizumab	18	214	Dostarlimab	2	428
Upadacitinib	18	232	Encorafenib/ Binimetinib	2	430
Durvalumab	16	248	Osimertinib	2	432
Nivolumab/Ipilimumab	16	264	Patisiran	2	434
Risdiplam	16	280	Polatuzumab Vetodin	2	436
Cemiplimab	14	294	Ribociclib	2	438
Dabrafenib/Trametinib	11	305	Selumetinib	2	440
Nivolumab	11	316	Axicabtagene Ciloleucel	2	442
Fenfluramine	11	327	Afatinib	1	443
Lorlatinib	10	337	Alentuzumab	1	444
Vaborbactam Meropenem	8	345	Amifampridine	1	445
Neratinib	7	352	Atezolizumab	1	446
Begelomab	7	359	Burosumab	1	447
Inotersen	6	365	Caplacizumab	1	448
Daunorubicin/Citarabine	5	370	Darolutamide	1	449
Siponimod	5	375	Devimistat	1	450
Eculizumab	4	379	Inotuzumab Ozogamicin	1	451
Ustekinumab	4	383	Lurbinectedine	1	452
Pembrolizumab	4	387	Midostaurine	1	453
Avapritinib	3	390	Pemigatinib	1	454
Belantamab Mafodotin	3	393	Poziotinib	1	455
Blinatumomab	3	396	Rucaparib	1	456
Cefiderocol	3	399	Sapanisertib	1	457
Esketamine	3	402	Tafamidis	1	458
Quizartinib	3	405	Talazoparib	1	459
Epidiolex	3	408	Teduglutide	1	460
Nintedanib	3	411	Tepotinib	1	461
Golodirsen	3	414	Trametinib	1	462
Alpelisib	2	416	Venetoclax	1	463

be considered that such price has not been re-negotiated yet and might undergo a discount upon re-negotiation. The results from this group are shown in Table IV, lower panel.

Discussion

In this study we observed that the requests of CDU processed by the EC of FPG increased in a linear manner in the last 3 years, from 45 requests in 2018 up to an estimated number of 260 requests in 2021. Such local increase probably reflects an overall increase at national level, although to our knowledge no official data are available to confirm this hypothesis.

The large majority of requests concerned drugs or combinations of drugs which had at least one indication approved by EMA/EC at the cutoff date of June 30, 2021. In fact, only 9 medicines out of 68 (namely begelomab, crenolanib, devimistat, golodirsen, lurbinectedine, poziotinib, quizartinib, sapanisertib and tepotinib), corresponding to 20 requests out of 463 (4.3%), had no indication approved by the European Medicines Agency (EMA)/EC at the cutoff date of June 30, 2021.

Table III. The 16 most requested drugs or combinations are listed in the left column. Center column reports the approved indications at the cutoff date of June 30, 2021. Indications that have been matter of CDU requests are highlighted in gray. Right columns report the price negotiation and reimbursement status at the cutoff date of June 30, 2021.

Medicine	Approved indications (June 30, 2021)	NHS reimbursement (June 30, 2021)
Niraparib	as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.	**GU n. 219, Sept. 09, 2018 (det. n. 1362/2018)** • 100 mg tab – 84-tab blister ex-factory price € 8.601,20 • 100 mg tab – 56-tab blister ex-factory price € 5.734,13 •100 mg tab – 28-tab blister ex-factory price € 2.867,07.
	as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.	**Not negotiated**
Olaparib	Ovarian cancer. As monotherapy for the: maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2- mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.	**GU n. 308, Dec. 12, 2020 (det. n. 1265/2020)** 100 and 150 mg tab – 56 tabs ex-factory price € 2.704,78
	Ovarian cancer. As monotherapy for the: maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.	**Not negotiated**
	Ovarian cancer. In combination with bevacizumab, for the: maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability	**Not negotiated**
	Breast cancer. As monotherapy for the treatment of adult patients with germline BRCA1/2- mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy or be considered unsuitable for endocrine therapy.	**GU n. 308, Dec. 12, 2020 (det. n. 1265/2020)** 100 and 150 mg tab – 56 tabs ex-factory price € 2.704,78
	Adenocarcinoma of the pancreas. As monotherapy for the maintenance treatment of adult patients with germline BRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen.	**Not negotiated**
	Prostate cancer. As monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent.	**Not negotiated**

Table contined

Table III. *(Continued).* The 16 most requested drugs or combinations are listed in the left column. Center column reports the approved indications at the cutoff date of June 30, 2021. Indications that have been matter of CDU requests are highlighted in gray. Right columns report the price negotiation and reimbursement status at the cutoff date of June 30, 2021.

Medicine	Approved indications (June 30, 2021)	NHS reimbursement (June 30, 2021)
Trastuzumab emtansine	Metastatic Breast Cancer. As a single agent, for the treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: • Received prior therapy for locally advanced or metastatic disease, or • Developed disease recurrence during or within six months of completing adjuvant therapy.	**GU n. 224, Sept. 26, 2014 (det. n. 944/2014)** 100 mg powder for concentrate for solution for infusion. ex-factory price € 2.035,83. 160 mg powder for concentrate for solution for infusion. ex-factory price € 3.257,32.
	Early Breast Cancer. As a single agent, for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy.	**Not negotiated**
Encorafenib	In combination with binimetinib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation	**GU n. 95, Apr. 9, 2020 (det. n. 289/2020)** 50 and 75 mg hard capsules 28- and 42-capsule blister ex-factory price € 2.587,49.
	In combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy	**Not negotiated**
Ocrelizumab	For the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.	**GU n. 204, Sept. 03, 2018 (det. n. 1319/2018)** 300 mg concentrate for solution for infusion ex-factory price: € 6.250,00.
	For the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.	
Trastuzumab Deruxtecan	For the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens.	**Not negotiated (Cnn)**
Upadacitinib	Rheumatoid arthritis. For the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). May be used as monotherapy or in combination with methotrexate.	**GU n. 306, Dec. 10, 2020 (det. n. 1208/2020)** 15 mg prolonged release tablets, 28-tab blister ex-factory price: € 1.320,32.
	Psoriatic arthritis. For the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. May be used as monotherapy or in combination with methotrexate.	**Not negotiated**
	Ankylosing spondylitis. For the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.	
Durvalumab	As monotherapy, for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumors express PD-L1 on ≥ 1% of tumor cells and whose disease has not progressed following platinum-based chemoradiation therapy.	**GU n. 209, Sept. 6, 2019 (det. n. 1289/2019)** 500-mg vials ex-factory price: € 2.770,09. 120-mg vials ex-factory price: € 1.097,22.
	In combination with etoposide and either carboplatin or cisplatin, for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC).	**Not negotiated**

Table contined

Table III. ***(Continued).*** The 16 most requested drugs or combinations are listed in the left column. Center column reports the approved indications at the cutoff date of June 30, 2021. Indications that have been matter of CDU requests are highlighted in gray. Right columns report the price negotiation and reimbursement status at the cutoff date of June 30, 2021.

Medicine	Approved indications (June 30, 2021)	NHS reimbursement (June 30, 2021)
Nivolumab/ ipilimumab	Melanoma. Ipilimumab in combination with nivolumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.	Ipilimumab monotherapy: **GU n. 152, Jul 3, 2018 (det. n. 970/2018)** 5 mg/ml, concentrate for solution for infusion. 10-ml vials ex-factory price: € 4.250. 40-ml vials ex-factory price: € 17.000 Nivolumab monotherapy: See below, Nivolumab alone Nivolumab/ipilimumab in combination not reimbursed by the NHS for this indication (Det. n. 752/2020, GU n. 188, Jul 28, 2020).
	Renal cell carcinoma (RCC). Ipilimumab in combination with nivolumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma.	Nivolumab/ipilimumab in combination not reimbursed by the NHS for this indication (Det. n. 752/2020, GU n. 188, Jul 28, 2020).
	Non-small cell lung cancer (NSCLC). Ipilimumab in combination with nivolumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumors have no sensitizing EGFR mutation or ALK translocation.	
	Malignant pleural mesothelioma (MPM). Ipilimumab in combination with nivolumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.	
	Mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC). Ipilimumab in combination with nivolumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy.	
Risdiplam	For the treatment of 5q spinal muscular atrophy (SMA) in patients 2 months of age and older, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies.	**Not negotiated (Cnn)**
Cemiplimab	Cutaneous Squamous Cell Carcinoma. As monotherapy, for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma (mCSCC or laCSCC) who are not candidates for curative surgery or curative radiation.	**GU n. 134, May 26, 2020 (det. n. 594/2020)** 350-mg concentrate for solution for infusion ex-factory price: € 6.975,00
	Basal Cell Carcinoma. As monotherapy, for the treatment of adult patients with locally advanced or metastatic basal cell carcinoma (laBCC or mBCC) who have progressed on or are intolerant to a hedgehog pathway inhibitor (HHI).	**Not negotiated**
	Non-Small Cell Lung Cancer. As monotherapy, for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in ≥ 50% tumor cells), with no EGFR, ALK or ROS1 aberrations, who have: • locally advanced NSCLC who are not candidates for definitive chemoradiation, or • metastatic NSCLC.	

Table contined

Table III. ***(Continued).*** The 16 most requested drugs or combinations are listed in the left column. Center column reports the approved indications at the cutoff date of June 30, 2021. Indications that have been matter of CDU requests are highlighted in gray. Right columns report the price negotiation and reimbursement status at the cutoff date of June 30, 2021.

Medicine	Approved indications (June 30, 2021)		NHS reimbursement (June 30, 2021)
Dabrafenib/ trametinib	Dabrafenib as monotherapy or in combination with trametinib	Trametinib as monotherapy or in combination with dabrafenib	GU n. 98, Apr 29, 2015 [Det. n. 401 (dabrafenib)/2015]; GU n. 2, Jan 3, 2017 [Det. n. 1546 (trametinib)/2016]. Dabrafenib 50-mg coated tablets, 120 tbs ex-factory price: € 5914,26 75-mg coated tablets, 120 tbs ex-factory price: € 8871,39 Trametinib 0.5-mg coated tablets, 30 tbs ex-factory price: € 1282,15 2-mg coated tablets, 30 tbs ex-factory price: € 5128,61
	is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation		
	Adjuvant treatment of melanoma. Trametinib in combination with dabrafenib is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.		GU n. 294, Dec 16, 2019 [Det. n. 1795 (trametinib)/1804 (dabrafenib)/2019)] Same prices as above
	Non-small cell lung cancer (NSCLC). Trametinib in combination with dabrafenib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation.		GU n. 294, Dec 16, 2019 [Det. n. 1797 (trametinib)/1804 (dabrafenib)/2019] Same prices as above
Nivolumab (Within the same indication, monotherapy -but not combination therapies- are reimbursed; not reimbursed indications are reported in italics)	Melanoma. Nivolumab as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. Adjuvant treatment of melanoma. Nivolumab as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.		GU n. 95, April 9, 2020 (Det. n. 314/2020) 10 mg/ml, concentrate for solution for infusion. 4-ml vials Ex-factory price: € 596,13. 10-ml vials ex-factory price: € 1.489,20. 24-ml vials ex-factory price: € 3.574,53.
	Non-small cell lung cancer (NSCLC). Nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumors have no sensitizing EGFR mutation or ALK translocation. Nivolumab as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults.		GU n. 95, April 9, 2020 (Det. n. 314/2020) 10 mg/ml, concentrate for solution for infusion. 4-ml vials ex-factory price: € 596,13. 10-ml vials ex-factory price: € 1.489,20. 24-ml vials ex-factory price: € 3.574,53.
	Malignant pleural mesothelioma (MPM). *Nivolumab in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma*.		
	Renal cell carcinoma (RCC). *Nivolumab as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults*. *Nivolumab in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma.* *Nivolumab in combination with cabozantinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma.*		GU n. 95, April 9, 2020 (Det. n. 314/2020) 10 mg/ml, concentrate for solution for infusion. 4-ml vials ex-factory price: € 596,13. 10-ml vials ex-factory price: € 1.489,20. 24-ml vials ex-factory price: € 3.574,53.

Table contined

Table III. ***(Continued).*** The 16 most requested drugs or combinations are listed in the left column. Center column reports the approved indications at the cutoff date of June 30, 2021. Indications that have been matter of CDU requests are highlighted in gray. Right columns report the price negotiation and reimbursement status at the cutoff date of June 30, 2021.

Medicine	Approved indications (June 30, 2021)	NHS reimbursement (June 30, 2021)
NIVOLUMAB (Within the same indication, monotherapy -but not combination therapies- are reimbursed; not reimbursed indications are reported in italics)	Classical Hodgkin lymphoma (cHL). Nivolumab as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.	GU n. 95, April 9, 2020 (Det. n. 314/2020) 10 mg/ml, concentrate for solution for infusion. 4-ml vials ex-factory price: € 596,13. 10-ml vials ex-factory price: € 1.489,20. 24-ml vials ex-factory price: € 3.574,53.
	Squamous cell cancer of the head and neck (SCCHN). Nivolumab as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy	GU n. 95, April 9, 2020 (Det. n. 314/2020) 10 mg/ml, concentrate for solution for infusion. 4-ml vials ex-factory price: € 596,13. 10-ml vials ex-factory price: € 1.489,20. 24-ml vials ex-factory price: € 3.574,53.
	Urothelial carcinoma. Nivolumab as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.	Not negotiated
	Mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC). Nivolumab in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy.	
	Oesophageal squamous cell carcinoma (OSCC). Nivolumab as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy. Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer (OC or GEJC). Nivolumab as monotherapy is indicated for the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.	Not negotiated
Fenfluramine	For the treatment of seizures associated with Dravet syndrome as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older.	Not negotiated (Cnn)
Lorlatinib	As monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after: • alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy; or • crizotinib and at least one other ALK TKI.	Not negotiated (Cnn)
Vaborbactam meropenem	For the treatment of the following infections in adults: • Complicated urinary tract infection (cUTI), including pyelonephritis. • Complicated intra-abdominal infection (cIAI). • Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP). Treatment of patients with bacteremia that occurs in association with, or is suspected to be associated with, any of the infections listed above. For the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.	GU n. 78, Mar. 31, 2021 (det. n. 328/2021) 1 g concentrate for solution for infusion; 6 vials ex-factory price: € 400,00

Table IV. Upper panel. Estimated virtual savings for requests classified as type 1a (see Results).

Medicine	N. of patients and year	Ex-factory price per Unit	Total number of Units dispensed	Estimate costs of therapies
Ocrelizumab	18 (2018)	€ 6.250,00/vial	198 vials*	€ 1.237.500,00
Nivolumab	11 (2018)	€ 1.489,20/10-ml vial € 596,13/4-ml vial	250 vials 57 vials	€ 372.300,00 € 33.979,41
NIRAPARIB	8 (2018)	€ 102,40/tablet	111x 93-tablet bottles*	€ 1.057.075,20
Vaborbactam Meropenem	8 (2020/21)	€ 400,00/6 vials	98 vials	€ 6.533,33
				€ 2.707.387,94

Lower panel. Estimated virtual savings for requests classified as type 2 (see Results).

Medicine	N. of patients and year	Ex-factory price per Unit	Total number of Units dispensed	Estimate costs of therapies
Trastuzumab emtansine	28 (2019-2021)	€ 2.035,83/100-mg vial € 3.257,32/160-mg vial	338 vials 236 vials	€ 688.110,54 € 768.727,52
Encorafenib	21 (2020/21)	€ 73,50/capsule	200 x 70-capsule boxes	€ 1.029.000,00
Durvalumab	16 (2020/21)	€ 2.770,09/500-mg vial	100 vials	€ 277.009,00
				€ 2.764.837,06

* Includes a small number of patients that were enrolled in CU programs in 2017.

The use of EAPs in the management of CDU is widespread. A list of the EAPs currently active in Italy is available in the AIFA website[6]. Ten out of the 16 more frequent CDU requests in our study were supported by EAPs included in the AIFA list. Overall, requests concerning 25 out of 68 medicines or associations were managed by currently active EAPs[6]. We cannot rule out that further requests were supported by EAPs that have been concluded meanwhile. In the case of CDU involving long-term treatments, EAPs usually specify the duration of free-of-charge supply, and often the wording is tailored specifically to the Italian system. For example, Roche compassionate use program No. AL 41711 (trastuzumab emtansine for breast cancer) states: "the availability will last up to 30 days after the publication in the GU of AIFA executive decision classifying the price and reimbursement for the new indication". In this case, the EAP even considers the delay commonly occurring between the publication in GU and the implementation of the decision at regional level.

Thus, if no other cause of stop (i.e., toxicity, progression of disease, voluntary patient withdrawal) occurs, the duration of long-term CDU treatments (as well as the duration of 'virtual saving', as above defined) is directly related to the duration of price and reimbursement (P&R) procedures. Then, a question arises as to how long it takes to have the price negotiated for a new indication. In a recent paper, Raimondo et al[7] estimated an average duration of 287 days, calculated from the start of procedure at the AIFA *Comitato Tecnico Scientifico* (CTS) to the publication in GU of the *determina AIFA*. This figure has been calculated over the period October 2018-April 2020. These authors also report that the average P&R procedure duration increased by 45 days compared to the period September 2015-March 2017, and that the length of procedures is mostly associated to the economic assessment at the *Comitato Prezzi e Rimborso* (CPR, i.e., the AIFA Committee involved in P&R assessments and decisions) level[7]. More recently, AIFA published the results of an internal survey on the timing of price and reimbursement procedures in the period January 2018-December 2020[8]. During this time, 2.476 assessment procedures were processed, 825 per year on average. The average duration of pro-

cedures, calculated as above, was 172 days for generic drugs and 370 days for all other drugs in 2018, and 164 days for generic drugs and 315 days for all other drugs in 2019. Data concerning 2020 were not available since several procedures were still underway in 2021[8].

In this study we could carry out an estimate of averted costs for the NHS only on a limited number of cases. Based on 7 cases only out of 68 (involving 110 patients out of 463), we could estimate a virtual saving of more than 5 millions of euros, calculated on the basis of official ex-factory prices. We are aware of the methodological limitations of our approach: ex-factory prices can undergo discounts in tendering procedures and can also be discounted when prices are re-negotiated in AIFA because of incoming indications. Thus, our approach tends to overestimate the real cost of treatments. Nevertheless, a projection of our esteems at the national level makes reasonable to postulate virtual savings associated to CDUs in the range of tens of millions of euros per year. Moreover, this source of saving adds up to those calculated by Jommi et al[5], who considered saving parameters different from that adopted in our study.

Conclusions

Access to unauthorized drugs through CDUs is undergoing a huge increase in the last few years. Such increase meets the ethical need to provide patients with the most recent, often innovative, therapeutic options. This primary accomplishment goes along with significant savings in the pharmaceutical expenditure of NHS.

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Conflicts of Interest
Daniela Pilunni, Viviana Daloisio, Rina Campopiano, Marcello Pani and Pierluigi Navarra declare no conflict of interest.

Ethics Approval
Ethical approval was not required for this study..

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Author's Contribution Statement
DP conceived the study, provided and analyzed the drug delivery data, critically reviewed the manuscript.
VD provided and analyzed the ethics committee data, critically reviewed the manuscript.
RC provided the drug delivery data, critically reviewed the manuscript.
MP provided the drug delivery data, critically reviewed the manuscript.
PN conceived the study, analyzed the ethics committee and drug delivery data, drafted the manuscript.

References

1) Watson TA. Global Perspective on Compassionate Use and Expanded Access. Ther Innov Regul Sci 2017; 51: 143-145.
2) European Parliament. 32004R0726 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Official Journal L136. 2004; 1-33. http://data.europa.eu/eli/reg/2004/726/oj. Last accessed August 31, 2021.
3) European Medicines Agency. Guideline on Compassionate Use of Medicinal Products, Pursuant to Article 83 of Regulation (Ec) No 726/2004 European Medicines Agency. London, UK, 2007; 1-8.
4) Ministero della Salute. DECRETO 7 settembre 2017 Disciplina dell'uso terapeutico di medicinale sottoposto a sperimentazione clinica (17A07305) (GU Serie Generale n.256 del 02-11-2017). https://www.gazzettaufficiale.it/eli/id/2017/11/02/17A07305/SG. (Last accessed August 31, 2021).
5) Jommi C, Pantellini F, Stagi L, Verykiou M, Cavazza M. The Economic Impact of Compassionate Use of Medicines. Research Square. DOI: https://doi.org/10.21203/rs.3.rs-678616/v1
6) Programmi_uso_compassionevole_27_luglio_2021 (1). Available at: https://aifa.gov.it/farmaci-a-uso-compassionevole. (Last accessed August 31, 2021).
7) Raimondo P, Casilli G, Isernia M, Lidonnici D, Ravasio R, Ronco V, Lanati E. Le tempistiche autorizzative di AIFA: un confronto tra le due commissioni consultive e tecnico-scientifiche succedutesi nel periodo 2015-2020. Glob Reg Health Technol Assess 2020; 7: 109-114. DOI: 10.33393/grhta.2020.2173
8) Rapporto sulle tempistiche di autorizzazione delle procedure di prezzi e rimborso dei farmaci nel triennio 2018-2020: risultati preliminari. Area Strategia ed Economia del Farmaco, Settore HTA ed Economia del farmaco. Settembre 2021. https://www.aifa.gov.it/documents/20142/1307543/2021.09.06_Rapporto_procedure_prezzi_rimborso_farmaci_triennio_2018-2020.PDF. (Last accessed September 10, 2021).