

The use of medicines in exceptional circumstances in Spain: adding perspective to early access

Abstract The use of medicines in exceptional circumstances refers to the use of non authorized medicines, or which are used outside the authorized conditions, and includes three different situations: (a) The use of medication in research or compassionate use; (b) The use of foreign medicines (medicines unauthorized in one country but authorized in others), and; (c) Off-label use (medicines outside the authorized conditions of use, or use out of indication). In Spain we intend to govern the period between authorization and price, with standard criteria, through Therapeutic Positioning Reports. The keys to manage this situation, in our opinion, could be: (1) A restrictive interpretation of access that can be made through the Therapeutic Positioning Reports, (2) with an agreement so that the medication is paid at the price at which finally it is financed, and (3) restricting this period of time to only a few months or less (e.g. orphan medicines).

Introduction

Access to medicines in exceptional circumstances (compassionate use, off-label use, and foreign drugs) is a health need. Many of these non-covered pharmacological needs are given in committed clinical situations, understanding such as chronic or severely debilitating diseases or those that they place patient's life in danger, and cannot be satisfactorily addressed with one authorized and commercialized medication.

The use of medicines in exceptional circumstances refers to the use of non authorized medicines, or which are used outside the authorized conditions, and includes three situations different well delimited in the Spanish Royal Decree (RD) 1015/2009 regulating the availability of medicinal products in special situations:

- (a) The use of *medication in research or compassionate use*;
- (b) The use of *foreign medicines* (medicines unauthorized in Spain but authorized in other countries, and;
- (c) *Off-label use* (medicines outside the authorized conditions of use or use out of indication).

The legislation limits the use of each one of them for those exceptional circumstances in which there is no other commercial therapeutic alternative and describe two different situations for each one, the *individual use* or those situations in which there may be a *collective use* (which the legislation states, respectively, temporary use authorization, use protocol or recommendations of use).

The Spanish procedure is absolutely guarantor [1], requiring for its authorization: 1) the informed consent of the patient; 2) the request of a specialist physician; 3) the conformity of the Medical Chief Director of the health-care center; 4) the conformity of the promoter or pharmaceutical company, and, finally; 5) the authorization by the Spanish Agency of Medicines and Medical Devices.

Methods

The *use of medicines after the commercialization authorization and until price / reimbursement decision* can be considered as a fourth category and it represents one of the biggest problems, especially in the case of orphan medicines and anticancer medicinal products [2]. It has special features, but from the point of view administrative manages the same as compassionate use.

Compassionate use

Compassionate use is what is known in the world as early access (medicines that are pending authorization). Early access really encompasses the individual compassionate use, the cohort compassionate use (or temporary authorization of use) and the expanded access (clinical trials with less stringent inclusion criteria).

Of the medicines that are authorized as compassionate use, approximately the half corresponds to medicines that have not been submitted even with authorization (most of the cases because they are still in clinical development and no have been authorized in any country of the world, and a minority that has already been authorized in other countries, especially the FDA, but not in the EU); The other half corresponds to a medication that has already been authorized in the EU and are pending the decision on price and financing. In a small percentage the drug was presented to authorization and was not authorized properly by withdrawal of the request during the evaluation, either by negative opinion.

The vast majority of compassionate authorized uses are for small cohorts of patients. With a big difference over the rest of therapeutic areas, oncology is the field in which greater numbers of medicines for compassionate use are authorized. The area of oncology is not only the percentage that represents a greater number of medicines, but it represents almost half of the compassionate authorized uses (patients) and total expense in compassionate use.

Foreign medicines

Foreign medicines come to cover three special needs: (a) medicines that are not authorized in Spain (and they have never been), though they may have or have been authorized their active principles and need another one pharmaceutical form not available in Spain, (b) medicines that are authorized in Spain but have supply shortages and that are temporarily imported as foreign medicines to cover that timely need (usually, important volumes), and (c) medicines that have been authorized in Spain and which, generally due to quality problems or loss of

commercial interest, have stopping to be marketed in Spain when its importation is necessary as foreign medication (usually low volumes).

Off-label use

The legislation left out of centralized authorization the use of medicines outside of indication or outside of the conditions of use authorized, to be understood as said centralization was an administrative burden (you must keep in mind that the vast majority of the use outside of indication are uses even well-established from the medicines). The legislation left the Agency's possibility to establish recommendations for use in those cases where one could be anticipated associated security problem or a significant impact on the system. In this sense recommendations have been established for use in a few cases, being the intent to go more in collaboration with the Autonomous Communities (AACC).

The Agency does not have data on the use without indication. The empowerment of the Policy of recommendations would allow for clear information for patients and health-care professionals, indicators and control exercised with the mechanisms available on those situations that may have a greater impact on security or spending in the National Health System (NHS).

Results

Medicines after marketing authorization and until the decision of price / reimbursement

The biggest problem is currently the management of medicines, between the period of authorization and the decision of price and financing, for two facts: (a) on one hand, though the number of new patients / year remains stable, the number of total authorizations for the continuation of treatment given that medicines do not end up being marketed effectively (this is significantly improved in the past two years); (b) for another, while there are early access programs in which the holder does not begin to charge for the medication until there is a decision on price and financing [3], others charge it medication from the first market in the world (USA, generally) or Europe (Germany, generally), which ends up increasing the cost in these programs because the price in the country of origin is more expensive.

The Agency manages the authorizations of compassionate use with restrictive criteria that they are not explicit to the professionals in order not to generate a demand for them part. In Spain we intend to govern the period between authorization and price with a criteria agreed with the AACC through the Therapeutic Positioning Reports (TPR). Table 1 shows the index of TPR currently available (May 2018). Most of this new drug targets include the recommendations provided by The Concise Guide to PHARMACOLOGY [4], focusing on anticancer drugs [5] but not only restricted to this area.

The keys to manage this situation, in our opinion, would be in (1) this restrictive interpretation of access (the medication still has no decision to price / financing) that can be made through the TPR, (2) with an agreement so that the medication (administered what is administered) is paid at the price at which finally it is financed or, if it is not financed, it is free, and (3) restricting this period of time to only a few months (six as a general rule as it marks the RD project of price / financing or less in special cases like orphan medicines).

With respect to these medicines, the Inter-ministerial Committee on Drug Prices agrees and issues Resolutions of price and financing by the General Directorate of the Basic Portfolio of Services of the National Health and Pharmacy System. The Inter-ministerial Committee for Drug Prices, attached to the Secretary General of Health and Consumer Affairs, is the competent body responsible for subject of the ex-factory price for each presentation of medication to be included, or already included, in the pharmaceutical benefit of the NHS. E.g. Establishing of singular reserves within the scope of the NHS, consisting of limiting their dispensation in the Hospital Pharmacy Services, without the need for a visa, to patients not hospitalized; Establishing a maximum cost per patient and the subsequent treatment will be carried out without cost for the NHS; Annual review of the prices now fixed, follow-up and control of the expense caused and of the consumption through the computerized process SEGUIMED. The laboratory is obliged to register in this application and to communicate on a monthly basis the information regarding the sales made of the medicine to the NHS.

Establishment of a maximum annual amounts ('ceiling') of expenditure in each of the following two years, for the entire NHS (including the Mutuality's, as well as Correctional Health Care), to count from the month of entry into the NOMENCLATOR the financing of this medicine and considering the price of the container according to pre-fixed annual amounts [6]. This annual ceiling is distributed among the AACC of the NHS, so that a regional ceiling is established for each of them based on the municipal census. If an AACC exceeds the established autonomic quota, the laboratory that holds the marketing authorization, undertakes to cover the total costs derived from supplying the medicine in that AACC. In the case of exceeding the maximum ceiling of expenditure set at the national level, the laboratory holder will be responsible for the total costs arising from the supply of the medicine throughout the national territory, regardless of whether any of the AACC had not exceeded their corresponding quota. Once the ceiling for expenditure corresponding to the second year has been completed, the price per container will be adjusted according to the number of containers billed in that second year, provided that said ceiling is exceeded.

Discussion

Transparency is an issue that has been given considered by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Society for Medical Decision Making (SMDM) Modelling Good Research Practices Task Force [7], yet there are few signs of improvement in practice. Even so, for sponsor-employed scientists and clinicians, they are qualified enough to participate as authors of company-sponsored research publications [8].

As proposed by Sampson and Wrightson, it could be a good strategy the creation of a registry and linked database of model-based economic evaluations [9]. Several mechanisms, such as publication bias, methodological errors, miss-interpretation of findings and fraud, might jeopardized Health Technology Assessment (HTA). We absolutely agree with Carswell, McWilliams, and Ryan main conclusion: many published reports of economic evaluations incorrectly report the study perspective [10].

The ISPOR has published Global Health Care Systems Road Maps (ISPOR roadmaps). These roadmaps provide important knowledge on decision-making processes for regulatory approval, pricing and reimbursement for, e.g. pharmaceuticals, under a country-specific perspective [11].

Several international examples, to give just some Health Technology Assessment (HTA) roadmap examples, are, the National Institute for Health and Care Excellence (NICE) HTA processes in UK [12]; In France the economic evaluation (improvement of medical benefit), quality assessment of the methodological issues of the economic impact of the drug, and the temporary authorisation for use (ATU) process [13]. Another practical example is the Act for Restructuring the Pharmaceutical Market in Statutory Health Insurance (AMNOG), introduced in Germany in 2011[14-16]. In the Netherlands, the National Health Care Institute (*Zorginstituut Nederland*, abbreviation is ZIN) carries out HTA and manages the basic health insurance package [17]. The Agency for Health Technology Assessment in Poland (AHTAPol) became a formal government department in 2009 [18]. The Swedish HTA roadmap appeared to be the most up-to-date. However, additional information regarding the decision-making process between the Dental and Pharmaceutical Benefits Board (*Tandvårds- och läkemedelsförmånsverket*, or TLV), county councils and financing body is now available [19].

The conditional marketing authorization (CMA) pathway was initiated in 2006, although it was later integrated within the PRiority MEDicines (PRIME) scheme. In this sense, in March 2016 the European Medicine Agency (EMA) implemented the PRIME scheme, combining three different approaches to deal with these issues: accelerated assessment (AA), CMA, and compassionate use [20]. By the year 2018, an evaluation of the PRIME 2-year experience was published [21]. On the other hand, the UK started Brexit during spring 2016 and by October, that year already had a parallel scheme named “Accelerated access” for its NHS [22].

Globally, A legislative proposal for a Regulation of the European Parliament and of the Council on health technology assessment and amending Directive 2011/24/EU, adopted by the European Union (EU) Commission on January 2018 to standardize the assessment of a benefit for new medicines and medical devices among EU Member States (MS). According to the EU commission, reinforced HTA co-operation at EU level would lead to more transparency of the added clinical value of new medicines and medical technologies and would allow patients faster access to innovative healthcare products. The proposed Regulation on HTA covers new medicines and certain new medical devices, providing the basis for permanent and sustainable cooperation at the EU level for joint clinical assessments in these areas. EU MS will be able to use common HTA tools, methodologies and procedures across the EU, working together in four sections: 1) on *joint clinical assessments* focusing on the most innovative health technologies with the most potential impact for patients; 2) on *joint scientific consultations* whereby developers can seek advice from HTA authorities; 3) on identification of *emerging health technologies* to identify promising technologies early; and 4) on continuing *voluntary cooperation* in other areas.

Finally, with real-world evidence (RWE) Pharmaceutical Sciences deals with accelerated drug research, and pharmacoeconomic studies are providing a strategic framework for pharmacy practice and pharmaceutical policy [23-36].

Conclusions

1. What is already known about the topic?

Drug treatment effect size is a crucial component in determining the health gain and overall value of a new pharmacological therapy.

2. What does the paper add to existing knowledge?

Despite huge uncertainties in treatment, reimbursement was granted in almost all cases, indicating that early access may be considered relatively more important compared with other attributes in value-based pricing decision-making.

3. What insights does the paper provide for informing health care-related decision-making?

Still, most applications for reimbursement within public health care are granted, and early access appears relatively more important than other factors in value-based pricing decision-making.

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