Office of Health Economics Consulting

Consulting Report

Comparing Access to Orphan Medicinal Products (OMPs) in the United Kingdom and other European countries

March 2017

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This study was commissioned and funded by Shire

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March 2017

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Funding and Acknowledgements

This study was commissioned and funded by Shire, and managed by Hanover Communications on behalf of Shire.

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EXECUTIVE SUMMARY

The European Commission's (EC) Orphan Medicinal Products Regulation intended to incentivise the research, development and marketing of new treatments for rare and chronically disabling or life-threatening diseases. Marketing authorisation granted to orphan medicinal products (OMPs) is however only the first step; patients have access to medicines once reimbursement or health technology assessment (HTA) decisions are implemented by national health systems.

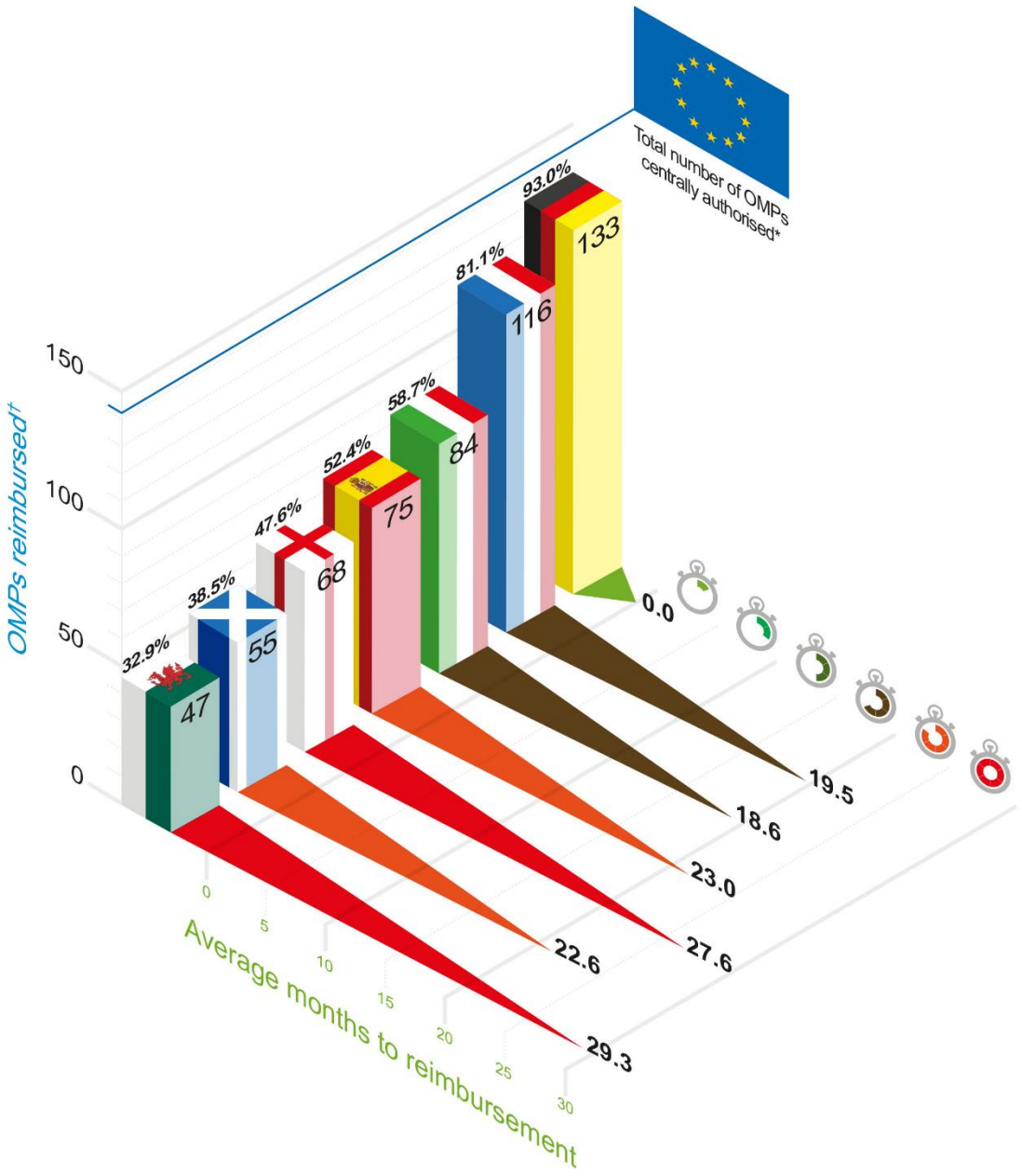
The primary objective of this study was to compare the availability of, that is the possibility of prescribing, and access to, that is the full or partial reimbursement by the public health service, OMPs in the devolved nations in the United Kingdom (UK) and in France, Germany, Italy and Spain.

Data were collated on: marketing authorisations, HTA decisions, centralised commissioning and/or reimbursement decisions, and respective dates of these events in the UK countries (England, Scotland and Wales), France, Germany, Italy and Spain for all the OMPs authorised since the implementation of the Regulation in 2000. Availability of and access to OMPs in each country was calculated (as a percentage) and compared. The average number of months from authorisation to reimbursement for OMPs in each country was also estimated.

Our analysis found that since the implementation of the Regulation in 2000, 143 OMPs obtained a marketing authorisation in the European Union (EU). These OMPs are most widely accessible in Germany and France. In the other countries between 30% and 60% of OMPs are reimbursed. In particular in England, less than 50% of centrally authorised OMPs are routinely funded by the NHS, with one-third of these recommended by NICE. The remaining products are directly procured and made available to patients by NHS England via commissioning policies or through the Cancer Drugs Fund. In Germany reimbursement is automatically granted to all medicines which receive a marketing authorisation, immediately after authorisation. In the other countries, the shortest time from authorisation to a reimbursement decision is observed in France and Italy which takes on average 19 months (see infographics below which refers to the comparison of access to OMPs across EU countries included in Figure 4 of the report).

A robust assessment of the degree of access to OMPs across Europe is limited by differences in the national HTA and reimbursement systems and the heterogeneous information made publicly available on their decisions. Nonetheless, our study suggests that the intended effect of the Orphan Medicinal Products Regulation to grant equal availability to OMPs to patients in the EU has been partially achieved, but significant variations in availability and access are observed in the countries included in our study.

Figure E1: Access of OMPs and average number of months to reimbursement of OMPs



* 143 OMPs obtained a marketing authorisation since the implementation of the EU Regulation on Orphan Medicines (Regulation (EC) No 141/2000).

† OMPs reimbursed refers to Health Technology Assessment (HTA) recommendations to use or inclusion in reimbursement lists in respective national health systems.

1. BACKGROUND AND OBJECTIVES

Orphan medicinal products (OMPs) are medicines used for diagnosing, preventing or treating life-threatening or chronically disabling diseases that are rare and affect not more than 5 in 10,000 persons in the European Union (EU) (prevalence criterion for designation of orphan status).[1] Pharmaceutical companies were unwilling to develop such medicinal products under normal market conditions, as the cost of bringing them to market would not be recovered by the expected sales of the products without incentives (insufficient return on investment).

In 2000 the Regulation (EC) No 141/2000 on Orphan Medicines established a procedure in the EU for the designation of OMPs and put in place incentives for the clinical development and protection of medicines for rare diseases. In addition, OMPs fall under the mandatory scope of Regulation (EC) No 726/2004 and therefore must be authorised in the EU through the centralised procedure. This legislation has led to an increased number of OMPs developed and authorised in the EU since its implementation in 2001. A report published by the Commission DG Health and Food Safety in February 2016 "Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products. State of Play 2015" (Ref. No. SWD (2015) 13 FINAL) describes initiatives put in place by the EU member states to increase the availability of OMPs in their countries.[2] Consequently, approximately 140 OMPs have received a marketing authorisation since 2001 for the benefit of European patients with rare and chronically disabling or life-threatening diseases. Marketing authorisation is however a first step, medicines are generally made available to patients when recommendations for pricing and reimbursement are published and implemented by the national health systems; these reimbursement decisions are made by each individual EU member state and can sometimes delay the access to new medical technologies and to OMPs in particular (Garau and Mestre-Ferrandiz, 2009).

A previous study conducted by the OHE (Garau and Mestre-Ferrandiz, 2009) showed considerable variation of access to OMPs across countries in the EU. The access was particularly limited in England and Wales since only two OMPs had received a positive recommendation from the National Institute for Health and Care Excellence (NICE) at the time of the study. Since then, there have been a number of changes in the pricing and reimbursement arrangements including performance based reimbursements, risk sharing and patient access schemes. This report presents an updated analysis of the access to OMPs in the United Kingdom (UK), specified as the devolved nations of England, Wales and Scotland, and in the four largest EU countries (France, Germany, Italy, and Spain).[3]

This study has informed the development of another report commissioned by Shire, and written by a steering group, on equity and access to OMPs and presented at a Rare Disease Summit on the 16th of March 2017 in London.

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[1] Regulation (EC) No 141/2000 (The Orphan Medicinal Products Regulation) http://ec.europa.eu/health/files/eudralex/vol-1/reg_2000_141/reg_2000_141_en.pdf

[2] This report can be accessed at the following URL: http://ec.europa.eu/health//sites/health/files/files/orphanmp/doc/orphan_inv_report_20160126.pdf

[3] Northern Ireland was not included in our analysis as there is no HTA agency in the country.

The primary objectives of the study were to:

- Quantify the "availability" of OMPs defined as the number of orphan products (sometimes approved in more than one therapeutic indication) which can be prescribed to patients in the UK, France, Germany, Italy and Spain compared to the number of OMPs which received a marketing authorisation between 2000 and the 31st of May 2016.
- Quantify the "access" to OMPs by looking at the Health Technology Assessment (HTA) and reimbursement decisions concerning OMPs for this same period in the respective national health systems.
- Estimating the average time (months) between the marketing authorisation and recommendation/reimbursement in each of these countries.
- Present key insights on market access and comparison among the countries considered in access and time to access.

Section 2 of the report describes the methods and data sources employed. Section 3 provides a country-by-country description of the data used and results of availability and access to OMPs based on the country information extracted. Section 4 compares key results of availability and access to OMPs in the selected countries. Section 5 provides a discussion on the limitations of the study. Section 6 concludes. Summaries of national policies affecting OMPs are included in the Appendix.

2. METHODS AND DATA SOURCES

The information extracted aimed at comparing the availability and access to OMPs in the EU countries included in the study. Below we provide the definition that was used for "availability" and "access". Note that, owing to the different regulations and information made available by the relevant bodies it was deemed necessary in some countries that availability and access be measured differently.

Availability was defined as the possibility that an OMP can be prescribed within the national health system and dispensed in pharmacies or hospitals (even if not reimbursed by the national health system) or is being used following clinical development, for example in compassionate use programmes or early access schemes.

Not all OMPs centrally authorised are immediately available following the granting of the marketing authorisation. Some countries have a national process of transposition of the marketing authorisation granted by the EC into their national law and sometimes pharmaceutical companies may decide not to market the OMPs for which they hold a marketing authorisation in all EU countries. Furthermore some OMPs may be made available before the granting of the marketing authorisation via early access schemes or compassionate use programmes. Therefore, the extraction of data on availability considered any decision issued by a national regulatory authority allowing the use of these OMPs in their territory. The information collected to measure the availability of OMPs authorised since 2001 includes (depending on the national laws and the data available in each individual country):

1. Whether these OMPs have been marketed in the country?
2. Whether these OMPs received an authorisation for use before the granting of the marketing authorisation, specifically through an early access scheme?
3. Whether these OMPs were referred to a national HTA evaluation programme?

We considered that an OMP was available, namely could potentially be prescribed by physicians regardless of reimbursement, when a decision was issued by a national regulatory authority allowing the use of these OMPs in a given country. Information on availability is not always made publicly available. Therefore, we used all available public sources of information to estimate the availability of OMPs authorised since 2001 in the countries included in our study. In the UK, the decision on use information was obtained from the respective evaluations published by the national HTA bodies and from the commissioning policies published by NHS England. In France, the marketing of OMPs generally followed the decisions published by the French regulatory authorities. In Germany, Italy and Spain the information on decision on use corresponds to the national process of transposition of the EC authorisation.

Access was defined as a full or partial reimbursement of an OMP by the public healthcare system. The information on reimbursement of centrally authorised OMPs was collected taking into account the different national reimbursement policies and included the rate of reimbursement, when applicable. For example, Germany grants an automatic full reimbursement to all authorised OMPs, conversely the reimbursement of OMPs in the National Health System (NHS) in England is not automatic. New OMPs are usually referred to NICE which assesses their cost-effectiveness. NICE makes recommendations concerning the funding (or not) of these medicines in the NHS which must be implemented by local commissioners. Specifically for England, we also considered specialised commissioning decisions or funding via the Cancer Drugs Fund (CDF). However, for the sake of clarity in the report, we refer to all of these funding decisions as OMPs being "reimbursed".

2.1. Data sources and data extraction

We obtained the list of OMPs authorised via the centralised procedure since 2001 from the European Medicines Agency's (EMA) and DG Health and Food Safety's websites. We have included all the medicinal products which have received an orphan designation and which have been authorised by the EC as OMPs, regardless of the subsequent expiry of the period of market exclusivity (and therefore loss of orphan status). We have used the current community register of medicinal products authorised via the centralised procedure published by the EC,[4] all the annexes of the Annual Reports published by the EMA since 2001 which contain a listing of the CPMP/CHMP opinions on OMPs and their authorisations[5] and the report "Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products. State of Play 2015" (Ref. No. SWD(2015) 13 FINAL) published by the Commission DG Health and Food Safety in February 2016.[6] The time period covered 2000, i.e. date of implementation of Regulation (EC) No 141/2000 on OMPs, to the 31st of May 2016 and the information extracted included the invented name, international non-proprietary name, orphan indication(s), date of EC decision (date of the marketing

[4] The Community registers of medicinal products for human use and orphan medicinal products are available at the following URL: https://ec.europa.eu/health/documents/community-register/html/index_en.htm

[5] The annual reports and annexes can be accessed at the following URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000208.jsp&mid=WC0b01ac058002933a

[6] This report can be accessed at the following URL: http://ec.europa.eu/health//sites/health/files/files/orphanmp/doc/orphan_inv_report_20160126.pdf

authorisation), WHO Anatomical Therapeutic Chemical (ATC) classification code with a distinction between anticancer vs non-anticancer OMPs.

Secondly, national data were collected for these centrally authorised OMPs concerning HTA evaluations, funding or commissioning, and/or a reimbursement decisions. Information on the date of publication of these decisions has also been collected to estimate the time which elapsed between the EC marketing authorisation and the national reimbursement decision. The date of the reimbursement decision could be documented for France, Italy and Spain. For the UK countries, the date of reimbursement which was considered is the date of publication of the HTA decision on the respective HTA agencies websites. We acknowledge that there might be further delays in access after the publication, for example NHS England has 3 months to make the technologies recommended by NICE available to patients. Reimbursement is automatically granted in Germany, therefore we considered that the reimbursement date coincides with the launch date.

The retrieval of decisions made by the Scottish Medicines Consortium (SMC) took into account that the manufacturer can resubmit a dossier for the same product after a negative decision. The resubmission with new evidence can change the outcome of the HTA evaluation to a positive decision granting access to the OMP in Scotland. In case of repeated submissions to the SMC, we have considered the publication of a positive HTA decision with its corresponding decision and publication dates, to define the time when the OMP was made available in Scotland.

NICE has published different Technology Appraisal (TA) Guidance for the same OMP indication in a number of cases: ruxolitinib for primary myelofibrosis, bosutinib for chronic myeloid leukaemia, trabectedin for recurrent ovarian cancer. For these OMPs we have considered the last NICE decision and its publication date. Also, NICE published two different TAs for the same therapeutic indication for two OMPs: sunitinib for metastatic renal-cell carcinoma and nilotinib for chronic myeloid leukaemia. In these cases, NICE has separately appraised the first-line and second-line indications; both of which were considered in our analysis.

For HTA decisions in UK devolved nations, we queried the OHE proprietary database on medicinal products (the Medicines Tracker). Given the expected impact of the CDF in England, the analysis on availability and access in the UK was also conducted for oncology and non-oncology products. To further inform the analysis of access and availability we also compared the estimated time to access for OMPs and non-OMPs using descriptive statistics and survival analysis for NICE appraised technologies.

Northern Ireland was not included in our analysis as there is no HTA agency in the country. In practice, most NICE decisions are implemented locally which means that a positive NICE decision leads to reimbursement in Northern Ireland.

External experts were commissioned to extract data from Italy, Spain and to validate the data from Germany. Additionally, OHE interviewed relevant experts in the UK to understand the implementation of different policies relating to OMPs (particularly the implementation of the Advisory Group for National Specialised Services and Highly Specialised Technology (HST) programmes). Table 1 details the names and affiliations of the OHE members and external experts involved in the conduct of this study. We developed a protocol to ensure a systematic and consistent approach to data extraction for the UK HTA systems and the other four EU countries. The protocol is available upon request.

Table 1. Experts consulted for data collection and interviews

Country	Expert who extracted the data	Expert interviewed or consulted
France	Francois Maignen OHE	Francois Maignen OHE
Germany	Karla Hernandez-Villafuerte OHE	Stefan Walzer General Manager & Founder at MArS Market Access & Pricing Strategy GmbH
Italy	Paolo Pertile University of Verona	Paolo Pertile University of Verona
Spain	Jaime Espin Escuela Andaluza de Salud Publica Granada	Jaime Espin Escuela Andaluza de Salud Publica Granada
England	Francois Maignen OHE	Josie Godfrey Former Head of Policy at AGNSS and former Associate Director at NICE HST programme
Scotland	Bernarda Zamora OHE	Sandra Auld Director ABPI Scotland at the time of interview
Wales	Bernarda Zamora OHE	Bernarda Zamora OHE
Northern Ireland	n/a	Colette Goldrick Director ABPI Northern Ireland

Note: Northern Ireland was not included in the data extraction as they do not have a specific HTA agency, details of their adoption process are however given in the Appendix.

The following information was collected for France, Italy, Germany and Spain in a standard format which included the following fields:

(1) OMPs: The chemical name, orphan indication and date of designation was collected for the products which received an orphan designation in the EU. We collected the invented and international non-proprietary names of the 143 OMPs centrally authorised since 2001 including the date of authorisation and the orphan indication. Both initial and extension of indications were included in our analysis.
(2) Pre-authorisation (early access scheme or compassionate use): This information was completed for France and Italy and identifies which centrally authorised OMPs were used in pre-authorisation programmes with a concise description of the programme.
(3) Marketing: In France, it was possible to collect information as to which OMPs had been launched in the French market with the date of marketing. No information was available for Germany, Italy and Spain. Instead, the information from a national register or transposition of the centralised authorisation was used for Germany and Spain. For Italy, this information was assimilated to the date at which the first decision was published by the Italian Medicines Agency (AIFA) (NB: the Italian HTA agency).
(4) HTA information: From the HTA bodies in France and Germany the information includes whether there is a HTA evaluation for each OMP, with publication date and outcome of the HTA decision. HTA decisions are not published in Italy and Spain.

(5) Reimbursement: The four countries have information relative to reimbursement of OMPs and dates of reimbursement decisions. The only consideration of reimbursement is by the public health system.

The experts accessed public information for each country from the national HTA bodies, and from other national regulations when needed, to complete the information of variables in fields (2) to (5), matched for the 143 OMPs and indications completed by OHE in field (1). A complete list of data sources is included at the end in the reference section.

For the UK, the information described above (including HTA evaluation and reimbursement of OMPs in England) was already available in the OHE Medicines Tracker since the year 2000 for England and since 2011 for Scotland and Wales. The information for Scotland and Wales from 2000 to 2011 was completed from the published HTA evaluations from the SMC and All Wales Medicines Strategy Groups (AWMSG), respectively.

3. RESULTS

3.1. Orphan designations and marketing authorisations

Orphan designation is based on the criteria laid down in Regulation (EC) No 141/2000 (including in particular a prevalence criterion). Orphan designations are granted by the EC on the basis of the scientific opinion given by the Committee for Orphan Medicinal Products (COMP) of the EMA. The Committee for Medicinal Products for Human Use (CHMP) and the Scientific Advice Working Party (SAWP) may also provide advice on the development of OMPs after designation via the protocol assistance. In a later step the CHMP reviews the applications for marketing authorisation and gives a scientific opinion to the EC on the granting of a marketing authorisation if the product satisfies the quality, safety and efficacy criteria established in the Directive (EC) No 2001/83/EC.

Between 2001 and the 31st of May 2016, the European Commission (EC) has granted 1,360 orphan designations, most of them granted on the basis of the prevalence criterion.[7] Out of these 1,360 products, 143 (10.5%) have obtained a marketing authorisation according to the centralised procedure. Of these, nearly 40% (56) of the products were products indicated in oncology.

Table 2 shows that there has been an increase in both orphan designations and central marketing authorisations, although the resulting approval rates (comparing the number of designations granted by the EC with authorisations during the same period of time) varies over time. Table 2 also shows the time between designation and authorisation averages 4 years and 7 months for the whole period. This is decreasing over time and is just over 15 months for the OMPs which obtained a designation in 2014.

[7] European Commission (2016), Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products. State of play 2015.

Table 2. Orphan Designations and Marketing Authorisations

	2001-2005	2006-2010	2011	2012	2013	2014	2015	2016 (Jan-May)	**Total**
Number of OMPs designations	173	355	86	118	124	182	185	137	**1,360**
Number of OMPs authorised	22	45	7	12	10	17	20	10	**143**
% OMPs Designations (*)	12.7%	12.7%	8.1%	10.2%	8.1%	9.3%	10.8%	7.3%	**10.5%**
Average months elapsed from designation to authorisation (**)	72.7	54.0	47.1	29.4	19.9	15.6	n/a	n/a	54.7

(*) This percentage denotes the proportion of OMPs authorised compared to the number of designations granted by the EC during the same period of time.
(**) The computation of months from designation to authorisation is specific to the product, the last orphan designation which was authorised was designated in 2014 (but authorised in later years)

3.2. The United Kingdom (UK)

The information on availability and access of OMPs presented for the United Kingdom is based on the information published by the HTA agencies in England (NICE), Scotland (SMC), and Wales (AWMSG). Northern Ireland does not have its own HTA agency, therefore it is not detailed separately in this analysis however the recommendations by NICE could be applied. More details on the OMPs policies in the four devolved nations can be found in the Appendix.

Table 3 details the results of the analysis for England, Scotland and Wales, while Table 4 and Table 5 specify this for oncology and non-oncology OMPs, respectively. Tables 3-5 present the number of OMPs available in the UK nations as the number of "OMPs with a decision on use". The information used to define an OMP as available or used in England was obtained from the NICE evaluation programmes (TA and HST), NHS England commissioning policies and inclusion in the CDF. For Scotland, the available OMPs are assumed to be those appraised by the SMC, since the consortium has a mandate to evaluate all authorised medicines. The Welsh agency adopts NICE decisions when available and sometimes evaluates medicines not referred to NICE. Therefore, availability in Wales is restricted to these medicines with an evaluation published in AWMSG or NICE.

Firstly, an OMP was considered as available in the UK nations if we could find information on any HTA evaluation published by these agencies regardless of the outcome of this evaluation (whether the OMP is recommended or not). For instance, many of the medicines not recommended by the HTA agencies can still be prescribed by the treating physician if they have a marketing authorisation and are marketed in the country.

We note that some OMPs can be made available before the granting of the marketing authorisation under the Early Access Medicines Scheme. This pre-authorisation use has been regulated since 2015 by the Medicines and Healthcare products Regulatory Agency (MHRA). The scheme sees the medicines' regulator giving a recommendation for use on an unlicensed medicine, allowing doctors to prescribe it under their own responsibility before it is authorised. This availability is not considered in the numbers presented below on "OMPs with decision on use" for the UK.

With regard to access, Tables 3-5 also present this information in terms of the number of OMPs reimbursed. We consider reimbursement as resulting from a national decision to provide NHS funding, not from case-by-case basis resulting from a nominative application for a patient under exceptional circumstances, e.g. an Individual Funding Request (IFR) in England and Wales and Individual Patient Treatment Request (IPTR) in Scotland.

The first reimbursement mechanism considered is a positive HTA decision, which mandates funding in the case of NICE, and is followed by provision by other commissioning bodies in Scotland and Wales. We have separated HTA positive recommendation in two groups: "recommended" when the medicine is recommended for routine funding in the NHS for the same indication as the one included in the marketing authorisation; and "optimised", when the use of the medicine includes a restriction of the approved indication (e.g. after specified prior treatment, restriction to a subgroup of patients where the use of the product is considered to be cost-effective).

In England, there are alternative commissioning routes for medicines which were either not referred to NICE or that NICE decided that the technology would be "not recommended" for routine funding. These commissioning routes are specified under the different NHS England Commissioning Policies[8] (regional guidelines, clinical commissioning policies, service specification, and highly specialised criteria). For oncology OMPs, the CDF funds or used to fund some OMPs with negative or no decision by NICE.

Table 3. Availability and access to OMPs in the UK

	England	Scotland	Wales
Number of OMPs centrally authorised	143*	143	143
#OMPs with a decision on use	120	96	84
% of OMPs centrally authorised	82.8%	67.1%	58.7%
#OMPs subject of a HTA Appraisal	53	96	84
% of OMPs centrally authorised	36.5%	67.1%	58.7%
#OMPs Reimbursed, of which	68	55	47
# OMPs with HTA Decision Recommended	11	34	28
# OMPs with HTA Decision Optimised	12	21	19
# OMPs with NHS England Commissioning	32		
# OMPs included in Cancer Drugs Fund	13		
% of authorised OMPs	46.9%	38.5%	32.9%

* For these 143 OMPs, 145 different indications were appraised by NICE in England (split indications for sunitinib and nilotinib). Reported percentages for England were calculated over 145 indications.

[8] https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/12/nhs-england-drugs-list-v11.pdf [Accessed in September 2016 nhs-england-drugs-list-v10.pdf]

Table 4. Availability and access to OMPs used in oncology in the UK

	England	Scotland	Wales
Number of Oncology OMPs centrally authorised	56*	56	56
#Oncology OMPs with a decision on use	49	45	42
% of Oncology OMPs centrally authorised	84.5%	80.4%	75.0%
#Oncology OMPs with HTA Appraisals	39	45	42
% of Oncology OMPs centrally authorised	67.2%	80.4%	75.0%
#Oncology OMPs Reimbursed, of which	33	26	21
# with HTA Decision Recommended	9	19	9
# with HTA Decision Optimised	9	7	12
# with NHS England Commissioning	2		
# included in Cancer Drugs Fund	13		
% of Oncology OMPs centrally authorised	56.9%	46.4%	37.5%

* For these 56 OMPs, 58 different indications were appraised by NICE in England (split indications for sunitinib and nilotinib). Reported percentages for England were calculated over 58 indications.

Table 5. Availability and access to non-oncology OMPs in the UK

	England	Scotland	Wales
Number of non-oncology OMPs centrally authorised	87	87	87
#Non-oncology OMPs with a decision on use	71	51	42
% of non-oncology OMPs centrally authorised	81.6%	58.6%	48.3%
#Non-oncology OMPs with HTA Appraisals	14	51	42
% of non-oncology OMPs centrally authorised	16.1%	58.6%	48.3%
#Non-oncology OMPs Reimbursed, of which	35	29	26
# with HTA Decision Recommended	2	15	19
# with HTA Decision Optimised	3	14	7
# with NHS England Commissioning	30		
% of OMPs centrally authorised	40.2%	33.3%	29.9%

Table 3 shows larger number of OMPs with a decision on use in England than in Scotland and Wales, with 120 (83%) out of 143 centrally authorised OMPs (145 specific indications) being considered in England. Scotland has slightly greater availability of OMPs than Wales. Again, it is important to note a different definition of the concept "decision on use/availability" in the three UK countries. Whilst, Scotland and Wales only include OMPs with an HTA evaluation, England also includes OMPs which are included in the list of medicines considered for NHS England Specialised Commissioning. Therefore, even though the SMC evaluates all new commercialised medicines, and Wales includes new medicines not being evaluated by NICE, the Scottish and Welsh figures may underestimate the number of OMPs available.

In Scotland, 39% of centrally authorised OMPs are reimbursed following a HTA decision. This broader access through HTA compared to the other devolved nations is observed both for oncology and non-oncology OMPs. However, England provides the broadest access when considering other routes of reimbursement since most non-oncology OMPs are made available via specific NHS England commissioning polices (30 vs 5 via NICE approval, see Table 5). In addition, 13 OMPs were made available at the time of the analysis via the CDF (note the CDF policy has since been modified). In total, 47% of centrally authorised OMPs are routinely funded in the NHS in England compared to 39% in Scotland and 33% in Wales. There is an overall broader access to medicines used in

oncology with 57%, 46%, and 38% of 56 centrally authorised OMPs in that therapeutic area which are made available in the NHS in England, Scotland and Wales, respectively.

A chronological analysis was undertaken of the time taken to issue a recommendation following the granting of the marketing authorisation in each of the devolved nations (except Northern Ireland). The first row of Table 6 reports the average months elapsing from EC authorisation and the publication of all HTA decisions (positive or negative). The second row reports the average months elapsing from EC authorisation and the publication of positive HTA decisions, which is slightly longer, by less than one month, compared to all the HTA decisions.

Table 6. Time to grant access to OMPs in the UK (average months elapsed since EC centralised authorisation)

	England	Scotland	Wales
To all HTA appraisals	26.9	21.9	28.7
To positive HTA decision recommended or optimised	27.6	22.6	29.3

When analysing the time between the marketing authorisation and the national HTA decisions presented in Table 6, the SMC appears to be quicker than NICE and AWMSG to issue its reimbursement recommendations with a respective difference of 5 and 7 months.

We have also compared the time taken by NICE to issue a recommendation after the marketing authorisation for OMPs and non-OMPs. Figure 1 presents Kaplan- Meier estimates of the survival function corresponding to these times (the ongoing evaluations were not censored). The median time taken by NICE to issue a recommendation is longer for OMPs than for non-OMPs (Table 7). However, the appraisals of some products referred to NICE took a very long time. For example, for topotecan the first TA was conducted in 2001 after 56 months of EC authorisation, but there were 4 successive TAs with the last 237 months had elapsed. Three appraisals were conducted for rivastigmine, the first TA was completed after 32 months and the last TA after 156 months. To control for the effect of these extreme observations and also to capture only duration to first HTA decisions, we also present Kaplan-Meir estimates which only include the first NICE TA (Figure 2). Although this Kaplan-Meir curve presents a shorter tail, the tail of the curve referring to non-OMPs is longer than for the OMPs. As a result, the average time taken by NICE to issue a reimbursement decision is largely affected by the medicines in the tail and it was longer for non-OMPs compared to OMPs. The median time is less sensitive to the extreme values included in the tail.

Figure 1. Months between EC authorisation and all NICE appraisals (the blue line refers to non-OMPs, the red line to OMPs)

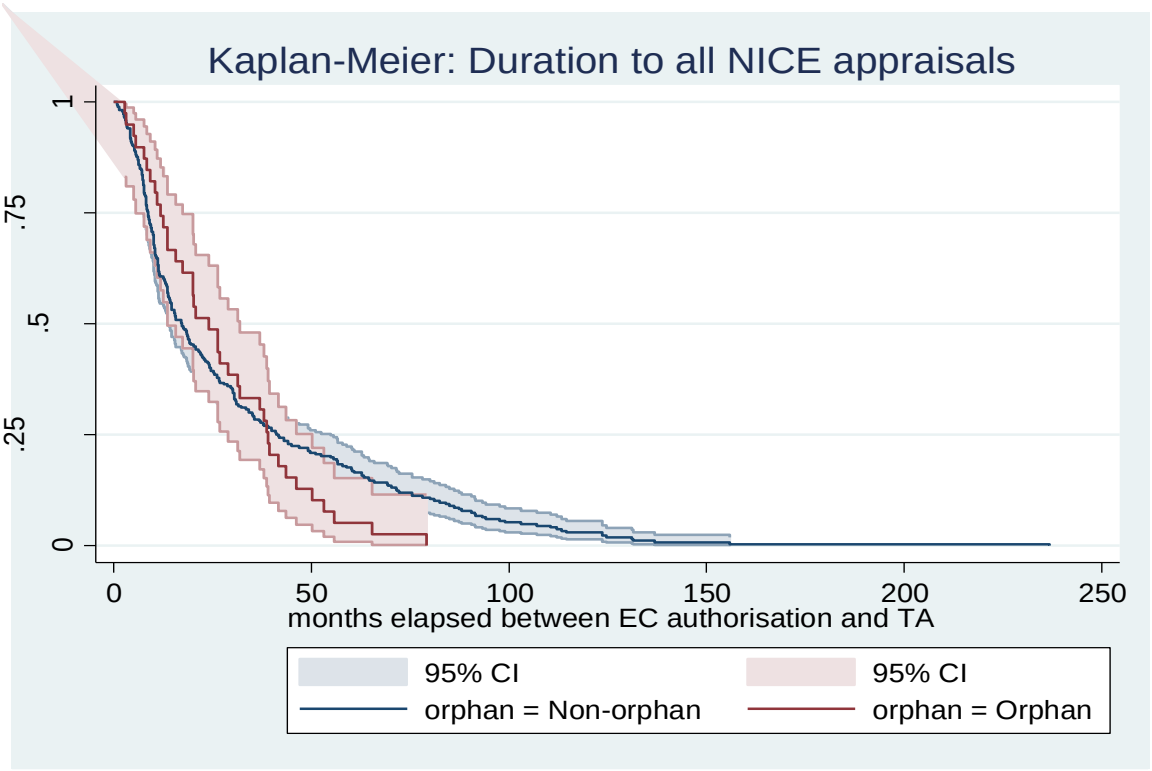


Figure 2. Months between EC authorisation and first NICE appraisals (the blue line refers to non-OMPs, the red line to OMPs)

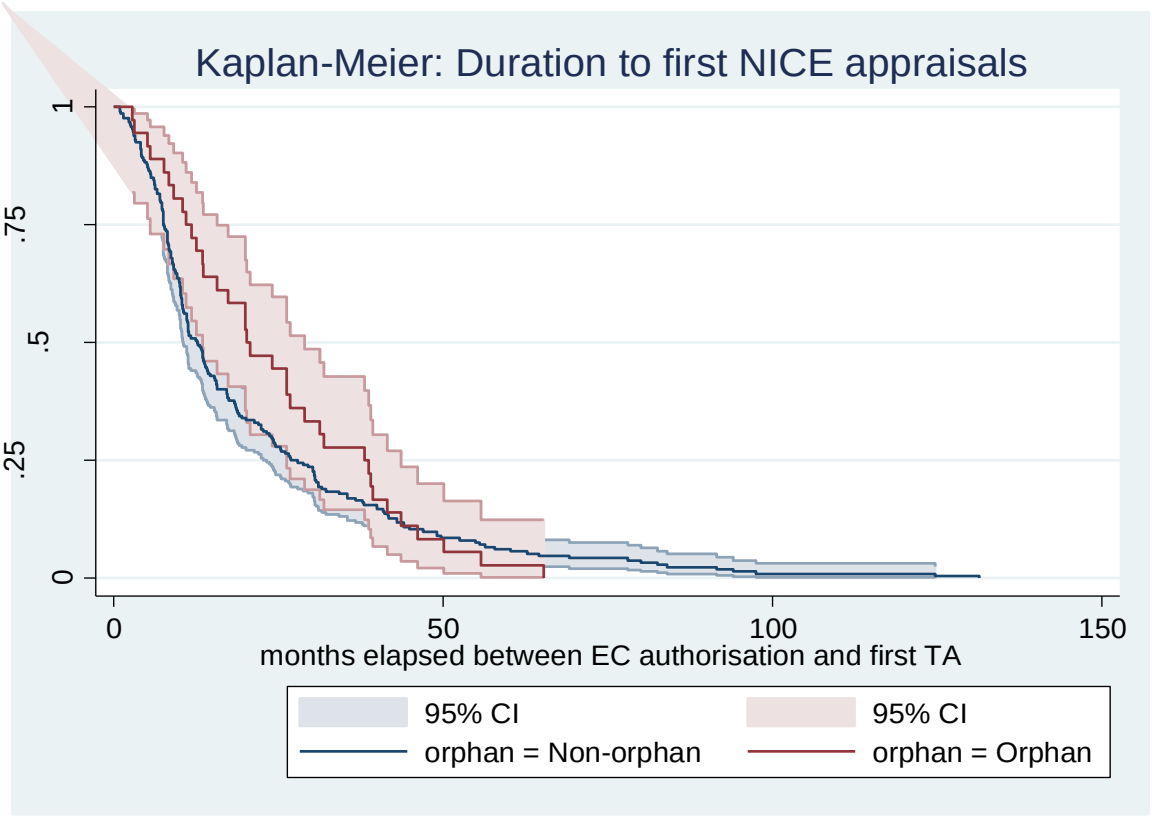


Table 7. Time used to issue NICE appraisals for OMPs and non-OMPs (median number of months between the marketing authorisation and the publication of NICE guidance)

	OMPs	Non-OMPs
	Median (95% CI) (N obs)	**Median (95% CI) (N obs)**
To all NICE appraisals	24.0 (15.6-31.2) (N=39)	17.2 (13.9-21.3) (N=267)
To first NICE appraisal	20.2 (13.4-29) (N=36)	12.7 (10.7-15.3) (N=212)

3.3. France

We obtained the specific information concerning the commercialisation of the OMPs in the official "base de données publique des medicaments" maintained by the Agence Nationale de la Securité des Medicaments (ANSM), The Haute Autorité de la Santé (HAS) and L'assurance Maladie[9] and on the evaluations conducted by HAS in France. We found instances where HAS evaluated OMPs which have not been marketed in France or even for which there was no documented access programme before the authorisation (for example, Glybera, alipogene tiparvovec, for familial lipoprotein lipase deficiency). In this case, availability in terms of "decision on use" is understood as the number of OMPs launched which are 109 out of the 143 OMPs centrally authorised (Table 8). Seven out of the 34 non-launched OMPs were made available through a pre-authorisation programme (Temporary Authorisation for Use), but we did not include these in the calculations of the number of products made available to patients. We present the access to OMPs through the Early Access Scheme available in France, the Temporary Authorisation of Use on a named patient basis (nominal ATU) or for all patients for a given indication (cohort ATU), separately.

In France, the number of HTA evaluations does not reflect the actual number of OMPs available in this country since the French HTA process reviews medicinal products regardless of whether they are marketed or not. There are 119 OMPs which have passed an HTA evaluation by HAS whilst only 109 OMPs have been marketed. In particular, 15 OMPs with a HTA evaluation had not been launched at the time of the analysis. Conversely, five OMPs have been marketed (but not reimbursed) in absence of any evaluation by the HAS.

In its recommendations, the HAS issues two different ratings, one on the Service Médical Rendu (therapeutic value) and one on the Amélioration du Service Médical Rendu (ASMR or added therapeutic value compared to the standard of care provided by the French healthcare system at the time of the appraisal). The Service Médical Rendu (SMR) rating granted by the HAS defines the reimbursement rate: 0%, 15%, 35%, 65% or 100%. Once a recommendation is issued by the HAS, the price of the medicine is subsequently subject to negotiations between the Pharmaceutical Company and the Ministry of Health, the reimbursement decision and the price are published in the French Official Journal. The ASMR determines the actual price of the medicine negotiated between the Company and the Ministry of Health. Reimbursement decisions by HAS are presented in Table 8.

[9] The database is accessible at the following URL: http://base-donnees-publique.medicaments.gouv.fr/

Note most patients with long term chronic disabling diseases (Affections de Longue Durée or ALD) have their medical expenses fully covered by the French National Health system (Sécurité Sociale/ l'Assurance Maladie) provided that an application for an ALD is submitted and approved by the Sécurité Sociale/l'Assurance Maladie. Consequently, the percentage of OMPs actually fully reimbursed by the French national healthcare system is certainly higher considering that many orphan diseases are generally considered to be long term diseases, with patients having their medical expenses including the medicines that they are prescribed for the treatment of the ALD fully reimbursed.

Table 8. Availability and access to OMPs in France

Number of OMPs centrally authorised	143
# OMPs with a decision on use	109
% of OMPs centrally authorised	76.2%
# OMPs with approved pre-authorisation use	83
% of OMPs centrally authorised	58.0%
# OMPs subject of an evaluation by the Haute Autorité de la santé (HAS)	119
# Positive HAS recommendations	115
% of OMPs centrally authorised	80.4%
# OMPs Reimbursed	116
% of OMPs centrally authorised	81.1%
% fully reimbursed of total reimbursed	56.9%

We found that 109 out of 143 centrally authorised OMPs (76%) are available in France. This figure is even larger when considering pre-authorisation access and HTA evaluation, which includes OMPs not launched in France. These alternate uses of availability explain the large access via reimbursement: 116 OMPs are reimbursed by the national health system, or 81% of all centrally authorised OMPs.

With respect to the time from authorisation to availability and access, Table 9 shows that HAS evaluations, are published on average 13 months after the marketing authorisation. Decisions on reimbursement can pre-date the authorisation and could artificially underestimate the actual delay in reimbursement if included in the analysis. Then, we also present delay in reimbursement excluding the OMPs whose reimbursement pre-dates EC authorisation. Nine OMPs with multiple indications were already available in France before authorisation (average 63.6 months in advance). Three OMPSs (carglumic acid, temsirolimus for mantel-cell lymphoma and ataluren) were reimbursed in France in advance of EC authorisation, indeed carglumic acid has been reimbursed since 2005 but was only authorised in 2011 (nNote: medicinal products made available via the ATU programmes are fully reimbursed by the French national health system). These have been made available via the pre-authorisation scheme.

The most relevant interpretation of duration from centralised authorisation to national availability and access should consider only OMPs made available after the granting of the authorisation. Table 9 shows the time elapsed to decision on use is nearly one year (12 months) on average. The reimbursement decision is on average 21 months, this is 8 months after the national HTA appraisal by HAS. All reimbursed medicines have a positive national HTA decision (recommended or optimised) by HAS, except daratumumab (Darzalex), which is reimbursed but was only recently authorised (May 2016).

Table 9. Time to grant access to OMPs in France (average months elapsed since EC centralised authorisation)

	All	With reimbursement after the authorisation
To decision on use	5.4	11.9
To all HTA appraisal by HAS	13.4	13.4
To positive HTA appraisal by HAS	13	13
To reimbursement	19.5	21.1

3.4. Germany

Information on availability in Germany is indicated by commercialisation of OMPs which implies their inclusion in the Lauer-Taxe database.[10] Reimbursement is automatic for these available medicines, and the HTA process introduced with the Act on the Reform of the Market for Medical Products (AMNOG) of 22 December 2010 only affected price negotiations but not reimbursement of OMPs. Those OMPs with a budget impact above €50m are subject to cost-benefit analysis by the independent Institute for Quality and Efficiency in Health Care (iQWiG), followed by a decision on "additional benefit" by the Federal Joint Committee (G-BA) which undertakes price negotiations.

Table 10. Availability and access to OMPs in Germany

Number of OMPs centrally authorised (including 76 products authorised since January 2011)	143
# OMPs with a decision on use	134
% of OMPs centrally authorised	93.7%
# OMPs subject of an evaluation by IQWiG/G-BA (since 2011)	45
# OMPs with positive G-BA recommendations (add. benefit)	37
% of OMPs centrally authorised since 2011 (37/76)	48.7%
# OMPs reimbursed	133
% of OMPs centrally authorised (133/143)	93.0%

Table 10 shows that 134 of the 143 centrally authorised OMPs are included in the Lauer-Taxe database register; these 134 OMPs are assumed to be available in Germany and all of them are fully reimbursed since their entry in the German market. Note bedaquiline which is indicated for pulmonary multidrug resistant tuberculosis (MDR TB), has been excluded from the reimbursement list due to not meeting package size regulation.

As discussed above, the HTA process was created in 2011 in Germany and it has evaluated 45 out of 76 centrally authorised OMPs since 2011. The HTA assessment is used in price regulations but does not affect access for the patient since reimbursement is mandatory regardless of the price.

[10] Lauer-Taxe database is made available at the following URL: https://www.lauer-fischer.de/LF/Seiten/Verwaltung/Kundencenter/1.aspx

Table 11 shows the time between the marketing authorisation to the inclusion in the national register and HTA decisions, where national register can pre-date centralised authorisation. Therefore, the relevant average delay is shown in the second column for OMPs with date post- EC authorisation. It is shown that all the processes are completed in an average period of less than a year, with 11 months for the relevant HTA decision to be considered by the G-BA for price negotiation. However, we note that as a result of price being reconsidered, medicines can be de-listed if companies cannot reach an agreement.

Table 11. Time to grant access to OMPs in Germany (average months elapsed since EC centralised authorisation, HTA decisions since 2011)

	All	With date post-EC authorisation
To decision on use	2.9	8.8
To HTA appraisal by IQWIG	7.1	7.1
To G-BA decision	10.9	10.9

3.5. Italy

The most comprehensive data on national availability is the registry of *Agenzia Italiana del Farmaco* (AIFA), which is the HTA agency publishing the list of medicines with a reimbursement decision or inclusion in the AIFA list;[11] this is the source of information to define general availability (decision on use) of OMPs in Italy. The inclusion in the registry by the AIFA follows the marketing authorisation in most cases, but there are instances where the AIFA published a decision before the granting of the marketing authorisation. Additionally, there is a pre-authorisation programme and all OMPs used in the early access scheme have systematically been registered by AIFA. Therefore, in contrast to the French case, general availability is not underestimated when considering separately availability in the form of pre-license.

The AIFA neither publishes the reports nor the date of its HTA decisions and evaluations. The information on drug reimbursement decisions is published in the "Gazzetta Ufficiale" (Italian Official Journal). Either the "local health authority" or the "region" can decide on reimbursement, except in the case of pre-authorisation use which is fully reimbursed (under the national law 648 of 1996).

Table 12 indicates an availability level at 87% which includes 125 OMPs, 84 of which are reimbursed by the national health system. There is availability of 41 OMPs prior to centralised authorisation via an early access scheme, and all of these OMPs are reimbursed.

[11] AIFA list of drugs: http://www.agenziafarmaco.gov.it/it/content/lista-aggiornata-dei-registri-e-dei-piani-terapeutici-web-based [Accessed in September 2016]

Table 12. Availability and access to OMPs in Italy

Number of OMPs centrally authorised	143
# OMPs with a decision on use	125
% of OMPs centrally authorised	87.4%
# OMPs with approved pre-authorisation use	41
% of OMPs centrally authorised	28.7%
# OMPs reimbursed	84
% of OMPs centrally authorised	58.7%

The time from authorisation to the inclusion in the AIFA register is just over 1 year (12 months), and reimbursement decisions are made within an average time of 19 months.

Table 13. Time to grant access to OMPs in Italy (average months elapsed since EC centralised authorisation)

	All	With date post-EC authorisation
To decision on use	11.2	12.4
To reimbursement	18.6	19.0

3.6. Spain

The AEMPS (Spanish Agency of Medicinal Products and Medical Devices) if required to transpose the marketing authorisation granted by the EC via a national code to allow the marketing of a medicine in Spain. Normally this national authorisation takes place soon after the granting of the authorisation by the EC and always before the reimbursement. Every medicine is Spain is approved for pricing and reimbursement by the Interministerial Commission for Pricing and Reimbursement. However, the HTA evaluation decision is not published. Therefore, the figures illustrating availability of OMPs in Spain are based on the information on the national authorisation by the Spanish Medicine Agency. There is no information on availability through pre-license programmes although medicines under clinical development can be used via compassionate use programmes since 2009.

The information on reimbursement of OMPs and on type of reimbursement of these products has been obtained from the BOT-PLUS database.[12] Most OMPs product are hospital prescribed and fully reimbursed. Those prescribed in outpatient visits are reimbursed at 90%, which is a special copayment for OMPs of 10% with a cap of €4.50 per prescription.

Table 14 shows low availability of OMPs in Spain, only 79 out of 143 centrally authorised OMPs are included in the AEMPS list. Most of these OMPs (75 out of 79) are reimbursed, including 9 OMPs partially reimbursed at 90% of their price.

[12] BOT-PLUS database at https://botplusweb.portalfarma.com/ [Accessed in September 2016]

Table 14. Availability and access to OMPs in Spain

Number of OMPs centrally authorised	143
# OMPs with a decision on use	79
% of OMPs centrally authorised	54.2%
# OMPs reimbursed	75
% of OMPs centrally authorised	52.4%
% fully reimbursed of total reimbursed	88.0%

The average delay between EC authorisation and inclusion in the Spanish Medicine Agency is of 9 months. Reimbursement decisions are delayed almost 2 years on average.

Table 15. Time to grant access to OMPs in Spain (average months elapsed since EC centralised authorisation)

	All
To decision on use	9.0
To reimbursement	23.0

4. COMPARATIVE ANALYSIS OF AVAILABILITY AND ACCESS ACROSS COUNTRIES

In this section, we compare the main results on availability and access for the three UK nations and the four European countries. These results are displayed in Figure 3 and Figure 4.

Figure 3. Comparison of Availability of OMPs across EU countries

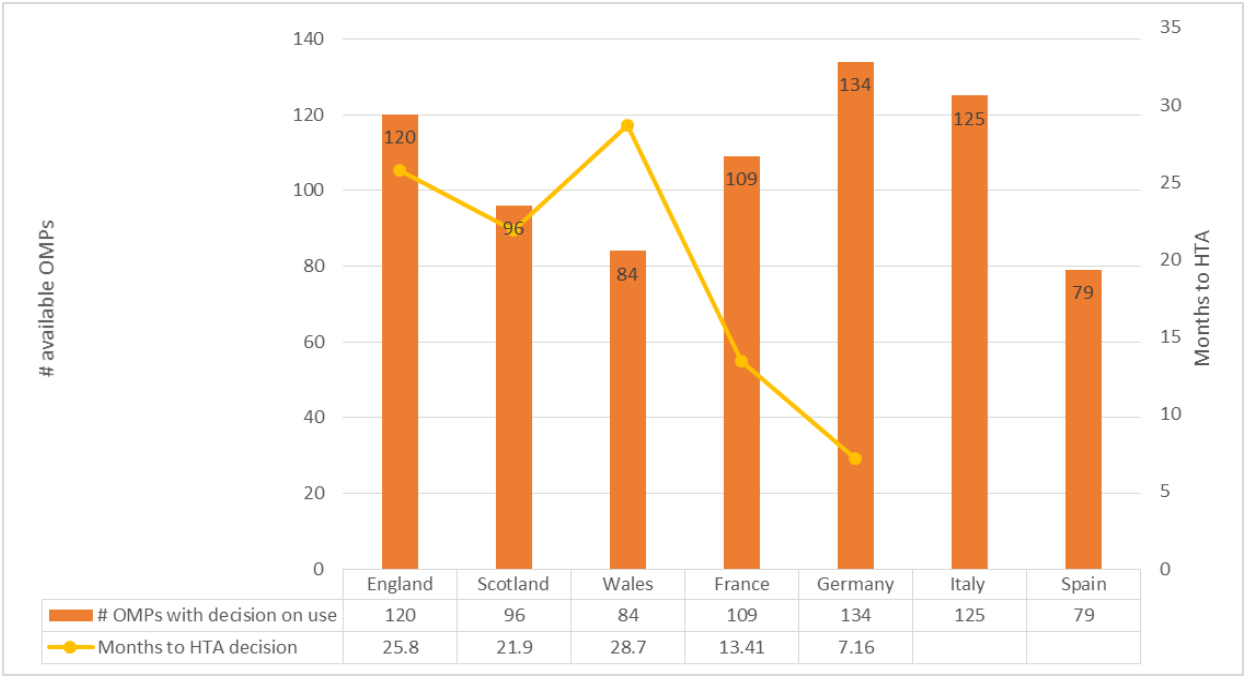
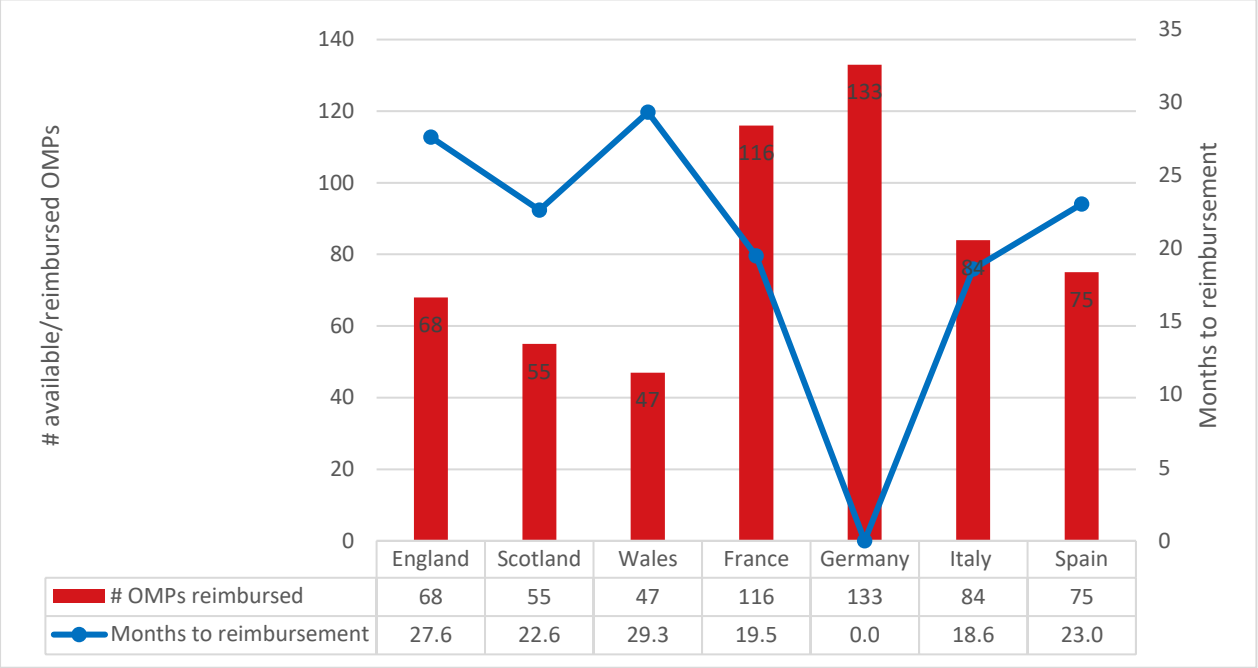


Figure 4. Comparision of Access to OMPs across EU countries



	England	Scotland	Wales	France	Germany	Italy	Spain
# OMPs reimbursed	68	55	47	116	133	84	75
Months to reimbursement	27.6	22.6	29.3	19.5	0.0	18.6	23.0

Since the EC Orphan Medicinal Products Regulation implementation in 2000, 143 OMPs have obtained marketing authorisation. These OMPs are most widely accessible in Germany and France. In Germany reimbursement is automatically granted to all medicines which receive a marketing authorisation, immediately after authorisation. In France OMPs are generally fully reimbursed via the ALD scheme (i.e. reimbursement of medical expenses for chronic diseases).

Germany has the shortest delay from the authorisation to the availability and access, taking into account that reimbursement decisions are automatic, with no delay from marketing authorisation. Moreover, reimbursement is only indirectly affected by HTA evaluations as these are used for price negotiations and that does not affect the patient free access.

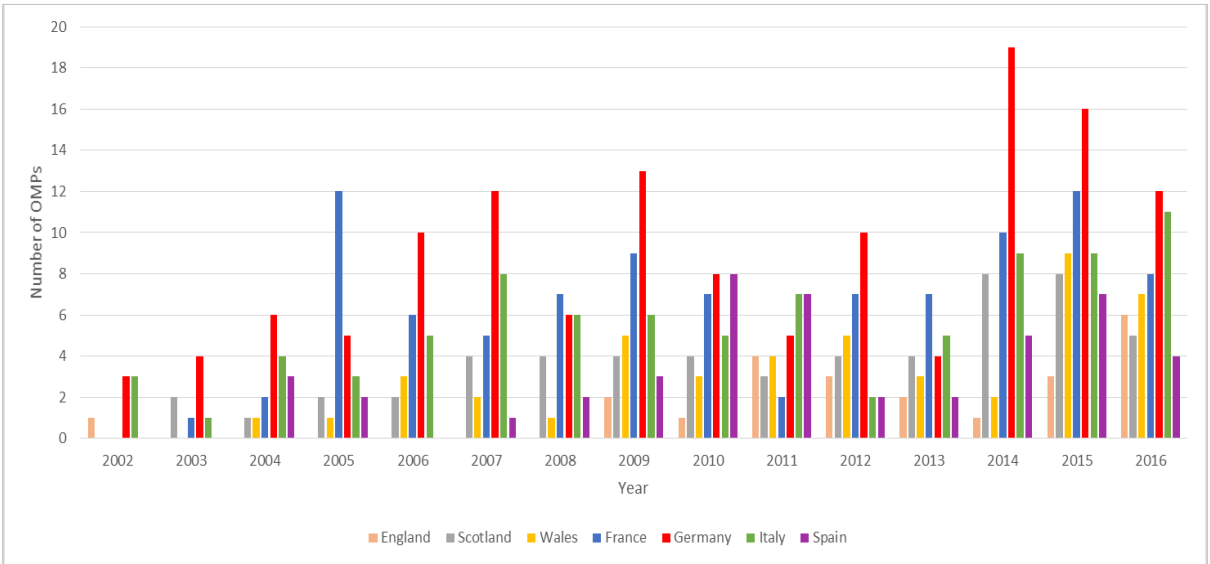
An average period of 19 months elapses between the authorisation and reimbursement in France and Italy, which is shorter than in the other countries (with the exception of Germany).

In England mechanisms providing access are diverse and cover less than 50% of all centrally authorised OMPs. Only one-third of OMPs routinely funded by the NHS received a positive decision from NICE. The remaining products are funded via NHS England specialised commissioning and the CDF. Notably these mechanisms have recently changed and are subject to further restrictions.

On average across all the seven countries it took 20 months between the granting of the authorisation and the HTA or reimbursement decision, this includes the immediate availability in Germany. If Germany is excluded, the average is 23.4 months between EC authorisation and reimbursement. As shown in Figure 4, Italy and France provides access (reimbursement) in time intervals below average (18.6 and 19.5 months

respectively). England and Wales are above average (27.6 and 29.3 respectively), while Scotland is similar to the average (22.6 months).

Figure 5. Comparison of reimbursement of OMPs by year



Note: there are missing dates for 45 OMPs in England, 21 OMPs in France and 18 OMPs in Spain.

Figure 5 shows the number of new reimbursement decisions concerning OMPs issued in each country per year between 2002 and 2016 (2016 only covers the months from January to May). Many reimbursement decision dates could not be documented, in particular those for OMPs reimbursed in England through NHS England commissioning policies or within the CDF. The same is true for many reimbursement decisions in France and Spain. Because of the missing dates, the numbers included in Figure 5 underestimate the actual number of reimbursement decisions issued in England, France and Spain.

Overall, a higher number of OMPs were reimbursed in 2014, 2015 and 2016 than in previous years in France, Germany, Italy, Spain and Scotland. The number of OMPs reimbursed in England and Wales decreased in 2014 compared to the previous years but subsequently increased in 2015 and 2016. This increased number of OMPs reimbursed in the national health systems of the countries included in the study is a logical consequence of a higher number of OMPs which have been authorised between 2014 and 2016 compared to the previous years (see Table 2).

Overall, the German and French healthcare systems reimburse the highest number of OMPs (see also Figure 4). We observed some variations over these years. France and Germany lead the ranking in number of OMPs reimbursed in most of the years but 2011 for which the countries which issued the highest number of reimbursement decisions were Italy and Spain. Italy also issued more reimbursement decisions concerning OMPs than Germany in 2013 and more than France in 2016.

5. LIMITATIONS

Several limitations of our study can be highlighted. The availability of OMPs has been documented using different criteria across the countries included in our analysis. Information on the actual marketing of medicines is not made systematically and

consistently publicly available. While many regulatory or HTA agencies publish information on the availability of OMPs in their country, the publication of HTA reimbursement decisions does not guarantee the actual availability of the medicine. This is for two reasons. Firstly, medicinal products are not systematically subject to a HTA evaluation, therefore the measure of the availability of OMPs via HTA decisions underestimates the number of products actually made available to patients. Secondly, some HTA agencies conduct evaluations involving OMPs that the marketing authorisation holder will subsequently decide not to market in this country, as was observed in France.

There are a number of mechanisms other than HTA approvals by which patients can access OMPs (including during the clinical development before the granting of the marketing authorisation). These include open extensions of pivotal clinical trials or compassionate programmes put in place and funded by the sponsors/marketing authorisation holders, early access schemes put in place by national regulatory authorities (e.g. France, UK) and individual patient funding requests (e.g. in the UK). Apart from examples of OMPs made available in pre-authorisation programmes, our data do not capture those alternative routes of funding in the national health systems and so might underestimate the actual number of OMPs available and accessible to patients.

Paradoxically, HTA positive recommendations might not necessarily lead to faster access to new technologies in practice since the recommendation needs to be implemented by the commissioning bodies in some countries included in our analysis (e.g. in the UK). In that sense our analysis might overestimate the number of OMPs actually reaching patients. Conversely, HTA negative recommendations do not necessarily impede the possibility of prescribing an OMP (e.g. in England). For that reason, our assumed number of reimbursed OMPs as those having a positive HTA decision in Scotland and Wales might underestimate the access to OMPs. Equally, the date of the positive HTA decision may be an unreliable surrogate variable to measure the time allowed to provide access to a given medicine to patients. This time to access to OMPs in clinical practice is shorter in the countries which have implemented early access schemes. This time is longer in countries where the implementation of HTA decisions is delayed (e.g. because of the budget impact of the medicine). Since the time to access new OMPs is affected by numerous factors, more research is required to have a better insight to the uptake of OMPs in clinical practice.

Our analysis was based on publicly available information. In some instances (in Spain), managed entry agreements are negotiated at regional level. No public information is available on these agreements. Equally, information on reimbursement is not published by the AIFA in Italy but dispersed among the publication of all laws and decentralised at different local jurisdictions.

Time elapsed between EU marketing authorisations included in our analysis and the dates of marketing in individual countries were not captured since our data sources do not include company statements on the dates of marketing of these products.

Cross-country comparisons need to be interpreted with caution since the way we defined and measured the availability of these products was not consistent across the countries included in the analysis owing to different national regulations and procedures. Finally, the availability of public information necessary to perform our study varies considerably across these different countries.

6. CONCLUSIONS

The annual numbers of orphan designations and marketing authorisations granted to OMPs have more than doubled between 2010 and 2015. One aim of the Orphan Medicinal Products Regulation (EC) No 141/2000 was that "patients suffering from rare diseases should be entitled to the same quality of treatment as other patients"; the Orphan Medicinal Products Regulation was therefore enacted to "stimulate the research, development and bringing to the market of appropriate medications by the pharmaceutical industry". Our study suggests that one of the intended effect of this regulation to grant equal availability to OMPs to patients in the EU via the implementation of the Orphan Medicinal Products Regulation was partially achieved with important variations in availability and access observed across the countries included in our study. In the countries considered in our study, we found that more than a half of centrally authorised OMPs were available, but that access to patients was further restricted by different national reimbursement policies, especially in the UK, Italy and Spain. Despite 15 years of Orphan Medicinal Products Regulation in the EU, there is still considerable variation in funding and provision of OMPs across individual EU countries. Our study was only conducted in 5 of the 28 EU member states. The assessment of degree of access to OMPs across Europe is limited by differences in the national HTA and reimbursement systems and the heterogeneous information made publicly available on their decisions.

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APPENDIX: DESCRIPTION OF THE ORPHAN MEDICINAL PRODUCT POLICIES AND REIMBURSEMENT PROCESSES IN THE COUNTRIES INCLUDED IN THE STUDY

BOX 1: OMPs policies in the UK

The Medicines and Healthcare products Regulatory Agency (MHRA)'s Early Access to Medicines Scheme started in April 2015. The scheme sees the medicines' regulator giving its scientific advice on an unlicensed medicine, allowing doctors to prescribe it under their own responsibility before it is licensed.

Nominative prescription and reimbursement of OMPs not approved for reimbursement through statutory funding policies. Medical services, including OMPs, not commissioned by the public health service can be publicly funded if a doctor or hospital consultant makes a nominative application for a patient under exceptional circumstances. The mechanisms are the Individual Funding Request (IFR) in England and Wales, and Individual Patient Treatment Request (IPTR) in Scotland.

ENGLAND

Advisory Group for National Specialised Services (AGNSS) was established in 2011 to give advice to Ministers on which specialised technologies should be nationally commissioned. AGNSS endorsed a work plan for national specialised commissioning for 2011/12. The decisions made concerned two OMPs: Eculizumab for the treatment of atypical haemolytic uraemic syndrome (recommended), and Tafamidis for familial amyloid polyneuropathy (not recommended). This programme has now been terminated.

National Institute for Health and Care Excellence (NICE). The Highly Specialised Technologies (HST) programme took over AGNSS in April 2013 to assess orphan drugs which fulfil some criteria (including a prevalence of the disease lower than 1:50 000 – this is a unique definition used in the UK only). Their decisions are mandatory for reimbursement by statutory finding. Three OMPs have been appraised under the HST to date, and five more are under an appraisal programme. Recently, a joint proposal by NICE and NHS England has been published, proposing a cost-effectiveness threshold for the OMPs evaluated via the HST programme of £100,000 per QALY.

Other OMPs are appraised by NICE under the Technology Appraisal programme.

A NICE positive decision (recommended or optimised) leads to a mandatory funding in the NHS. This funding should be made available within three months from the date that the Technology Appraisal Guidance has been issued unless an extension has been authorised by the Secretary of State.

The Cancer Drugs Fund (CDF) was established by the Government in April 2011 as a temporary solution to support clinicians and their patients gain access to cancer drugs not routinely available on the NHS. The CDF has benefitted over 95,000 patients but due to financial pressures, a new system has been established starting in July 2016. In the new system, **NICE** can also recommend to include some OMPs used in oncology where there is uncertainty in **the CDF whilst new evidence is collected**.

NHE England has alternative commissioning policies securing the reimbursement of some OMPs (clinical commissioning policies, agreed regional guidelines, and highly specialised criteria).

BOX 1: OMPs policies in the UK (cont.)

SCOTLAND

The Scottish Medicines Consortium (SMC) appraises all new medicines. The SMC decisions are not mandatory on reimbursement. However, SMC advice is followed in most of the cases by NHS Boards and Area Drug and Therapeutic Committees (ADTCs) reimbursement decisions.

In 2013 the SMC adopted a new policy for special assessment of OMPs, with three main novelties:

- Orphan and ultra-orphan status are included as a "modifier" criterion. The use of modifiers in submissions became common in 2013/2014, especially for cancer medicines, allowing to accept a higher incremental cost-effectiveness ratio (ICER) or uncertainty for these medicines.
- Patient and Clinical Engagement Groups (PACE). PACE gives patient groups and clinicians a stronger voice in SMC decision making, and allows a more flexible approach in considering medicines for end of life treatment and rare diseases.
- Patient group submissions include patient and carers views and experience as part of the information to be evaluated.

New Medicines Fund was created in 2014 with £40m to support the costs of prescribing OMPs. This fund expands and replaces the Rare Conditions Medicines Fund established in 2013.

WALES

The **All Wales Medicines Strategy Group (AWMSG)** appraises all new licensed medicines, with no cost-effectiveness threshold, providing that an assessment is not on the intended work programme for NICE within the succeeding twelve months.

Health boards are expected to implement NICE guidance and **statutory funding directives apply with regards to NICE technology appraisals.** Since April 2009, health boards have also had a legal requirement to implement AWMSG recommendations within three months.

In 2015, new policy for assessment of OMPs. This policy introduces similar criteria to those introduced in Scotland:

- Additional evaluation criteria (e.g. severity of the disease, unmet need, innovation) where the ICER is above the accepted threshold. These criteria add to the end of life criterion introduced in 2011.
- Apart from the manufacturer's submission, the AWMSG will take into account the opinion of clinical experts and submitted views of patients/patient organisations/patient carers summarised in the Clinical and Patient Involvement Group (CAPIG).

BOX 1: OMPs policies in the UK (cont.)

NORTHERN IRELAND

There is no HTA agency in Northern Ireland. Since 2006 the Department of Health, Social Services and Public Safety (HPSS), a part of Health and Social Care (HSC), reached a formal arrangement in which it reviews NICE decisions to determine whether they are locally applicable. Any required amendments are made and the decision then ratified and reflected by local HSC trusts. In practice, most NICE decisions are implemented locally, meaning that a positive NICE decision should lead to reimbursement in Northern Ireland.

Northern Ireland has recently adopted a decision to **reimburse the ultra-orphans appraised by NICE HST** process, to date this includes:

- eculizumab for Atypical hemolytic uremic syndrome – 2015;
- elosulfase alfa for mucopolysaccharidosis, type IVa – 2015;
- ataluren for Duchenne muscular dystrophy – 2016;
- five OMPs are under HST evaluation.

A **Policy Guidance** is being drafted aiming at achieving equal access to OMPs as England. The manufacturer should bear the responsibility of guaranteeing the same managed entry agreement as in England.

BOX 2: OMPs policies in France

Pre-authorisation access: compassionate use programmes include Autorisations Temporaires d'Utilisation (ATU) granted by the French National regulatory authority, the Agence Nationale de Securité des Médicaments (ANSM) either on a named patient basis (nominal ATU) or by indication (cohort ATU). Products in ATU are fully reimbursed.

Once authorised, reimbursement follows the Service Médical Rendu (SMR) granted by HAS: reimbursement rate (0%, 15%, 35%, 65% or 100%).

Patients with chronic illnesses (ALD) have their medicines fully reimbursed by the national health system.

For high costs medicines, price regulation and negotiation is based on the HAS criterion of Amélioration of Service Médical Rendu (ASMR). If ASMR qualifies between exceptionally innovative to very good (I, II, III), the price of the OMP is accepted at its European level and the OMP reimbursed and made available via the "liste-en-sus" or "retrocession" procedures. For OMPs with ASMR IV or V, the price is regulated depending on its comparator medicine. Nonetheless, **most OMPs follow a price-volume agreement**, often used in combination with a 'cap' restricting annual sales to a certain limit but obliging to provide the drug to all eligible patients, so that the company must payback for any excess to this limit.

BOX 3: OMPs policies in Germany

National Plan of Action for People with Rare Diseases was published in 2013.

Pre-authorisation access: There is not a formal authorisation programme in place but it can be authorised on a case by case basis - physicians could request the use for a particular patient provided that it is end of life treatment, and there is no alternative treatment.

Tax exemptions and research incentives

The Act on the Reform of the Market for Medical Products (AMNOG) of 22 December 2010 includes special allowances for OMPs:

- Benefit is considered proven at EC market authorisation for OMPs with budget impact less than €50m per year. Thus, once authorised at European level, **all OMPs are fully reimbursed** by the statutory health insurance (GKV) at the price set by the manufacturer.

Those OMPs with a budget impact above €50m are subject to cost-benefit analysis by the independent institute iQWiG, followed by price negotiation. This process allows for lower evidentiary requirements than for general medicines (lower statistical significance levels (10% rather than 5%) and surrogate endpoints) and is completed in 12 months after EC marketing authorisation.

BOX 4: OMPs policies in Italy

Pre-authorisation access: compassionate use

National scientific advice fee reductions, €8m research fund, dedicated fund for unauthorised orphan drugs awaiting approval (€17m in 2013).

Special pricing and reimbursement arrangements for OMPs:

OMPs are allowed a price premium with respect to the reference price of the therapeutic category and the comparative daily cost for drugs with same therapeutic indication (Law 326/2003).

The pricing and reimbursement decision must take no more than 100 days (Legge di Stabilita 2014).

Economic protection/risk sharing mechanism in the price-volume agreements against exceeding pharmaceutical expenditure ceiling on a list of OMPs approved by the Italian Medicines Agency (AIFA) in February 2014.

Many OMPs have been reimbursed subject to the creation of a national disease registry to track patient eligibility, collect data on treatment response and other outcomes in clinical settings.

Law 648 allows the reimbursement of pharmaceuticals for which no therapeutic alternative exists (they may be commercialised in a foreign country or being in research and development pipeline) or pharmaceuticals to use for an indication which is different from those for which it has already been registered (provided that this can be considered an appropriate use, given the information available). Under this regime, the use is fully reimbursed by the NHS.

Cnn class addresses the problem that, on average, the time to reimbursement in Italy exceeded that of most other countries. Cnn products can be available before the price is negotiated between the producer and AIFA. Either the "local health authority" or the "Region" can decide to reimburse its use

BOX 5: OMPs policies in Spain

Pre-authorisation access: law from 2009 authorising use of drugs in R&D process for patients not participating in clinical trials (compassionate use).

National scientific advice and research fund for rare diseases (€16m in 2014).

Centralised online information and applications related to available OMPs managed by the Agency of Medicines and Medical Devices (AEMPS).

There are **no specific departures from the standard pricing and reimbursement process** for OMPs coverage decisions.