



## COUNTRY PROFILE: CANCER MEDICINES SHORTAGES

# BULGARIA

### Introduction

EIU indicators	2018 ratings
Political environment rating (10=high)	5.9
Effectiveness of system in policy implementation (5=high)	3.0
Infrastructure rating (10=good)	6.4
Level of corruption (5=low)	2.0

Healthcare spending in Bulgaria as a share of its gross domestic product (GDP) was 8.2% in 2015, which is below the European Union (EU) average of 9.9%. In terms of health spending per capita, Bulgaria ranks third from the bottom, with only two countries, Lithuania and Romania, spending less. Bulgaria also has the highest level of out-of-pocket payments (OOPs) in the EU—48% compared with an EU average of 15%.<sup>1</sup>

In 2015, pharmaceuticals and medical products accounted for more than 40% of total health spending in the country representing the highest level in the EU. Pharmaceuticals also accounted for the largest share of out-of-pocket payments by the population.<sup>1</sup> Since the introduction of centralised social health insurance in 1998, the health care system has been through multiple reforms and frequent changes in the basic benefit package.<sup>1</sup> By law, all citizens must be insured by the National Health Insurance Fund (NHIF) in order to have the right to access care. However, a significant proportion of the population (12% in 2013) is not covered by health insurance.<sup>1,2</sup>

In the context of low healthcare funding from public sources and high levels of health inequality, is it not surprising that five-year cancer survival for cervical, breast and colon cancer remains lower than in most EU countries.<sup>3</sup> In fact, cancer is the second leading cause of death in the country after cardiovascular diseases. In 2015, it accounted for 19% of all deaths in men and 14% of all deaths in women.<sup>1</sup> These outcomes reflect the inadequate quality of care and the low levels of cancer prevention and early detection activities in the absence of a national cancer control plan in the country.<sup>1</sup>

The 'ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe' found that the formulary availability for a number of cancer medicines in Bulgaria lagged behind that of countries in Western Europe.<sup>4</sup> Since 2015 there has been a lot of progress on the availability of cancer medicines in the country, and the NHIF has made a positive decision for reimbursement of many innovative medicines which are now included on the positive medicines list (PML). Nevertheless, there is a hidden problem that escapes the attention of policymakers in the country—the shortages of inexpensive, essential cancer medicines. According to the definition of the European Medicines Agency (EMA), a medicine shortage "occurs when supply cannot meet demand at a national level."<sup>5</sup> While cancer medicines shortages are widespread across Europe as reported in the 2018 European Association of Hospital Pharmacists (EAHP) survey,<sup>6</sup> their impact on patient care, as well as the causes and the potential solutions vary from country to country.

## What is happening on the ground?

There is no robust evidence about the magnitude of cancer medicines shortages in Bulgaria. The news section on the Bulgarian Drug Agency (BDA) website provides information on product withdrawals from the market, but there is no reporting system for medicines shortages in place.<sup>6,7</sup> There are few published studies, such as the 2014 and 2018 EAHP surveys and the ESMO study, that provide very limited information.<sup>4,6</sup> The ESMO study found that all of the 11 cancer medicines from the WHO Model List of Essential Medicines included in the investigation were listed in the Bulgarian national formulary and were fully reimbursed by the NHIF.<sup>4</sup> However, in terms of actual availability the picture was much different. There were issues with the uninterrupted supply of four products: bleomycin (for germ cell tumour), carboplatin (for adjuvant breast cancer and ovarian cancer), cisplatin (for sarcoma, germ cell tumour, and ovarian cancer), and doxorubicin (for sarcoma).<sup>4</sup>

Three years later, our interviews with healthcare professionals in the country confirm that shortages of essential cancer medicines are still an unavoidable part of the life of cancer patients in Bulgaria (Table 1).

**Table 1. Examples of cancer medicines affected by shortages in 2018**

Cancer Medicine	Indication
Carmustine	Brain tumours (glioblastoma), multiple myeloma, non-Hodgkin lymphoma
Dacarbazine	Malignant melanoma, Hodgkin lymphoma, sarcoma
Lomustine	Brain tumours (glioblastoma), malignant melanoma
Mitomycin	Colorectal and urothelial cancer
Procarbazine	Brain tumours
Methotrexate	Leukaemia, sarcoma

Source: Interviews (October 2018)

According to the interviewed health professionals in Bulgaria, shortages affect a large number of inexpensive, old, generic medicines. Many of the missing medicines are used for the treatment of childhood cancers, where often no alternative treatments are available, which can threaten patients' outcomes and may result in increased medication errors, delayed administration or denial of life-saving therapy. In 2015, a group of oncologists sent a letter to the Ministry of Health about the shortages situation and the authorities reacted with surprise. No action followed as the constant changes of governments and ministers preclude the development of a consistent policy on medicines shortages in the country.\* While there is some information and media coverage on the issue of medicines shortages in general, there is a lack of awareness about cancer medicines shortages among stakeholders outside of the affected hospitals.

\* Expert interviews

Health professionals emphasise that shortages in the country occur frequently, especially in public oncology hospitals. The shortages affect not only cancer medicines but also pain medicines used in palliative care. Sporadic shortages can last from a few weeks to a couple of months, however, in some cases, medicines can be unavailable for years. For example, the shortage of mitomycin, used for the treatment of bladder and gastro-intestinal cancers, has been ongoing for almost two years. Another example is methotrexate, used for treating leukaemia and sarcoma, which has been affected by four or five shortages so [now] the shortage situation is considered as chronic. The medicine is only episodically available and in big package sizes, which creates the potential for wasting a scarce product.\*

### **Case study. No medicines for people with brain tumours**

Many of the medicines experiencing shortages are those used for the treatment of brain tumours such as glioblastoma. As one of the most common types of brain tumours, glioblastomas are categorised by WHO as grade IV and are associated with “rapid progression and fatal outcomes”.<sup>8</sup> Treatment regimens may include individual products (e.g. carmustine) or combination chemotherapy with PCV (procarbazine, lomustine, vincristine).<sup>9</sup> When even one of these medicines is missing from the hospital pharmacy, patients with grade IV brain tumours are left without treatment as no alternatives exist. While for other types of cancer a range of innovative medicines have been developed in the last decades, the treatment of brain tumours mostly relies on inexpensive, old, generic medicines, but policymakers appear to be unaware of this fact.

Healthcare providers state that national treatment guidelines may sometimes recommend the use of products that are no longer imported in the country and this can cause unnecessary delays in treatment until an alternative product is identified.\* For this reason, they highlighted the need to update the national pharmacotherapeutic guidelines after a product withdrawal.<sup>9</sup>

In case of shortages the first option is to identify an existing alternative treatment. However, alternative medicines may not have the same therapeutic efficacy and are often more expensive than the medicine in short supply, which has a negative impact on patients’ outcomes, the hospitals’ pharmaceutical budget and may impair the sustainability of the health system. As a result, some patients may be left without access to the treatment they need. The second option is the use of individual authorisations for import of unauthorised products in the country, based on a 2011 legislation (Ordinance No.10).<sup>10</sup> According to the Ordinance No.10, the Bulgarian Drug Agency (BDA) coordinates the protocols for importing a product authorised in an EU Member State for use by a particular patient in Bulgaria and the product is then supplied by a wholesaler.<sup>10</sup> The prescription of the unauthorised medicine has to be approved by a committee of three hospital physicians and requires explicit patient consent. This method is hardly sustainable as medicines procured for a single patient are usually expensive. With some exceptions, most of the products imported based on Ordinance No.10 are not covered by the NHIF, increasing the financial burden for the patient. Moreover, the system relies on the goodwill of the healthcare staff as the administrative tasks for processing individual use authorisations can be very time-consuming. And last but not least, the whole process takes time, and often cancer patients do not have the luxury of time, or as one interviewee noted, cancer progression does not wait for promises or paperwork.

\* Expert interviews

*Left with no other options, some patients might resort to self-treatment using information available online, and the potential for harm is serious.*

In fact, patients are those mostly affected by shortages. Confronted with a diagnosis that is often perceived as a death sentence, they are often left to overcome the hurdles of shortage situations that might affect their treatment outcomes. To overcome the issue some patients attempt to procure the products themselves by purchasing the missing medicines in a country not affected by the shortage. Some of the destinations for “medicines tourism” are neighbouring countries such as Macedonia and Turkey as they are outside the EU and use different supply channels. The individual procurement of the prescribed medicines is a possible solution only for oral medicines as the intravenous medicines procured by patients in another country cannot be administered in hospitals as the safety and Good Pharmacy Practice cannot be guaranteed. Thus, left with no other options, some patients might even resort to self-treatment using information available online, and the potential for harm is serious.\*

Pharmacists and healthcare providers are also affected by medicines shortages and often face an ethical dilemma, which might be outside their professional competencies: deciding whether a patient should contribute to an expensive alternative treatment, thus increasing the individual financial burden, or whether the hospital should cover the additional cost only for few patients, leaving the others untreated.

### **Why do inexpensive cancer medicines go missing?**

Globally, one of the most commonly reported causes for shortages is manufacturing or quality issues that lead to disruptions in the production and distribution of medicines.<sup>11</sup> Based on the limited information available for Bulgaria there is no evidence that manufacturing or quality issues may cause supply disruptions of essential cancer medicines. In fact, when shortages are reported by the national media or mentioned in the public domain, they are often discussed in the context of parallel trade.

### **Main reasons for cancer medicines shortages in Bulgaria**

#### ***Economic causes***

The stakeholders we interviewed agree that cancer medicines shortages in Bulgaria are the result of economic causes. These include a complex mix of business and commercial causes that can lead to product withdrawals or to parallel exports by wholesalers. According to the Bulgarian Association for Medicines Parallel Trade Development, product withdrawals are the main reason for shortages of medicines that “do not perform well on the market”.<sup>12</sup> Other stakeholders representing healthcare providers affirm that the current tendering system for medicines procurement for public hospitals can lead to shortages when no bidders participate in the tenders.\* The lack of interest in participating in tenders is mostly related to the low prices of generic medicines and the small volumes of contracts, which can lead to shortages.

Other key drivers of medicines shortages are the commercial interests of wholesalers, especially in the case of inexpensive, generic cancer medicines needed for treatment of some cancers, for example brain cancer, that affect a relatively small number of patients. The pharmaceutical policy in Bulgaria mandates external reference pricing, and prices are based on the lowest price of 17 reference countries. When the price in the reference countries goes down, this drives automatic price reduction of medicines.<sup>13</sup> The price gap is seen as a good business opportunity by wholesalers which re-export the products to the countries with higher prices, as permitted by the regulation of free movement of goods within the European Union. Thus, in many cases, it is the wholesalers and not the healthcare

\* Expert interviews

policymakers who decide whether cancer patients have access to essential medicines or are left without treatment when no appropriate alternatives are available. This highlights that access to essential cancer medicines in Bulgaria might be considered below any commercial interest.

### Regulatory causes

Currently, there is no legal mechanism to ensure the continuous supply of specific medicines in the country. When wholesalers do not make profits from importing small volumes of inexpensive medicines, they have no incentive for maintaining these products in stock. As public hospital pharmacies are supplied exclusively by wholesalers and cannot purchase medicines directly from the Marketing Authorisation Holders (MAHs), this might lead to medicines shortages. This gap of accountability has been recognised by the national competent authorities, and over the last few years a number of measures have been introduced to prevent medicines shortages (Table 2).

*Ultimately, wholesalers can decide whether cancer patients have access to essential medicines or are left without treatment.*

**Table 2. Who is involved in tackling shortages in Bulgaria and what are the current initiatives?**

Competent authority	Responsibilities and current initiatives
Bulgarian Drug Agency (BDA)	<ul style="list-style-type: none"> <li>• Receives notifications from the MAH for temporary or permanent medicinal product discontinuations as required by EU regulations.</li> <li>• A 2014 amendment of the Medicinal Products in Human Medicine Act (MPHMA) introduced a requirement for wholesalers to notify the BDA for each case of exporting a medicine included on the positive medicines list (PML). BDA can ban the export under certain conditions, such as insufficient quantities to satisfy population needs, risk for temporary shortages, or a threat to population health.</li> <li>• A 2018 amendment of the MPHMA mandated the BDA to develop an electronic system for the monitoring and analysis of the stock availability of medicinal products included on the PML.<sup>14</sup> This system will aim to prevent medicines shortages related to parallel exports.<sup>14</sup></li> </ul>
Ministry of Health National Council of Medicinal Products Prices and Reimbursement (NCMPPR)	<ul style="list-style-type: none"> <li>• The Ministry of Health and the NCMPPR receive written notifications by MAHs not later than 18 months prior to the date of discontinuation of the sales of the medicinal products from the PML.<sup>10</sup></li> <li>• The Minister of Health may, for reasons related to the protection of public health, instruct the Executive Director of the BDA to authorise the procurement of a medicinal product that has been authorised in an EU Member State.<sup>10</sup></li> </ul>

### Looking into the future

The recent legislative measures address one of the main drivers of medicines shortages in Bulgaria—parallel trade. While this is a significant first step to tackle the issue of shortages, there is no guarantee that the measures will be sufficient to prevent the shortages and to stop the withdrawals of essential cancer medicines from the market.

- The amendments of the Medicinal Products in Human Medicine Act from 12 October 2018 address, for the first time, the issue of medicines shortages in an actionable way.<sup>14</sup> The Act envisages an online platform for monitoring stock availability relative to patient needs, which is expected to be piloted in 2019 with a small number of manufacturers, wholesalers and pharmacies.
- The new law requires daily updates of the stock availability by all stakeholders. When stocks fall below 65% of the quantities required for meeting patients' needs in the country the affected medicines will be included on a list of products banned for export. The law also specifies fines for violations of the export bans.

- Inexpensive, essential cancer medicines are critical for high quality patient care and even a small delay in treatment initiation can have an impact on the course of the disease. Therefore, further measures to address the causes leading to product withdrawals by the MAHs are direly needed.
- Unlike many other problems in healthcare, the solution for cancer medicines shortages does not require substantial government investment. Since 2015 a number of innovative cancer medicines have been included on the PML and, as the procurement mechanisms for innovative medicines are different from the ones of inexpensive, essential medicines, they have not been affected by shortages or withdrawals from the market. What is required is commitment and collaboration of the relevant health authorities and institutions to ensure that cancer patients have access to the medicines they need at all times, especially inexpensive, essential products.

### Possible solutions

#### Solution 1

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#### Develop a list of essential cancer medicines

- This initiative should involve national competent authorities, policymakers, as well as professional organisations of oncologists and oncology pharmacists. The list should include all essential medicines required for the treatment of cancer patients, including those on the WHO Model List of Essential Medicines.
- The availability of essential cancer medicines should be a priority when rolling out the tracking system envisaged by the 2018 amendment of the Medicines Act.

#### Solution 2

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#### Create a task force to address medicines shortages

- The task force should include representatives of national regulatory authorities, policymakers, healthcare professionals, patients, and the pharmaceutical industry.
- The task force should develop a strategy to mitigate and prevent shortages. The strategy needs to ensure that all stakeholders in the medicines supply chain are accountable for the uninterrupted supply of medicines.

#### Solution 3

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#### Develop a reporting system for medicines shortages

- The existence of a publicly available reporting system will improve the visibility of the issue of shortages, facilitate communication among stakeholders, and reduce the impact of shortages on patient care.
- The system should gather information from a range of stakeholders such as patients, oncologists, pharmacists, wholesalers, MAHs, regulators and policymakers.
- Data collection should be based on the EMA template for reporting and monitoring of shortages<sup>15</sup> and should include information about causes, as well as alternative treatments where available.

### Solution 4

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#### **Establish procurement models designed to prevent shortages**

- Based on the list of essential cancer medicines and the number of cancer patients in the country the procurement model for the public hospital system should be redesigned to ensure that patients' needs are met.
- A centralised procurement model may be considered to ensure that MAHs/wholesalers participate in tenders and commit to supplying the essential medicines required for the treatment of cancer patients and prevent product withdrawals from the market.
- Consider shortening the supply chain to allow hospital pharmacies to purchase missing essential medicines directly from MAHs in situations of shortages.

### Solution 5

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#### **Use international collaborations to facilitate exchanges of products in short supply**

- Develop bilateral or multilateral initiatives, such as with the signatories of the 2016 Sofia Declaration, to prevent or mitigate shortages.<sup>16</sup>
- Develop mechanisms to facilitate rapid exchanges of medicinal products across borders when one country faces a shortage situation.<sup>16,17</sup>

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