

Role of the EMA specific marketing authorization procedures for early access on the time to patient access in Bulgaria

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Abstract

Despite the early access procedures for marketing authorization (MA) valid throughout the European Union still in the most of the Member states patient access to innovative medicines depends on cost-effectiveness, budget impact assessment and negotiations for price discount with the public payers.

Retrospective analysis on the availability and time to market access of medicines authorized under the European medicines agency's specific procedures for early access shows that despite the shortening of the time to market access after 2013, for most medicines still exceeds 365 days. This is due to the fact that requirements for pricing and reimbursement across EU is fixed to some degree and medicines with MA for early access are subject to the same legal requirements as the medicines with standard centralized marketing authorization. Some specific national legal requirements for pricing and reimbursement decisions, population of interest and manufacturers intentions to enter certain markets should also be considered.

Keywords

market access, specific procedures for early access, marketing authorization

Introduction

In 2005, the European Medicine Agency (EMA) imposed centralized procedure for marketing authorization (MA) for all biotechnology medicines and innovative therapies for chronic diseases with higher social burden and developed some specific procedures for early access in attempt to provide timely access to patients, especially in areas with increased unmet medical needs. Conditional marketing authorization (CA) and marketing authorization under exceptional circumstances are granted to a medicine that addresses unmet medical needs of patients on the basis

of less comprehensive data than normally required. These two types of marketing authorizations are valid for one year during which the marketing authorization holders must be in a position to provide the comprehensive clinical data in the future (EMA 2021).

EMA also developed a mechanism for accelerated assessment which reduces the timeframe for the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) to review a marketing-authorisation application. The medicines could be evaluated if the CHMP decides the product is of major interest for public health and therapeutic innovation (EMA 2021).

The further market and patient access, however, depends also on the market size and the local pricing and reimbursement procedures in the Member States which currently are not fully synchronized across the European Union.

Studies also show that the average delay in time to market and patient access for innovative medicines in Europe is approximately 400 days but for many Eastern European countries is above the average for the European Union (EU) (Uyl-de Groot et al. 2020). Despite the centralized procedure for marketing authorization valid throughout the EU for oncology medicines, still the time to patient access varies among the Member states mainly due to the local legal requirements for pricing and reimbursement decisions. Recent studies show significant variation in the time to market access to innovative medicines, and countries in which the decision making is based on cost-effectiveness assessment and negotiations with national regulatory authorities, a delay to patient access is observed (Ades et al. 2014; Pauwels et al. 2014; Ferrario 2018).

Despite the introduction of health technology assessment (HTA) as an instrument for transparent reimbursement decisions, still there are differences in the HTA methodologies applied across the European countries (Wilking and Jönsson 2005; Leyens and Brand 2016).

In order to foster patient access to innovative therapies, some countries have developed methodologies for market access agreements to reduce the financial burden and uncertainty for the public payers by sharing the risk between the payer and the manufacturer (Pauwels et al. 2014).

Reimbursement decision of innovative medicines in Bulgaria depends on cost-effectiveness and budget impact assessment and negotiations for price discount with the National Health Insurance Fund (NHIF). This prompted our interest to examine the current state and time to patient access for innovative medicines under the EMA specific procedures for marketing authorization for early access.

Methods

A retrospective analysis of the EMA database was conducted in order to assess the marketing authorizations by type, number and therapeutic areas in the period of year 1996–2020. Patient access for these medicines in Bulgaria was evaluated through the following indicators:

- degree of availability, measured by the number of medicines available to patients (Availability Index, AI) and based on the formula:

$$AI = \frac{\text{number of medicines included in the Positive Drug List (PDL)}}{\text{number of medicines with granted marketing authorization in EU}}$$

- average elapsed time between obtaining a marketing authorization and time of inclusion in the Positive Drug List in Bulgaria, measured in days based on the methodology of EFPIA (European Federation of and IQVIA for W.A.I.T. concept – *Waiting to access innovative therapy*.

Further analysis compared the time to market access in Bulgaria of medicines with standard centralized procedure for marketing authorization and those granted for use under the specific procedures for early access.

Data was proceeded through descriptive statistics with XLSTAT 2016 (Addinsoft) and R statistical language (4.0.1). Kruskal-Wallis test was used to establish a statistically significant difference for non-parametric data.

Results and discussion

Since its establishment to 2020, EMA had made scientific evaluation of 1503 medicines out of which 1192 were granted with centralized marketing authorization (MA). For 49 medicines marketing authorization was refused and for 262 – withdrawn.

For the observed period, 34 medicines received marketing authorization through conditional approval (CA), 37 –exceptional circumstances (EC) and 40 –accelerated assessment (AA) Table 1.

Table 1. Analysis of the marketing authorizations by type and number.

Indicator	Number of medicines
Scientific assessment	1503
Marketing authorization (MA)	1192 (79%)
Conditional approval (CA)	30 (2.5%)
Exceptional circumstances (ES)	29 (2.4%)
Accelerated assessment (AA)	38 (3.2%)
Refused MA	49 (3%)
Conditional approval (CA)	0
Exceptional circumstances (ES)	0
Accelerated assessment (AA)	0
Withdrawn MA	262 (18%)
Conditional approval (CA)	4 (1.5%)
Exceptional circumstances (ES)	8 (3%)
Accelerated assessment (AA)	2 (0.8%)

The first marketing authorization with procedure for early access was granted in 2006 when two innovative medicines received marketing authorization under EC. AA was conducted for the first time in 2007. CA was granted in 2010 for two medicines but shortly after that it was withdrawn for both of them, so the first CA for a medicine in EU which is still authorized was granted in 2011. For the observed period, 2016 was the year with the highest number of early access marketing authorizations – 13 new medicines were granted marketing authorization under the specific procedures.

In 2009 we noticed the highest number of granted marketing authorization with a total of 144 positive decisions. After 2013, a trend for a constant number on an annual basis was observed – an average of about 76 – Fig. 1.

The main therapeutic areas were rare, infectious and oncological diseases in which unmet medical needs have been identified.

Of the medicines, 31 granted with marketing authorization under the procedures for early access were included in the Positive Drug List (PDL) in Bulgaria between 2006

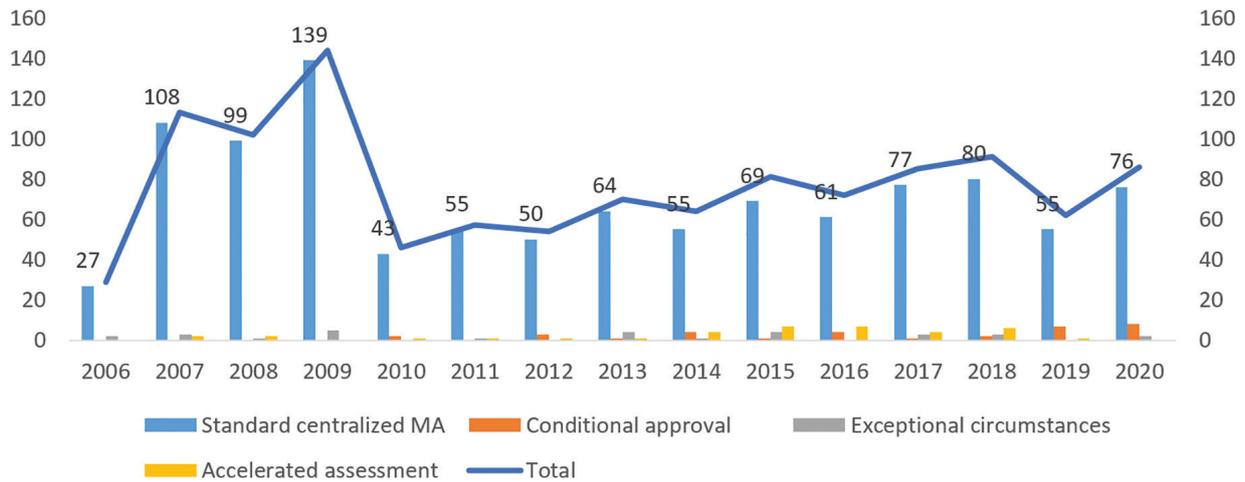


Figure 1. Number of marketing authorizations for 2006–2020.

and 2020. Three medicines have registered price in Bulgaria but are still not covered with public expenditures.

For the observed period, medicines authorized under the AA were associated with the highest average availability index – AI (0.39, SD 0.38) in Bulgaria, and the conditional marketing authorization led to the shortest average market access time – (AVG W.A.I.T. 760 days, SD 302) – Table 2.

Table 2. Average AI and time to market access in Bulgaria.

Availability Index	
Conditional approval	mean = 0.17 (SD 0.35)
Exceptional circumstances	mean = 0.08 (SD 0.21)
Accelerated assessment	mean = 0.39 (SD 0.38)
W.A.I.T. (avg)	
Conditional approval	mean = 760 (SD 302), n = 4, median = 730
Exceptional circumstances	mean = 1642 (SD 182), n = 2, median = NA
Accelerated assessment	mean = 1004 (SD 637), n = 9, median = 730

Time to market access was different for each medicine. In the first years of the period under review access time took longer but after 2013, a tendency for a significant reduction to 1–2 years from marketing authorization was observed – Fig. 2.

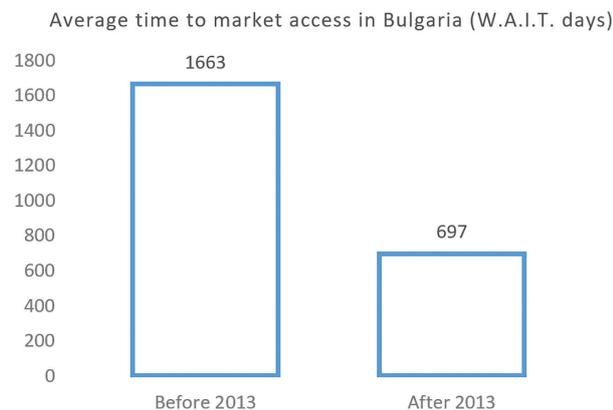


Figure 2. Average time to market access.

At first glance, the average time to market access of medicines with standard centralized marketing authorization (1036 ± 692) and those under the specific procedures for

early access show quite differing values (760 ± 302 for CA, 1642 ± 182 for EC and 1004 ± 637 for AA). As data is lacking for many of the listed years (because of no market access for the drugs), a statistically significant difference could not be established (p = 0.15). However, the median values for CA and AA are equal, both 730, and there is not sufficient data for median calculation of EC (n = 2).

Table 3. Average time to market access and availability index of medicines with standard centralized marketing authorization and the procedures for early access.

Availability Index	
Marketing authorization under early access procedures	mean = 0.36 (SD 0.27)
Marketing authorization under standard centralized procedure	mean = 0.42 (SD 0.18)
W.A.I.T. (avg)	
Marketing authorization under early access procedures	mean = 1091 (SD 584), n = 12, median = 913
Marketing authorization under standard centralized procedure	mean = 1036 (SD 667), n = 14, median = 801

Discussion

To our knowledge, this is the first study on national level providing general overview on the time to market access of innovative medicines authorized under the EMA specific procedures for early access.

The results show that despite the shortening of the time to market access after 2013, for most medicines it is still over 365 days. From one side, this could be explained with the fact that in Bulgaria the legislation for pricing and reimbursement of medicines is fixed and medicines with MA for early access are subject to the same legal requirements as the medicines with standard centralized marketing authorization. On other hand, we have to also consider the potential of the pharmaceutical market in Bulgaria, the epidemiological profile of the diseases, the population of interest and the position of the manufactures, and their intention to place the medicines to the Bulgarian market.

The findings of the current study confirm the results from another study which evaluated the time to patient

access to the new direct-acting agents (DAAs) for treatment of chronic hepatitis C in Bulgaria. The study showed that the new medicines reached the Bulgarian market within 1–2 years from marketing authorization. Out of seven DAAs, only one was authorized in the European Union through standard centralized procedure, the rest of the medicines received authorization through the accelerated assessment (Tsekov et al. 2020).

A study evaluating the market access for pharmaceuticals EMA's accelerated assessment procedure in France, Germany and the UK showed that timeframe from approval to reimbursement decision varied between the HTA (health technology assessment) bodies of the selected countries with HAS (Haute Autorite de Sante) providing the quickest and NICE (National Institute for Care and Health Excellence) – the slowest route to market access. This could be attributed to the fact that access to market in France was facilitated by the Temporary Authorization for Use (ATU) scheme. The authors concluded that alignment between the regulators and HTA authorities is needed to overcome the gap between marketing authorization and market access which is evident also for the medicines with early access authorization procedures (Parviainen et al. 2016).

For medicines granted marketing authorization through conditional approval and exceptional circumstances between 2016 and 2017 NICE recommended additional commercial arrangement in order to provide market access. The odds of carrying a commercial arrangement were higher for products of this type of marketing authorization compared to those with full authorization (Pinilla-Dominguez et al. 2020).

Despite the centralized procedure for marketing authorization valid throughout the European Union (EU) still

the time to patient access varies among the Member states mainly due to the local legal requirements for pricing and reimbursement decisions (Wilking and Jönsson 2005; Godman et al. 2018).

In order to bridge the gap between marketing authorization and market access across the EU, EMA developed some initiative for early dialogue between pharmaceutical manufacturers and regulators. The adaptive pathways set early engagement of drug regulators, HTA bodies and manufactures, and provide possibility for conditional approval with public coverage with shared risk and early market access especially in areas with increased medical needs (Vella Bonanno et al. 2017; Makady et al. 2019; Pontes et al. 2020).

Conclusions

Despite the centralized procedure for marketing authorization and the procedures for early access valid throughout the European Union (EU) still the time to patient access varies among the Member states mainly due to the local legal requirements for pricing and reimbursement decisions, population of interest and manufactures intentions to enter certain markets. The requirements for pricing and reimbursement of medicines across EU is fixed to some degree and medicines with MA for early access are subject to the same legal requirements as the medicines with standard centralized marketing authorization. In this respect further studies should be conducted to evaluate and propose possible mechanisms to bridge the gap between marketing authorization and market access, especially for medicines authorized under the procedures for early access.

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