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# Reimbursement of innovative pharmaceuticals in English and Spanish hospitals—The example of isavuconazole

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## Abstract

**Background:** Kron et al (Mycoses, 64, 2021, 86) found cost savings for the use of the innovative pharmaceutical isavuconazole in the inpatient setting in Germany (Bismarck-based healthcare system). Little is known about the reimbursement of innovative pharmaceuticals in the inpatient setting of Beveridge-based healthcare systems.

**Objectives:** The aim of this study was to evaluate the market access process and reimbursement of isavuconazole, exemplary for innovative pharmaceuticals, in England and Spain.

**Patients/Methods:** Market access processes of both countries were described. Focussing on typical patient clusters for isavuconazole treatment, reimbursement data regarding inpatients with (i) allogeneic haematopoietic stem cell transplantation or (ii) acute myeloid leukaemia was considered. Data were publicly available and of high topicality (England 2020/2021, Spain 2018). Discounting and a currency conversion to Euro were applied.

**Results:** This study showed that market access processes of both countries are broadly similar. Further, full reimbursement of isavuconazole as an innovative pharmaceutical may lead to reduction in resource utilisation. Without medication costs, isavuconazole can thus result in cost savings for both patient clusters due to a reduction in length of stay.

**Conclusions:** Expenses for innovative pharmaceuticals may be balanced or even lead to cost savings due to a reduction in length of stay. The latter contributes to a greater patient benefit. For both healthcare system, the analyses highlighted drugs' cost-effectiveness and assessing its added value into reimbursement decisions is highly relevant.

**KEYWORDS**
antifungal treatment, Beveridge healthcare system, invasive aspergillosis, invasive fungal diseases, invasive mucormycosis, isavuconazole

## 1 | INTRODUCTION

Critically ill or immunocompromised patients are especially prone to suffer from opportunistic invasive fungal diseases (IFD), such as invasive aspergillosis (IA) or invasive mucormycosis (IM).[1,2] Recently published studies reported rising incidences worldwide for both pathogens.[3,4] Moreover, the severity of IFD is reflected in its high mortality rates, potentially exceeding 80% in IA and 90% in IM—depending on the primary underlying disease, further risk factors and treatment.[5,6]

Considering the fatal outcomes of IFD, a high scope of unmet patients' needs and the urgency to implement innovative antifungal treatment options are required. From the European perspective, market access of innovative pharmaceuticals is based on approval by the European Medicines Agency (EMA). Since 1 January 2021, the Medicines and Healthcare products Regulatory Agency (MHRA) regulates and approves medicines and medical devices in the United Kingdom (UK). Besides clinical safety and efficacy, the cost-effectiveness of an innovative product is increasingly relevant for the integration into clinical practice. Moreover, an adequate and cost-covering reimbursement for hospitals contributes to standardised application in patient care.

The reimbursement of services and pharmaceuticals relies highly on the structural orientation of the underlying healthcare system. Generally, healthcare systems are distinguishable in Bismarck or Beveridge-based[1] or hybrid forms derived from one of both. Focussing on the systems' financing, Bismarck-based healthcare systems are traditionally decentralised and funded through (mainly) social insurance contributions. In comparison, Beveridge-based healthcare systems are centrally structured, being (mainly) funded through general taxation.[7] Most comparisons of healthcare systems in the international contexts are focussed on health care spending on capita or gross domestic product (GDP) benchmarking by considering healthcare-related (direct) costs.[8] The study at hand, however, compared healthcare systems regarding their reimbursement and remuneration processes.

The study was conducted based on study results by Kron et al.,[9] which analysed cost-containment and reimbursement strategies of isavuconazole (ISA) as an example for innovative antifungal treatment regimens for IA and IM in Germany.[9] To reveal potential differences and incentives in the reimbursement of innovative products compared to other countries, the primary aim of this study was to analyse the market access process and reimbursement of ISA in England and Spain. Focussing on these countries was particularly interesting as both are representatives of Beveridge-based healthcare systems and are thus structured fundamentally differently to Germany (Bismarck-based).[10] Even though the underlying reimbursement system of all three countries is based on the same logic, potential system- and country-specific differences were to be evaluated.

## 2 | PATIENTS / METHODS

We described the market access processes of England and Spain to demonstrate the journey of new pharmaceuticals from EMA / MHRA approval into clinical routine. Country-specific reimbursement for both the inpatient stay and the administration of innovative (mostly high-cost) drugs was analysed from the hospital management perspective.

The included patient cohort was based on immunocompromised inpatients who (i) underwent allogeneic haematopoietic stem cell transplantation (HSCT) or (ii) patients who were treated for acute myeloid leukaemia (AML), both populations well known for their high risk of developing IFD and typical patients (clusters) for ISA treatment.[11–14] The analyses assumed a reduction in length of stay (LOS) in hospital by two days for patients receiving ISA as published by Maertens et al.[15] Results were primarily given in the respective national currency. However, for comparison reasons, British Pound Sterling (£) were converted into Euro (€). With a yearly, constant rate of 3%, costs were updated to 2020 values. This was necessary as the analysis was based on remuneration catalogues of different years.[16] Due to the interactive nature of the model and the use of robust real-life data, a sensitivity analysis was not performed.[17]

### 2.1 | Identification of reimbursement data of England

In this analysis, English HRG (Health Resource Group) data were retrieved from the publicly available National Tariff Workbook

[1]Comparable with National Health Service.

**TABLE 1** Reimbursement analysis in England under the use of ISA

| HRG code | Upper LOS threshold in days | Non-elective spell tariff | HRG reimbursement for 45 days (non-elective spell tariff x MFF) | Cost savings due to reduced LOS of 2 days by ISA |
|---|---|---|---|---|
| SA20A, SA21A, SA22A, SA23A[b] | n/a | No national price | £ 40,774 (€ 44,852) | £ 1812 (€ 1993) |
| SA25G | 75 | £ 16,318 (€ 17,950) | £ 17,971 (€ 19,768) | £ 799 (€ 879) |
| SA25H | 67 | £ 11,764 (€ 12,940) | £ 12,956 (€ 14,252) | £ 576 (€ 633) |
| SA25J | 54 | £ 8438 (€ 9282) | £ 9293 (€ 10,222) | £ 413 (€ 454) |
| SA25K | 47 | £ 7356 (€ 8092) | £ 8101 (€ 8911) | £ 360 (€ 396) |
| SA25L[a] | 26 | £ 5375 (€ 5913) | £ 12,323 (€ 13,555) | £ 548 (€ 602) |
| SA25Ma | 15 | £ 3357 (€ 3693) | £ 10,127 (€ 11,138) | £ 450 (€ 495) |

*Note:* HRG Definitions: SA20A, Bone Marrow Transplant, Allogeneic Graft (Sibling), 19 years and over; SA21A, Bone Marrow Transplant, Allogeneic Graft (Volunteer Unrelated Donor), 19 years and over; SA22A, Bone Marrow Transplant, Allogeneic Graft (Cord Blood), 19 years and over; SA23A, Bone Marrow Transplant, Allogeneic Graft (Haplo-Identical), 19 years and over; SA25G, Acute Myeloid Leukaemia with CC Score 12+; SA25H, Acute Myeloid Leukaemia with CC Score 9-11; SA25J, Acute Myeloid Leukaemia with CC Score 6-8; SA25K, Acute Myeloid Leukaemia with CC Score 4-5; SA25L, Acute Myeloid Leukaemia with CC Score 2-3; SA25M, Acute Myeloid Leukaemia with CC Score 0-1.

Abbreviations: CC, complexity and comorbidity; HRG, Health Resource Group; ISA, isavuconazole; LOS, length of stay; MFF, market forces factor; n/a, not available.

[a](Non-elective spell tariff + flat rate of £ 306 (€ 336) for number of days above upper LOS threshold) × MFF.

[b]Assumption, based on NICE (2019), p. 168.[31]

2020/2021 which is published annually by NHS England and NHS Improvement.[18] According to the specified patient cohort relevant for an ISA treatment, appropriate HRG codes were identified. For each of the identified HRG codes, the non-elective spell tariffs were considered due to reasons of completeness and public access. These tariffs represent averaged resource costs for cases lying between the lower and upper threshold of LOS and vary according to their complexity and comorbidity (CC).

To calculate the HRG reimbursement for a 45-day ISA treatment, the non-elective spell tariff was multiplied with the market forces factor (MFF). The MFF helps to relativise unavoidable cost disparities of healthcare providers from different geographic locations in England, that is higher salaries or more expensive land.[19] In this study, the MFF of the Cambridge University Hospitals NHS Foundation Trust was used exemplarily as it reflects the approximate average of the MFF range from approx. 1.0 to 1.25.[18,19] In case the 45-day ISA treatment exceeded the upper LOS threshold, reimbursement for outlier days was additionally calculated using the additional daily payments given by the National Tariff Workbook 2020/2021. For currency conversion, a factor of € 1.1 per £ 1 was applied.[20]

As all incurring costs for ISA treatment are fully reimbursed,[21] drug expenses were not included in the analysis.

## 2.2 | Identification of reimbursement data of Spain

Relevant data for the cost analysis (Table 1) were retrieved from the latest publicly available sources for the year 2018, published by the Ministry of Health (Ministerio de Sanidad, Consumo y Bienestar Social), Certificates of Discharge of the National Health System Register.[22] These data of interest for our patient cohort included information regarding the AP-GRD codes ('All-Patient' Grupos Relacionados por el Diagnóstico) of the relevant patient clusters, such as average length of stay (ALOS) in days, upper LOS threshold (days) and the regular total reimbursement values in € for each AP-GRD below the upper LOS threshold. As reimbursement data for treatment days above the upper LOS threshold (outlier days) did not exist within the screened sources, we assumed the costs per potential outlier day to be the averaged costs per day based on the ALOS. This was relevant for the case that the 45-day ISA treatment exceeded the upper LOS threshold. As in public hospitals in Spain, the costs of ISA are reimbursed according to the actual consumption. Specific drug acquisition costs were disregarded within our analysis.

## 2.3 | Ethics statement

No ethical approval was required for this study as the underlying data were retrieved from publicly available sources.

# 3 | RESULTS

## 3.1 | Costs and reimbursement in English hospitals

As shown in Figure 1, the budgets of the English healthcare system are held by 135 regional entities called Clinical Commissioning Groups (CCG).[23] However, approval for market access and the assessment of the cost-effectiveness of drugs take place at a national level for England, Wales and Scotland, respectively. Thereby,

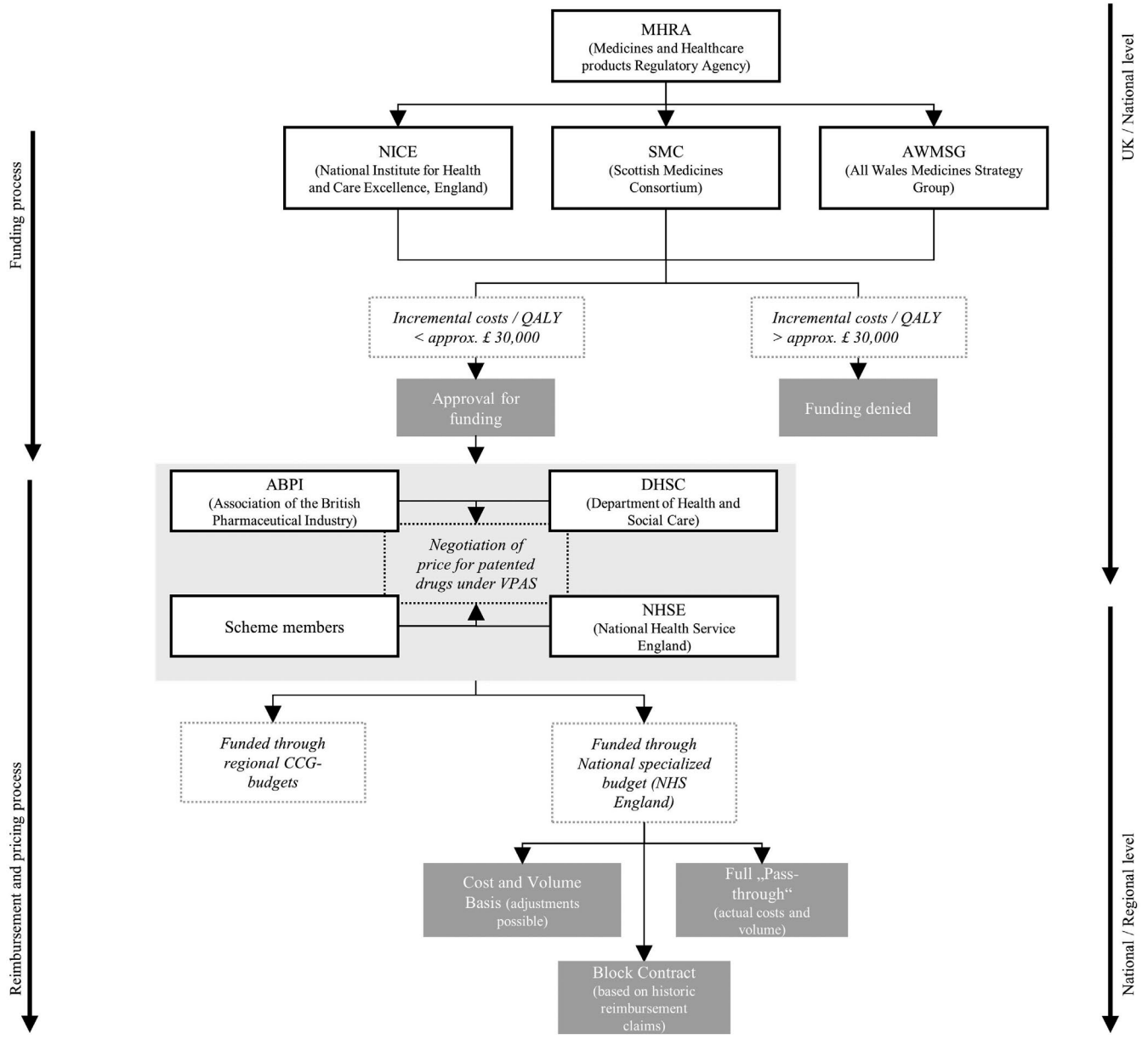


**FIGURE 1** Market Access Scheme in England. The market access procedure for pharmaceuticals in England is presented. The process is described from official approval to reimbursement in clinical routine. ABPI, Association of the British Pharmaceutical Industry; AWMSG, All Wales Medicines Strategy Group; CCG, Clinical Commissioning Groups; DHSC, Department of Health and Social Care; MHRA, Medicines and Healthcare products Regulatory Agency; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SMC, Scottish Medicines Consortium; QALY, quality-adjusted life year; PPRS, Pharmaceutical Pricing Regulation Scheme; UK, United Kingdom; VPAS, Voluntary Scheme for Branded Medicines Pricing Access

a drug's positive recommendation is based on a maximum threshold of £20,000–£30,000 per quality-adjusted life year (QALY).[24] Focussing on ISA and England, the National Institute for Health Care Excellence (NICE) would have been responsible for evaluating the incremental costs per QALY to build a basis for decision-making regarding the drug's approval and the subsequent pricing process. However, a formal assessment was not conducted by NICE but by Weidlich et al and Floros et al.[25,26]

Drug prices are negotiated between the Department of Health and Social Care (DHSC), NHS England, the Association of the British Pharmaceutical Industry (ABPI) and further scheme members considering inter alia cost-effectiveness and by using the Voluntary Scheme for Branded Medicines Pricing and Access (VPAS) with the goal to promote access of innovations by containing national spending.[27] Pharmaceutical companies can give additional discounts at a regional level. Specialised services including treatment of rare diseases and high-cost drugs are reimbursed through block contracts directly managed by NHS England. Thereby, reimbursement depends on historic reimbursement claims.[28–30]

Considering patients with an allogeneic HSCT, four HRG codes (SA20A, SA21A, SA22A and SA23A, all referring to allogeneic bone marrow transplantation) were identified. As none of these

HRG codes were priced nationally and remuneration is not publicly accessible, the HRG reimbursement over 45 days was estimated based on existing publications.[31] Thus, cost savings due to a reduced LOS of 2 days were £ 1812 (€ 1993) for all allogeneic HSCT HRG codes.

HRG codes covering patients suffering from AML were, however, priced nationally and thus enabled the calculation of the actual 45-day HRG reimbursement. The MFF of the Oxford Health NHS Foundation Trust of 1.10132 was included exemplarily.[18] Six HRG codes, namely SA25G, SA25H, SA25J, SA25K, SA25L and SA25M, were identified which varied according to their CC score. As the duration of the 45-day ISA treatment was above the upper LOS threshold for HRG codes SA25L and SA25M, a daily flat rate of £ 306 (€ 336) was added. Cost savings due to a reduced LOS of 2 days thus ranged from £ 360 (€ 396) in SA25K to £ 799 (€ 879) in SA25G for AML HRG codes. The underlying data and cost-saving results are summarised in Table 1.

### 3.2 | Costs and reimbursement in Spanish hospitals

Receiving approval by the EMA in October 2015, the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) authorised the use of oral and parenteral ISA for the Spanish market in February 2016.[32,33]

As displayed in Figure 2, the AEMPS as an independent institution commissions the assessment of new drugs on behalf of the Ministry of Health by drawing up a therapeutic positioning report (IPT). Thereby, AEMPS evaluates the drug's added value by considering efficacy, safety and epidemiological data. Cost-effectiveness analyses are currently not mandatory for this decision-making process.[34] As part of the Ministry of Health, the General Directorate of Basic Portfolio of Services of the National Health and Pharmacy System (DGCCSSNS—Dirección General de Cartera Común de Servicios del Sistema Nacional de Salud y Farmacia) decides whether the drug is suitable for funding.[35] Yet, an official funding approval does not equal the actual reimbursement in clinical practice as healthcare budgets are allocated regionally. Therefore, the Comisión Interministerial de Precios de Medicamentos y Productos Sanitarios (CIPM)—consisting inter alia of members of four different ministries and three members from different Autonomous Communities (AC)—decides on public reimbursement by considering the IPT and the drug's budget impact.[34] Findings of the value dossier are relevant for the negotiation about the reimbursement pricing process (for patented drugs) which takes place at a national level between the Ministry of Health and the respective pharmaceutical company.[34] Having reached an agreement (less mandatory rebate of, that is 4% for orphan drugs),[36–38] decision-making power is forwarded to the AC. On regional level, further discounts can be negotiated between the AC and the pharmaceutical company. Depending on regional regulations, different committees, such as in hospitals the Comisión de Farmacia y Terapéutica, may then additionally decide whether the drug is included in the hospital portfolio.[34,39]

Considering patients who underwent an allogeneic HSCT, four AP-GRD codes (007-1, 007-2, 007-2, and 007-4) were identified. Only in one AP-GRD (007-1), the upper LOS threshold was below the assumed 45-day ISA treatment, meaning that the assumption for daily costs above the upper LOS threshold was used as described within the responsible methods section. The total cost savings per patient due to a shortened overall LOS with ISA treatment within this patient cluster ranges between € 1279 in 007-1 and € 1860 in 007-4.

For the cluster of patients with AML, the upper LOS threshold of the AP-GRD with the lowest severity level (690-1) was below the predefined 45-day ISA treatment. Outliers were calculated as aforementioned. The total cost savings per patient due to a shortened overall LOS with ISA treatment within this patient cluster ranges between € 642 in 690-2 and € 1056 in 690-1. Results for the Spanish reimbursement analysis are summarised in Table 2.

### 3.3 | Comparison of Spanish and English values and patient clusters

Our AP-GRD and HRG data could be grouped into two clusters: patients treated for AML (cluster 1) and patients who underwent allogeneic HSCT (cluster 2). Figure 3 opposes both clusters for England and Spain. It shows that the mean reimbursement for allogeneic HSCT cases was higher than for AML cases. In cluster 1, both the mean reimbursement and the mean cost savings were greater in Spanish hospitals; however, the opposite was true for cluster 2. Further, while in cluster 1 the mean reimbursement of England accounted for approximately 64% compared to the Spanish values, in cluster 2 the mean reimbursement of Spanish hospitals accounted for approximately 74% compared to England. As a reduced LOS of 2 days was assumed for both clusters, the mean cost savings are proportionally stable.

## 4 | DISCUSSION

To our knowledge, this is the first health-economic analysis focussing on reimbursement and market access mechanisms of ISA in different (English and Spanish) healthcare systems. Potential differences regarding access of innovative products between England and Spain (Beveridge-based healthcare systems), and Germany (Bismarck-based healthcare system) were to be evaluated.

Both market access processes showed similarities in their overall structure. While the funding process takes place at a national level, the reimbursement process happens mainly in the respective regions as healthcare budgets are allocated accordingly. Yet, differences could be seen in the negotiation during price-setting and in the translation into clinical routine.

Cost savings for the administration of ISA in the inpatient setting were found for patients with an allogeneic HSCT and AML across all analysed codes in Spain and England (AP-GRD and HRG,

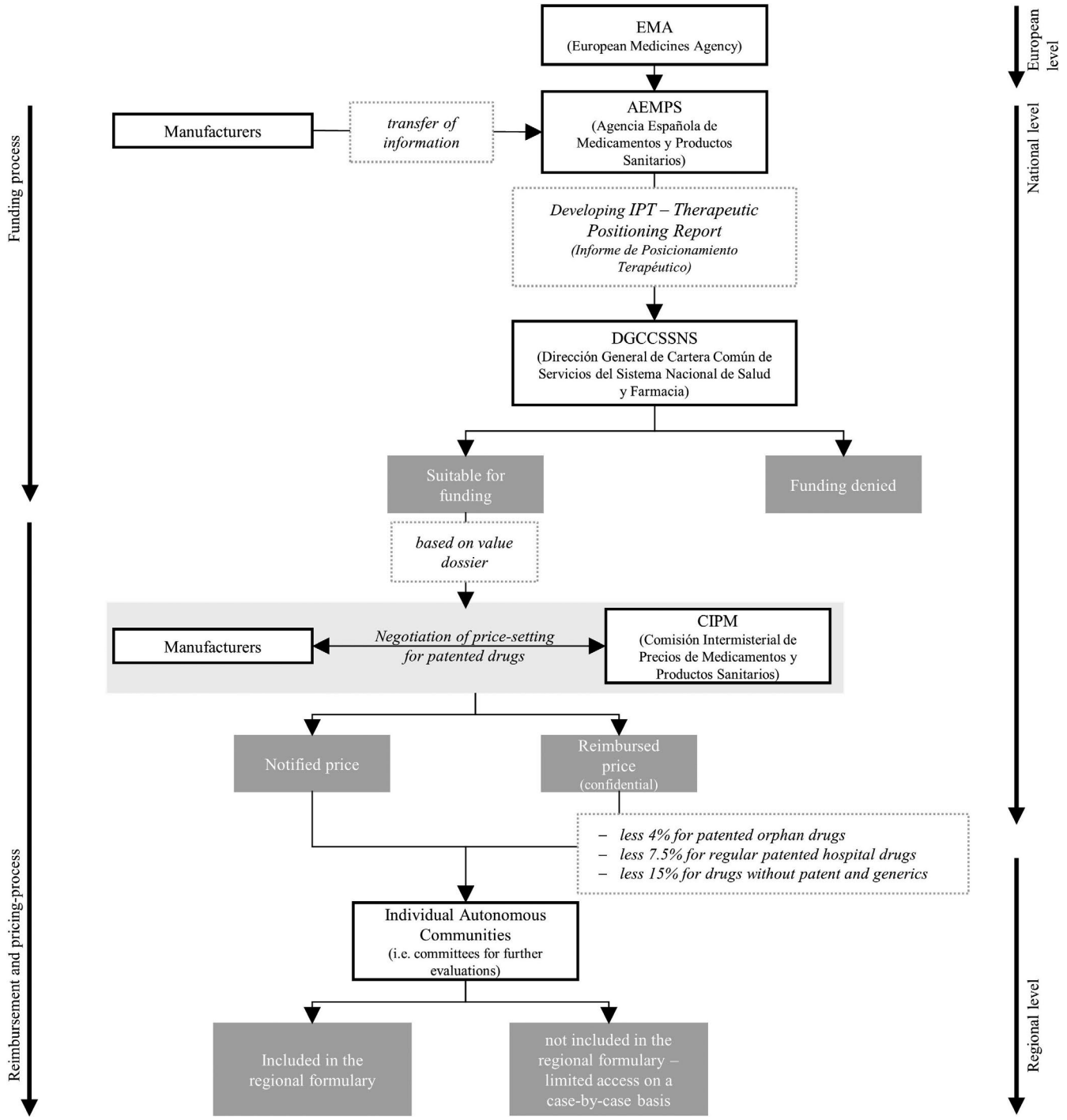


**FIGURE 2** Market Access Scheme in Spain. The market access procedure for pharmaceuticals in Spain is presented. The process is described from official approval to reimbursement in clinical routine. AEMPS, Agencia Espanola Medicamentos y Productos Sanitarios; CIPM, Comision Intermisterial de Precios de Medicamentos y Productos Sanitarios; DGCCSSNS, Dirección General de Cartera Común de Servicios del Sistema Nacional de Salud y Farmacia; EMA, European Medicines Agency; IPT, Informe de Posicionamiento Terapeutico

respectively). By comparing the analysis at hand with the study by Kron et al.,[9] it could be confirmed that the administration of ISA for the defined patient cohort leads to cost savings in England and Spain as well, due to a full reimbursement and despite a different structural orientation of the underlying healthcare system.[9]

For both Beveridge representatives, approved innovative products such as ISA were fully reimbursed. The administration of ISA in Spanish and English hospitals was cost covering (oral and parenteral) and the application of ISA did not lead towards financial risks for hospitals. Rather, our study results show that the use of ISA in treatment of IA and IM results in a reduction of resource use and, consequently, cost savings. ISA thus is beneficial from both a medical and a hospital management perspective. Focussing on the German Bismarck study, Kron et al.[9] described that drug costs for the administration

**TABLE 2** Reimbursement analysis in Spain under the use of ISA

| AP-GRD | Upper LOS threshold in days | ALOS in days | AP-GRD reimbursement below upper LOS threshold | AP-GRD reimbursement for 45 days | Cost savings due to reduced LOS of 2 days by ISA |
|---|---|---|---|---|---|
| 007-1[a] | 43 | 27 | € 26,786 | € 28,770 | € 1279 |
| 007-2 | 50 | 30 | € 30,256 | € 30,256 | € 1345 |
| 007-3 | 58 | 37 | € 32,723 | € 32,723 | € 1454 |
| 007-4 | 124 | 57 | € 41,842 | € 41,842 | € 1860 |
| 690-1[a] | 26 | 11 | € 8715 | € 23,769 | € 1056 |
| 690-2 | 64 | 17 | € 14,455 | € 14,455 | € 642 |
| 690-3 | 77 | 24 | € 20,844 | € 20,844 | € 927 |
| 690-4 | 86 | 33 | € 22,509 | € 22,509 | € 1000 |

*Note:* AP-GRD Definitions: 007-1, Allogenic Bone Marrow Transplantation – level of severity 1; 007-2, Allogenic Bone Marrow Transplantation – level of severity 2; 007-3, Allogenic Bone Marrow Transplantation – level of severity 3; 007-4, Allogenic Bone Marrow Transplantation – level of severity 4; 690-1, Acute Leukaemia – level of severity 1; 690-2, Acute Leukaemia – level of severity 2; 690-3, Acute Leukaemia – level of severity 3; 690-4, Acute Leukaemia – level of severity 4.

Abbreviations: ALOS, average length of stay; AP-GRD, 'All-Patient' Grupos Relacionados por el Diagnóstico; ISA, isavuconazole; LOS, length of stay.

[a]AP-GRD reimbursement below upper LOS threshold + average reimbursement per day below upper LOS threshold for days above upper LOS threshold.

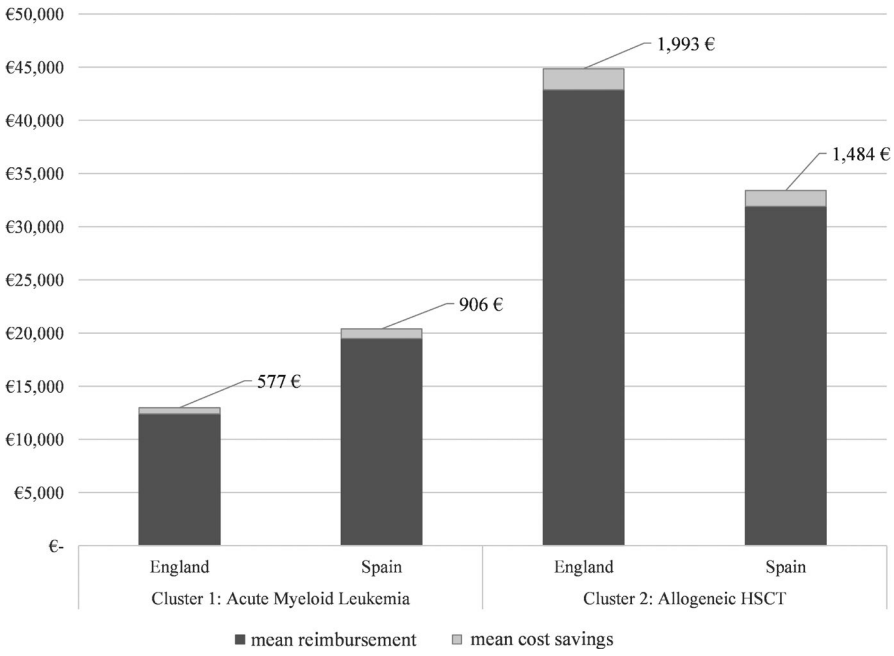


**FIGURE 3** Comparison of cost savings in the use of ISA considering two clusters. The two indications 'acute myeloid leukaemia' and 'allogeneic HSCT' are compared considering their mean cost savings in England and Spain, respectively. HSCT, haematopoietic stem cell transplantation; ISA, isavuconazole

of ISA are not automatically reimbursed and cost coverage depends on a highly bureaucratic negotiation process.[9] With regard to the study at hand, complex negotiations between healthcare providers (Germany) / Ministry of Health (Spain and England) and the pharmaceutical companies were not country-specific but affected all healthcare system designs in Europe.

## 4.1 | Methodological considerations

Although best practices for cost and reimbursement analyses were followed, this study has some limitations. Due to country-specific modifications of the English and the Spanish Beveridge system, reimbursement processes may vary during the years. Reimbursement processes are most often dynamic and ongoing, which should be also considered interpreting current study results. Yet, as each of the hospital (management) systems are based on diagnosis-related groups (DRG), the countries' systems were – up to a certain extent – comparable.[40]

The analyses of both countries focussed on haematological diagnoses and treatments irrespective of the CC level and did not consider any other underlying diseases. However, patients with lower CC levels rarely occur in IA or IM. For reasons of completeness, we nevertheless examined all identified codes for both clusters.

In the English analysis the HRG codes SA20A, SA21A, SA22A and SA23A national tariffs were not publicly available as there were no

prices set across any setting.[18] As the assumed tariff was retrieved from the sum of the weighted average of harvesting costs and allogeneic transplant costs for elective patients,[31] the reimbursement of our calculation may have been overestimated. Yet, other data were not publicly accessible.

## 4.2 | Further implications

For further implications, we suggest to not only analyse the reimbursement of innovative pharmaceuticals at a hospital level but also to consider the system perspective. Recently, innovative funding strategies are more in focus of scientific discourse, with the aim to make reimbursement systems more transparent and sustainable. These strategies aim at reforming traditional reimbursement processes by facilitating a rapid market access and shared-cost risk schemes for effective, innovative products. One of these funding strategies is the so-called 'value-based pricing' (VBP) concept which is covered by the report of the expert panel on effective ways of investing in health by the European Commission.[41] Within this concept, value is defined as the therapeutically added value of a drug. VBP aims to set innovation and affordability in context with each other.[41,42] Even though VBP may have drawbacks, such as incentivising research for high-cost drugs (against rare diseases) with a potential negative impact on healthcare budgets, it also brings major advantages. For instance, VBP contributes to (i) an in-depth assessment of cost-effectiveness focussing on patient-related outcomes[41] and thereby (ii) increases transparency while reducing current confidential 'black box' reimbursement deals.

The English healthcare system is defined as a 'value-based health care' as it aims to have the patients' interests in the centre of all processes, not only the reimbursement one. However, such a comprehensive system needs all affected stakeholders to pull together by unifying culture, language, and behaviour.[43] This example shows that reformation of a healthcare (or reimbursement) system is a process rather than a fast changeover.

We encourage debate to improve the development of traditional reimbursement systems towards more innovative approaches while also focussing on the alignment of processes across country borders. However, the concept would prevent a neglect of country-specific differences, that is in healthcare budgets which can exemplarily be seen in the health expenditures, given in shares of GDP (9.6% [UK] and 8.9% [Spain] in 2017).[44]

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### CONFLICT OF INTEREST

S. M. Wingen-Heimann has received research and travel grants from Astellas and Merck; research grants from Basilea, Gilead, and 3M; travel grants from Pfizer Inc; lecture honoraria from Astellas and Merck; and is a consultant to Basilea, Gilead, and Merck. C. Thielscher has received grants, advisory board, and consultancy fees from EMDR Institute, Johnson & Johnson, Medical Columbus and Roeser Medical. A. Kron received consultancy honoraria from Takeda, BMS, AbbVie, Novartis and MSD. S. Grau has received lecture honoraria from MSD, Pfizer and Angellini. D. A. Enoch has received consultancy honoraria from Pfizer and MSD. C. Micallef has received consultancy honoraria from Mundipharma and Pfizer. OAC is funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy—CECAD, EXC 2030—390661388 and has received research grants from, is an advisor to, or received lecture honoraria from Actelion, Allecra Therapeutics, Al-Jazeera Pharmaceuticals, Amplyx, Astellas, Basilea, Biosys, Cidara, Da Volterra, Entasis, F2G, Gilead, Grupo Biotoscana, IQVIA, Janssen, Matinas, Medicines Company, MedPace, Melinta Therapeutics, Menarini, Merck/MSD, Mylan, Nabriva, Noxxon, Octapharma, Paratek, Pfizer, PSI, Roche Diagnostics, Scynexis and Shionogi. F. Kron received lecture honoraria and/or advisory board and consultancy honoraria from Pfizer Inc, MSD, Bristol Myers Squibb, Novartis, Takeda, Shire, Amgen, Janssen-Cillag, Celgene, Gilead, Bayer, Mundipharma, Riemser, Medac, Jazz Pharmaceuticals, Medipolis, Aposan, Hogan Lovells, Simon Kucher, Orphoz-McKinsey and Aktiva Gesundheitsberatung. J. Jeck, J. Bonn and F. Jakobs have nothing to disclose.

### AUTHOR CONTRIBUTIONS

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Investigation (equal); Methodology (equal); Supervision (supporting); Validation (equal); Writing-original draft (supporting); Writing-review & editing (equal). **Florian Kron:** Conceptualization (equal); Funding acquisition (lead); Investigation (equal); Methodology (equal); Project administration (lead); Resources (lead); Supervision (lead); Validation (equal); Visualization (equal); Writing-original draft (lead); Writing-review & editing (equal).

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## REFERENCES

1. Enoch D, Ludlam H, Brown N. Invasive fungal infections: a review of epidemiology and management options. *J Med Microbiol*. 2006;55(Pt 7):809-818.
2. Bajpai V, Khan I, Shukla S, et al. Invasive fungal infections and their epidemiology: measures in the clinical scenario. *Biotechnol Bioprocess Eng*. 2019;24:436-444.
3. Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. *J Fungi*. 2019;5(1):26.
4. Erjavec Z, Kluin-Nelemans H, Verweij P. Trends in invasive fungal infections, with emphasis on invasive aspergillosis. *Clin Microbiol Infect*. 2009;15(7):625-633.
5. Cornely O, Alastruey-Izquierdo A, Arenz D, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. *Lancet Infect Dis*. 2019;9(12):e405-21.
6. Ullmann AJ, Aguado JM, Arikan-Akdagli S, et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clin Microbiol Infect*. 2018;24(Suppl 1):e1-e38.
7. van der Zee J, Kroneman M. Bismarck or Beveridge: a beauty contest between dinosaurs. *BMC Health Serv Res*. 2007;7:94.
8. Health Expenditure Per Capita. Health at a Glance 2019: OECD Indicators; 2019. https://www.oecd-ilibrary.org/sites/876d99c3-en/index.html?itemId=/content/component/876d99c3-en. Accessed December 01, 2020.
9. Kron F, Wingen-Heimann S, Jeck J, Lazzaro C, Cornely O, Thielscher C. Principal-agent theory-based cost and reimbursement structures of isavuconazole treatment in German hospitals. *Mycoses*. 2021;64(1):86-94.
10. Lameire N, Joffe P, Wiedemann M. Healthcare systems—an international review: an overview. *Nephrol Dial Transplant*. 1999;14(Suppl_6):3-9.
11. Jantunen E, Anttila VJ, Ruutu T. Aspergillus infections in allogeneic stem cell transplant recipients: have we made any progress? *Bone Marrow Transplant*. 2002;30(12):925-929.
12. Caira M, Girmenia C, Fadda RM, et al. Invasive fungal infections in patients with acute myeloid leukemia and in those submitted to allogeneic hemopoietic stem cell transplant: who is at highest risk? *Eur J Haematol*. 2008;81(3):242-243.
13. Pagano L, Caira M, Candoni A, et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. *Haematologica*. 2006;91(8):1068-1075.
14. Pagano L, Caira M, Candoni A, et al. Invasive aspergillosis in patients with acute myeloid leukemia: a SEIFEM-2008 registry study. *Haematologica*. 2010;95(4):644-650.
15. Maertens JA, Raad II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. *Lancet*. 2016;387(10020):760-769.
16. General Methods Version - 6.0 of 05.11.2020. 2020; Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). https://www.iqwig.de/methoden/allgemeine-methoden_version-6-0.pdf?rev=180500. Accessed March 24, 2021.
17. von der Schulenburg J-M, Greiner W, Jost F, et al. German recommendations on health economic evaluation: third and updated version of the Hanover Consensus. *Value Health*. 2008;11(4):539-544.
18. Annex DtA: The national tariff workbook, 2020/21. 2020; National Health Service Improvement. https://www.england.nhs.uk/publication/national-tariff-payment-system-documents-annexes-and-supporting-documents/. Accessed April 15, 2021.
19. A guide to the market forces factor - A joint publication by NHS England and NHS Improvement. 2019; National Health Service Improvement / National Health Service England. https://improvement.nhs.uk/documents/4995/1920_Guide__to_MFF.pdf. Accessed March 24, 2021.
20. WÄHRUNGSRECHNER: BRITISCHE PFUND - EURO (GBP IN EUR). https://www.finanzen.net/waehrungsrechner/britische-pfund_euro. Accessed December 1, 2020.
21. Blueteq established as the system for High Cost Drugs Management Process in NHS England's Commissioning Intentions 2016/2017!. Blueteq Ltd. http://www.blueteq.com/latestnews/ArticleID/2/Blueteq-established-as-the-system-for-High-Cost-Drugs-Management-Process-in-NHS-Englands-Commissioning-Intentions-2016-2017. Accessed December 01, 2020.
22. Registro de Altas de los Hospitales Generales del Sistema Nacional de Salud. CMBD. Norma Estatal. 2018; Ministerio de Sanidad, Consumo y Bienestar Social. https://www.mscbs.gob.es/estadEstudios/estadisticas/cmbd.htm. Accessed December 01, 2020.
23. About CCGs. National Health Service Clinical Commissioners (NHSCC). https://www.nhscc.org/ccgs/. Accessed December 01, 2020.
24. Drummond M, de Pouvourville G, Jones E, Haig J, Saba G, Cawston H. A comparative analysis of two contrasting European approaches for rewarding the value added by drugs for cancer: England versus France. *Pharmacoeconomics*. 2014;32(5):509-520.
25. Weidlich D, Hicks M, Floros L, Patel J, Charbonneau C, Sung A. Pin18-estimating the budget and clinical impact of introducing isavuconazole for the treatment of patients with possible invasive Aspergillosis in the United Kingdom. *Value Health*. 2018;21:S223-S224.
26. Floros L, Pagliuca A, Taie AA, et al. The cost-effectiveness of isavuconazole compared to the standard of care in the treatment of patients with invasive fungal infection prior to differential pathogen diagnosis in the United Kingdom. *J Med Econ*. 2020;23(1):86-97.
27. The 2019 Voluntary Scheme for Branded Medicines Pricing and Access - Chapters and Glossary. 2018; Department of Health & Social Care / Association of the British Pharmaceutical Industry. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/761834/voluntary-scheme-for-branded-medicines-pricing-and-access-chapters-and-glossary.pdf. Accessed March 23, 2021.
28. Specialised Services. National Health Service England. https://www.england.nhs.uk/commissioning/spec-services/. Accessed January 18, 2021.
29. High cost drugs. 2012; GOV.UK. https://www.gov.uk/government/news/high-cost-drugs--2. Accessed March 23, 2021.
30. Contracts and payment guidance October 2020 – March 2021. 2020; National Health Service. https://www.england.nhs.uk/wp-content/uploads/2020/09/C0768-finance-guidance-with-annex-3-added-23-september-2020-.pdf Accessed March 24, 2021.

31. Single Technology Appraisal - Treosulfan with fludarabine for malignant disease before allogeneic stem cell transplant [ID1508] / Committee Papers. 2019; National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/ta640/evidence/appraisal-consultation-committee-papers-pdf-8828294941. Accessed March 24, 2021.
32. FICHA TECNICA CRESEMBA 100mg capsulas duras. Agencia espanola de medicamentos y productos sanitarios / Centro de información de medicamentos. https://cima.aemps.es/cima/dochtml/ft/1151036002/FT_1151036002.html. Accessed March 24, 2021.
33. FICHA TECNICA CRESEMBA 200mg polvo para concentrado para solucion para perfusion. Agencia espanola de medicamentos y productos sanitarios / Centro de información de medicamentos. https://cima.aemps.es/cima/dochtml/ft/1151036001/FT_1151036001.html. Accessed March 24, 2021.
34. Oliva-Moreno J, Puig-Junoy J, Trapero-Bertran M, Epstein D, Pinyol C, Sacristán J. Economic evaluation for pricing and reimbursement of new drugs in spain: fable or desideratum? *Value Health*. 2020;23(1):25-31.
35. Funciones Dirección General de Cartera Básica de Servicios del Sistema Nacional de Salud y Farmacia. Ministerio de Sanidad, Consumo y Bienestar Social. https://www.mscbs.gob.es/organizacion/ministerio/organizacion/sgralsanidad/dgcbssnsyfF.htm. Accessed March 23, 2021.
36. Real Decreto-ley 8/2010, de 20 de mayo, por el que se adoptan medidas extraordinarias para la reducción del déficit público; Capítulo V, Artículo 8. 2010; BOE-A-2010-8228; Boletin Oficial del Estado - Legislacion Consolidada. https://www.boe.es/buscar/pdf/2010/BOE-A-2010-8228-consolidado.pdf. Accessed March 24, 2020.
37. Real Decreto-ley 8/2010, de 20 de mayo, por el que se adoptan medidas extraordinarias para la reducción del déficit público; Capítulo V, Artículo 9. 2010; BOE-A-2010-8228; Boletin Oficial del Estado - Legislacion Consolidada. https://www.boe.es/buscar/pdf/2010/BOE-A-2010-8228-consolidado.pdf. Accessed March 24, 2021.
38. Real Decreto-ley 8/2010, de 20 de mayo, por el que se adoptan medidas extraordinarias para la reducción del déficit público; Capítulo V, Artículo 10. 2010; BOE-A-2010-8228; Boletin Oficial del Estado - Legislacion Consolidada. https://www.boe.es/buscar/pdf/2010/BOE-A-2010-8228-consolidado.pdf. Accessed March 24, 2021.
39. Pinyol C, Calvente N, Espinosa C, Gilabert T, Carlos M (from the ISPOR Regional Spain Chapter). Market access in Spain. In: Güvenç Koçkaya AW, ed. *Pharmaceutical Market Access in Developed Markets*. Turin: SEEd Medical Publishers; 2018:77-98.
40. Geissler A, Scheller-Kreinsen D, Quentin W, Busse R. DRG-systeme in Europa. *Bundesgesundheitsblatt-Gesundheitsforschung-Gesundheitsschutz*. 2012;55(5):633-642.
41. Expert Panel on effective ways of investing in Health (EXPH). Innovative payment models for high-cost innovative medicines. *Health*; 2018. https://ec.europa.eu/health/sites/health/files/expert_panel/docs/opinion_innovative_medicines_en.pdf. Accessed March 24, 2021.
42. Morrison E, Webb D. UK Health Technology Assessment and value based pricing. In: Babar Z, ed. *Pharmaceutical Prices in the 21st Century*. Switzerland: Springer International Publishing; 2015:371-388.
43. Hurst L, Mahtani K, Pluddemann A, et al. Defining value-based healthcare in the NHS: The CEBM Report. Centre for Evidence-Based Medicine. 2019.
44. Current healthcare expenditure relative to GDP, 2017. 2020; Eurostat - Statistics Explained; 2017. https://ec.europa.eu/eurostat/statistics-explained/index.php/Healthcare_expenditure_statistics Accessed December 01, 2020.


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