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Original Article

Medicinal products under additional monitoring: a comparative analysis of market access

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Abstract

Introduction: In 2010, the European Union (EU) introduced new pharmacovigilance legislation that established an additional monitoring (AM) measure for certain medicines following their marketing authorization. Since 2013, a black inverted triangle (▼), accompanied by a brief explanatory sentence, has been displayed on their leaflet and in the summary of product characteristics. This symbol is uniformly used across all EU member states to indicate medicines subject to AM.

Aim: To analyze the medicines under AM listed by the European Medicines Agency (EMA) and compare them with those available on the pharmaceutical market in Bulgaria.

Material and methods: A descriptive analysis was performed on the EMA's list of medicines under AM as of February 23, 2024 (EMA/245297/2013 Rev. 119). Additionally, the study assessed the market access and affordability of these medicines in Bulgaria by examining their inclusion in the Positive Drug List (PDL). Public electronic registers of the National Council on Prices and Reimbursement of Medicinal Products in Bulgaria were used for this analysis.

Results: The EMA's list comprised a total of 358 medicines, of which 90 were available on the Bulgarian pharmaceutical market as of February 2024. The analysis revealed that the majority of these medicines were new active substances (n=27, 30%), new biologicals (n=12, 13.3%), and medicines requiring post-authorization safety studies, PASS (n=21, 23.3%).

Conclusion: Notably, only 25% of medicines under AM authorized in the EU were marketed in Bulgaria, with a significant proportion of these being new active substances, particularly in therapeutic areas such as oncology, hematology, and neurology.

Keywords

additional monitoring, EMA, inverted black triangle, pharmacovigilance

Introduction

After receiving marketing authorization, some medicinal products in the European Union (EU) are subject to additional monitoring (AM). Their package leaflet and Summary of Product Characteristics (SmPC) are labelled with a black inverted triangle (▼), accompanied by a short sentence explaining the meaning of the symbol, which reads, *"This medicinal product is subject to additional monitoring."*[1,2]

The concept of AM for medicinal products was introduced with changes to the EU pharmacovigilance legislation in 2010 and came into effect in 2012.[1,2] The black inverted triangle, previously used in the United Kingdom (UK) to identify new active substances, has been adopted by the European Medicines Agency (EMA) to identify medicinal products under AM.[3,4] Similarly, after the adoption of Regulation (EC) No. 1027/2012 (which came into effect in 2013), Spain discontinued the use of the yellow triangle, which had previously been used to indicate new active substances.[3]

The black inverted triangle is now used across all EU member states to denote medicines subject to AM. Since autumn 2013, this symbol has been printed on the package leaflets of these medicines, but it is not displayed on the outer packaging.[5] In addition to the EU and the UK, the Black Triangle Scheme has also been introduced in Australia since 2018.[6]

When a medicinal product is placed under AM, healthcare providers (HCPs) and patients are encouraged to report any suspected adverse drug reactions (ADRs) to the competent authorities. The AM concept serves as an example of a regulatory risk-minimization measure undertaken at the EU level.[7] It aims to reduce the risk associated with medicinal products that are not well-studied and for which the available drug utilization data is not sufficiently comprehensive and conclusive.[5] However, only limited data regarding the impact of the black triangle symbol on reporting levels of ADRs is published in the scientific literature.[8]

Although the concept was introduced 13 years ago, only a few studies have assessed the awareness of HCPs and patients regarding the black triangle symbol and AM process.[9-12] All medicinal products undergo monitoring after receiving marketing authorization, but the black inverted triangle indicates that a medicine is subject to enhanced surveillance. This is typically due to the lack of sufficient information, for example, when the medicine is new to the pharmaceutical market or when evidence on its long-term use remains limited.[5]

The assignment of black triangle status is mandatory in the cases presented in **Fig. 1**.[1]

In addition to the cases presented in **Fig. 1**, other medicinal products may also be placed under AM based on an opinion from the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA.[1]

EMA maintains a list of medicines under AM, which was first published in 2013 and has since been reviewed monthly by PRAC. Medicinal products can be added to the EMA's list either after their initial marketing authorization or at any time during their lifecycle.[5,13] These medicines remain under AM for five years or until PRAC decides to exclude them from the list. The up-to-date list of medicines subject to AM is publicly available on the EMA's website. The list contains the following information: product name, active substance(s), reason(s) on the list, marketing authorization holder, link to product information (European public assessment report, EPAR), and date of inclusion on list.[14]

The national competent authorities of EU member states (for Bulgaria – the Bulgarian Drug Agency) are required to provide a link to the EMA's list of medicines under AM on their official websites.

Aim

Our primary objective was to analyze the medicines under AM listed by the EMA and compare them with those available on the pharmaceutical market in Bulgaria. Additionally, we evaluated the access to these medicines at the national level by examining data on their inclusion in the Positive Drug List (PDL), as well as their reimbursement status and payment levels.

Materials and methods

A retrospective documentary analysis was conducted on the EMA's list of medicines under AM as of February 23, 2024 (EMA/245297/2013 Rev. 119), published on the offi-

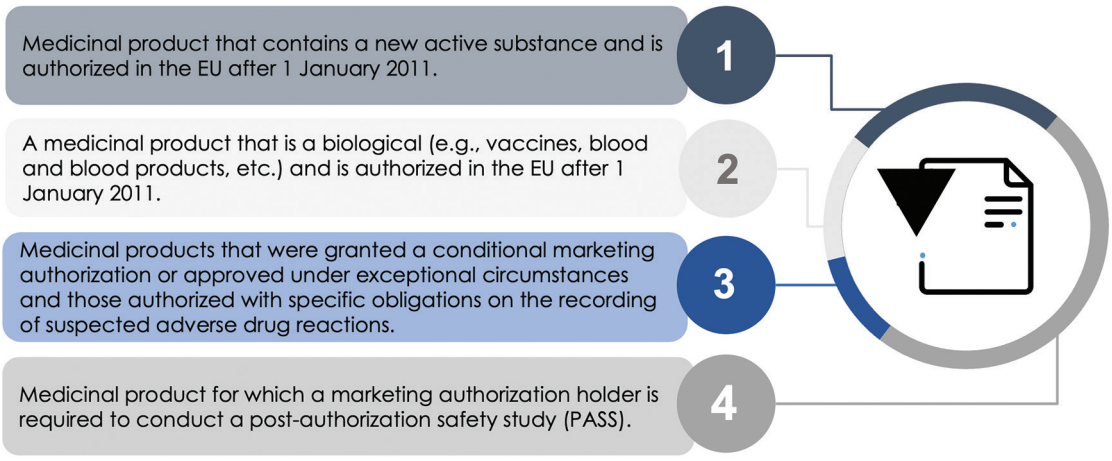

Figure 1. Medicinal products with a mandatory black triangle status.[1]

cial website of the Agency. The availability and affordability of these medicines in Bulgaria were evaluated through a descriptive analysis of data from the Ceiling Prices Register and the PDL.

For this study, public electronic registries of the National Council on Prices and Reimbursement of Medicinal Products (NCPR) were searched, along with the EMA's list of medicines under AM, available at www.ema.europa.eu.

The analyzed medicinal products were classified into the following groups:

- New active substances;
- New biological products;
- New active substances that are also new biological products;
- Medicinal products subject to post-authorization safety studies (PASS);
- Medicinal products authorized under exceptional circumstances;
- Medicinal products authorized under conditional approval;
- New active substances that are also new biological products and are authorized under conditional approval;
- Medicinal products that are new active substances, new biological products, and are subject to PASS;
- Medicinal products that are new active substances and are authorized under conditional approval;
- Medicinal products authorized under exceptional circumstances and subject to PASS;
- Medicinal products subject to restrictions regarding safety and efficacy.

Additionally, medicinal products under AM available on the Bulgarian pharmaceutical market were classified by therapeutic areas in which they are applied.

SmPCs and EPARs of the medicinal products under AM that were included in the EMA's list in 2023 and the first two months of 2024, as well as those available on the Bulgarian pharmaceutical market as of February 2024, were comprehensively analyzed.

Medicinal products under AM with orphan designation, biosimilars, and those used in the treatment and prevention of COVID-19 available to Bulgarian patients were reviewed and classified by reason for inclusion in the EMA's list, therapeutic area/indication for use, and data about inclusion in PDL, as well as reimbursement status/payment level. The study utilized publicly available datasets, eliminating the requirement for ethical approval.

Results and discussion

As of February 2024, the EMA's list of medicinal products under AM (EMA/245297/2013 Rev. 119) included 358 medicines. Among these, 90 medicinal products were available on the Bulgarian pharmaceutical market as of 29 February 2024. Price registration is a mandatory requirement for the placement of a medicinal product, authorized under the EU centralized procedure in accordance with Regulation (EC) No 726/2004, on the national market in Bulgaria.

Based on the criteria for inclusion in the EMA list for AM, the medicinal products available in Bulgaria were classified into several groups **(Table 1).**

The available medicinal products under AM on the Bulgarian pharmaceutical market were classified according to their therapeutic areas of application. The majority of medicines under AM belonged to the therapeutic areas of oncology (n=25, 27.8%), hematology (n=12, 13.3%), and neurology (n=11, 12.2%) **(Fig. 2)**.

Only 25% of AM medicines authorized in the EU were marketed in Bulgaria. In contrast, a similar study conducted in Spain revealed that more than 60% of medicines under AM authorized between 2017 and 2019 in the EU were available on the national level, primarily antineoplastic and immunomodulatory drugs.[15]

Financial accessibility of medicinal products under AM

The analysis of financial accessibility reveals that, as of February 29, 2024, eighty-four medicines under AM (considering valproates separately, n=11) were included in the PDL **(Supplementary Table)**. Forty-five medicines under AM were added in both Annex 1 and Annex 2 of the PDL **(Fig. 3)**.

Annex 1 includes medicines that are either fully reimbursed (100%) or partially reimbursed (up to 50% or 75%) by the National Health Insurance Fund (NHIF). Medicinal products included in Annex 2 are paid by the hospital budgets and are reimbursed at a 100% rate.

For 14 medicines under AM, only a limit price was registered, without reimbursement status **(Fig. 3)**. Consequently, these medicines must be paid for out-of-pocket by patients, as they are not reimbursed by the NHIF.

COVID-19 medicines under AM

As of February 29, 2024, three medicinal products subject to AM and indicated for the treatment or prevention of COVID-19, were available on the Bulgarian pharmaceutical market (Comirnaty®, Veklury®, and Paxlovid®). Two of these medicinal products – Comirnaty® and Veklury® (INN remdesivir) – were not listed in the PDL. Nonetheless, Bulgarian patients still have access to these medications through a special mechanism established at the EU level, given their indication for the prevention and treatment of COVID-19, respectively.

Veklury® (INN: remdesivir) was the first medicine to receive centralized conditional marketing authorization from the European Commission for the specific treatment of COVID-19 in patients with pneumonia requiring supplemental oxygen. In Bulgaria, Veklury® is provided through the EU Framework Agreement for the joint award of public contracts for medical countermeasures, ratified by the Na-

Table 1. Medicinal products under AM available on the Bulgarian pharmaceutical market (distribution according to the criteria by which the medicine is assigned the status "under additional monitoring") as of February 29, 2024.

Reason(s) on the EMA list	EMA's list* n = 358 n (%)	Bulgarian national market* n = 90 n (%)	Difference n = 268 n (%)
New active substance	102 (28.5)	27 (30.0)	75 (28.0)
New biological	70 (19.6)	12 (13.3)	58 (21.6)
PASS	44 (12.3)	21 (23.3)	23 (8.6)
Medicinal products authorized under CMA	8 (2.2)	2 (2.2)	6 (2.2)
Medicinal products authorized under exceptional circumstances	23 (6.4)	4 (4.4)	19 (7.1)
New active substance + new biological	56 (15.6)	16 (17.8)	40 (14.9)
New active substance + new biological + CMA	15 (4.2)	1 (1.1)	14 (5.2)
New active substance + new biological + PASS	3 (0.8)	0 (0.0)	3 (1.1)
New active substance + CMA	13 (3.6)	5 (5.6)	8 (3.0)
New active substance + new biological + CMA + PASS	5 (1.4)	0 (0.0)	5 (1.9)
New active substance + authorized under exceptional circumstances	5 (1.4)	0 (0.0)	5 (1.9)
New active substance + new biological + authorized under exceptional circumstances	7 (1.9)	0 (0.0)	7 (2.6)
New active substance + new biological + authorized under exceptional circumstances + PASS	1 (0.3)	0 (0.0)	1 (0.4)
New active substance + PASS	2 (0.5)	0 (0.0)	2 (0.7)
New biological + PASS	1 (0.3)	0 (0.0)	1 (0.4)
Exceptional circumstances + PASS	1 (0.3)	1 (1.1)	-
New active + CMA + PASS	1 (0.3)	0 (0.0)	1 (0.4)
Restrictions with regards to the safe and effective use of the medicinal product	1 (0.3)	1 (1.1)	-
Total	**358 (100.0)**	**90 (100.0)**	**268 (100.0)**

CMA: conditional marketing authorization; PASS: post-authorization safety study; * Note: One annex of EMA's list is counted as 1 product e.g., valproates.

tional Assembly of the Republic of Bulgaria by law (promulgated in SG No. 26 of 2020). This provision falls under Framework Agreement No. SANTE/2020/C3/048, signed between the European Commission and the marketing authorization holder of Veklury®. Under this Framework Agreement, the Republic of Bulgaria, represented by the Minister of Health, ensures the necessary supply for the treatment of Bulgarian citizens.[16]

Bulgaria also has guaranteed access to adapted vaccines by virtue of Supplementary Agreement No. 5 to the Purchase Agreement for the further development, production, purchasing options, and supply of COVID-19 vaccine for EU Member States (SANTE/2021/03/020).[17] As of February 2024, the only COVID-19 vaccine available and administered in Bulgaria is Comirnaty®.

Paxlovid® (nirmatrelvir/ritonavir) is a medicinal product indicated for the treatment of COVID-19. It is dispensed by a medical prescription and is used for the outpatient treatment of mild to moderate COVID-19 cases in adults who do not require supplemental oxygen. Paxlovid®is included in Annexes 1 and 2 of the PDL.

Orphan medicines under AM

Our analysis shows that, as of February 2024, 18 medicinal products under AM available on the Bulgarian pharmaceutical market had an orphan designation, representing 20% of the total AM medicines. Most of these products (n=7) belong to ATC code L: Antineoplastic and immunomodulating agents, followed by ATC code A: Alimentary tract and metabolism (n=5). **(Fig. 4)**.

Medicinal products under AM added to the EMA list in 2023

In 2023, a total of 36 medicinal products were added to the EMA list of AM. As of February 29, 2024, only two of these medicines were available on the Bulgarian pharmaceutical market – Tibsovo® (INN: ivosidenib) and Bekemv® (INN: eculizumab). As of this date, only a limit price had been registered for Tibsovo®, and the product was not included in the PDL. Tibsovo® (ivosidenib) is an orphan medicine, indicated for the treatment of adult patients with acute

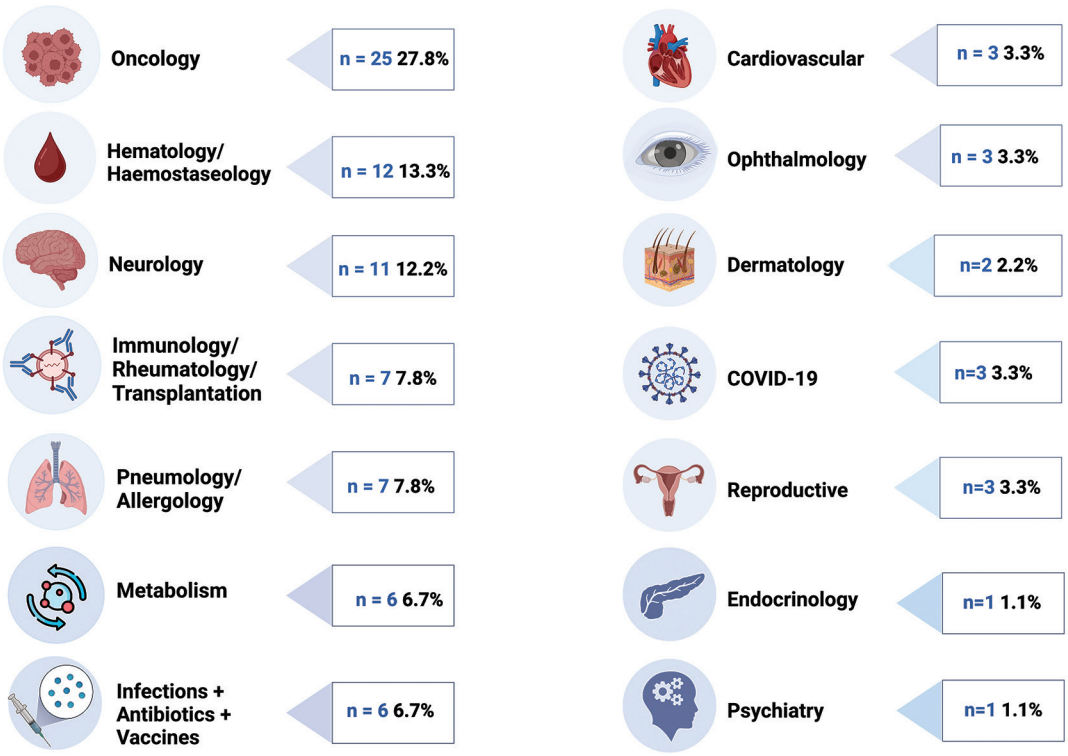

Figure 2. Distribution of analyzed medicinal products under AM according to the therapeutic area in which they are applied, n=90 (Created with BioRender.com). Note: One annex of EMA's list is counted as 1 product (e.g., valproates).

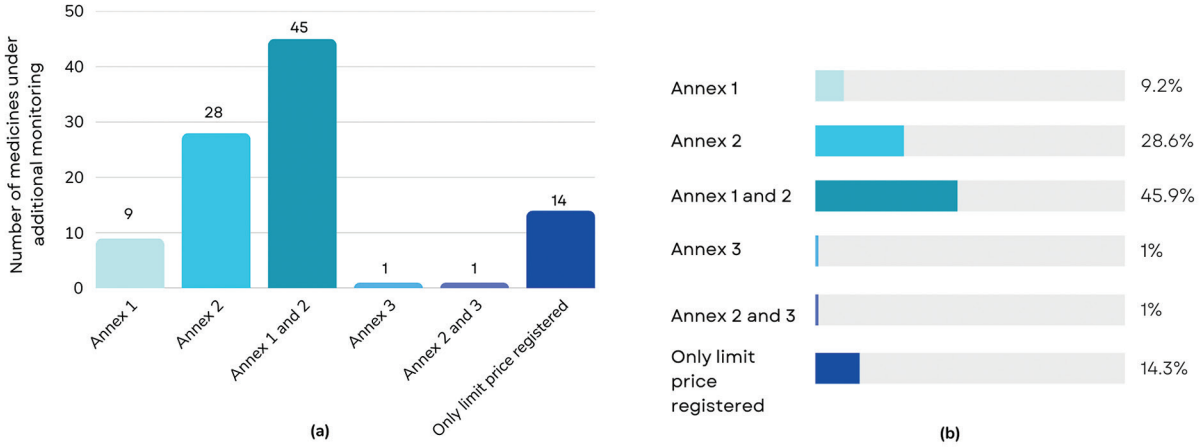

Figure 3. Reimbursed medicines under AM in Bulgaria (valid for February 2024); **(a)** absolute frequency; **(b)** relative frequency. Note: Medicinal products containing sodium valproate or valproic acid are evaluated separately rather than as one product, as outlined in the EMA list of AM (n=11).

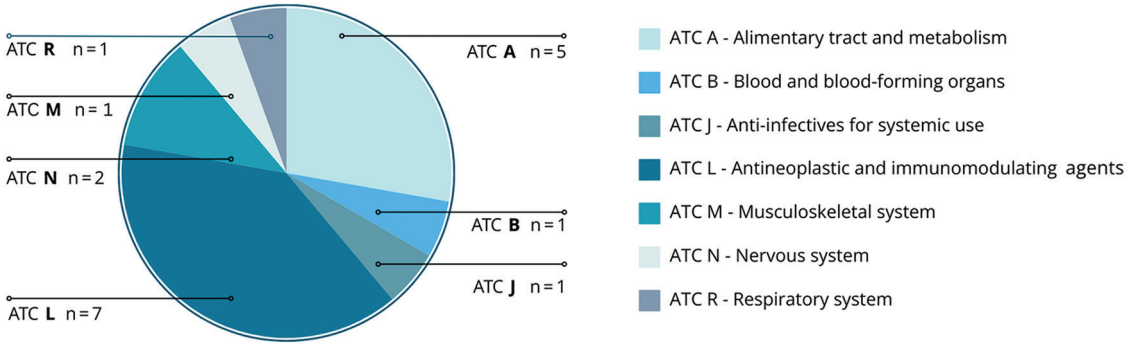

Figure 4. Orphan medicines under AM available in Bulgaria classified according to the ATC system.

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myeloid leukaemia or cholangiocarcinoma.[18] Tibsovo® is subject to restricted medical prescription. The reason for its inclusion in the list of medicines under AM is that it is a new active substance. Tibsovo® was registered in the Ceiling Prices Register maintained by the NCPR on July 6, 2023.

As of February 29, 2024, Bekemv® (eculizumab) was included in the PDL, Annex 1 and was reimbursed at 100%. Bekemv® is a medicine used to treat adults and children with paroxysmal nocturnal hemoglobinuria. Bekemv® is a biosimilar medicine and is also subject to restricted medical prescription.[19] The reason for its inclusion in the AM list is that it is a new biological product. Bekemv® received marketing authorization on April 19, 2023 and was added to the PDL in Bulgaria on December 20, 2023.

Does the status of AM lead to an increase in ADRs reporting?

The inverted black triangle does not indicate that a medicine is dangerous. It aims to raise awareness and encourage HCPs and patients to report any suspected ADRs related to medicines under AM, thereby facilitating the ongoing benefit-risk assessment.

In September 2017, EMA conducted a questionnaire-based online survey across various countries in the European Economic Area (EEA) to assess both patients' and HCPs' awareness regarding the concept of AM.[10] The findings revealed that approximately 50% of respondents had previously encountered the black triangle symbol, while 20% of all respondents, regardless of their prior awareness, misinterpreted its meaning. The survey included 34 respondents from Bulgaria, of whom 23 were patients, and the remaining 11 were HCPs.[10]

A study by Segec et al. aimed to assess whether the inclusion of medicines in the AM list increases the reporting of ADRs for those medicines in the EEA. The analysis of the EudraVigilance database indicated limited evidence of a modest and gradual increase in ADR reporting for some new products. However, no significant increase was observed for products subject to AM due to the requirement to conduct a PASS.[8]

A questionnaire-based study from Finland evaluated the awareness of HCPs (physicians, pharmacists, and nurses) regarding medicines under AM.[9] The results showed that only 40% of HCPs engaged in patient care consistently or frequently recognized whether a particular medication is subject to AM. Furthermore, 53% of HCPs rarely or never informed patients about a medicine's AM status. Among all HCPs surveyed, pharmacists demonstrated the best knowledge, although they did not fully acknowledge their role in enhancing pharmacovigilance efforts.[9] A more recent Spanish study highlighted that community pharmacists could play a significant role in ensuring the appropriate and safe use of medicines under AM.[20]

According to a nationwide Bulgarian study conducted among 316 adults, only 21.5% of respondents were aware of the meaning of the inverted black triangle symbol.[12]

These findings suggest that the concept of AM is not widely recognized among the general public, and the accompanying symbol still remains largely unfamiliar. Limited awareness, both among the public and, in some cases, HCPs, may contribute to the underreporting of ADRs related to medicinal products under AM or may even result in the avoidance of intake of these medications. This raises concerns regarding the appropriateness of labeling medicinal products without first or concurrently implementing educational initiatives to inform the public about the significance and purpose of such labeling. Furthermore, the development of specialized methodologies for post-marketing data collection related to AM is essential, as these approaches should extend beyond conventional methods for ADR reporting and evaluation.[21]

Conclusion

Our analysis revealed that as of February 2024, only 25% of the medicines under AM authorized at the EU level were marketed in Bulgaria. The majority of these medicines were classified as new active substances, followed by those requiring PASS and new biologics. Notably, most of these medicines were associated with therapeutic areas such as oncology, hematology, and neurology. Since medicines under AM continue to be authorized in the EU each year, it is essential to raise awareness among both HCPs and the general public regarding the inverted black triangle symbol. Increased understanding of its significance could help improve ADR reporting, thereby strengthening pharmacovigilance and ensuring better patient safety.

Author contributions

Conceptualization: R.S.: methodology: R.S.; investigation: R.S. and D.A.; recourses: R.S. and D.A., software: R.S.; writing—original draft preparation: R.S.; writing—review and editing: R.S. and D.A; visualization: R.S.; supervision: R.S.

We do confirm that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated above in this document have been met, and that each author believes that the manuscript represents honest work.

Conflict of interest

We have no conflicts of interest to disclose.

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Supplementary Table

Appendix 1. Medicinal products under AM available on the Bulgarian pharmaceutical market (valid for February 2024)

Trade name	INN	ATC-code	Therapeutic indication/s (MeSH)	Reason on the EMA's list of AM	Date of inclusion on EMA's list of AM	Inclusion in PDL in Bulgaria	Reimbursement level
1. Adynovi	rurioctocog alfa pegol	B02BD02	Hemophilia A	PASS	January 2018	Yes	Annex 1 (100%) and Annex 2 (100%)
2. Aklief	trifarotene	D10AD06	Acne vulgaris	New active substance	December 2021	No	-
3. Alymsys[b]	bevacizumab	L01FG01	• Colorectal neoplasms • Breast neoplasms • Ovarian neoplasms • Peritoneal neoplasms • Non-small-cell lung carcinoma • Renal cell carcinoma and uterine cervical neoplasms	New biological	April 2021	Yes	Annex 2 (100%)
4. Anoro Ellipta	umeclidinium bromide vilanterol	R03AL03	• Chronic obstructive pulmonary disease (COPD)	PASS	June 2014	Yes	Annex 1 (75%) and Annex 2 (100%)
5. Aspaveli[a]	pegcetacoplan	L04AA54	• Hemoglobinuria	New biological	January 2021	Yes	Annex 1(100%)
6. Atriance	nelarabine	L01BB07	• T-cell acute lymphoblastic leukaemia (T-ALL) • T-cell lymphoblastic lymphoma (T-LBL)	Authorized under exceptional circumstances	April 2013	Yes	Annex 2 (100%)
7. Bavencio	avelumab	L01FF04	• Neuroendocrine tumors	New active substance and new biological	September 2017	Yes	Annex 2 (100%)
8. Benlysta	belimumab	L04AA26	• Systemic Lupus Erythematosus	PASS	April 2013	Yes	Annex 1 (100%) and Annex 2 (100%)
9. Beovu	brolucizumab	S01LA06	• Wet macular degeneration	New active substance and new biological	February 2020	Yes	Annex 1(75%) and Annex 2(100%)
10. Bekemv[b]	eculizumab	L04AA25	• Paroxysmal nocturnal hemoglobinuria	New biological	April 2023	Yes	Annex 1 (100%)
11. Bimzelx	bimekizumab	L04AC21	• Psoriasis	New active substance and new biological	September 2021	Yes	Annex 1 (75%)
12. Blincyto[a]	blinatumomab	L01FX07	• Precursor cell lymphoblastic leukemia-lymphoma	PASS	December 2015	Yes	Annex 2 (100%)

13. Bretaris Genuair	aclidinium bromide	R03BB05	• Chronic obstructive pulmonary disease (COPD)	PASS	April 2013	Yes	Annex 1 (75%) and Annex 2 (100%)
14. Brimica Genuair	aclidinium formoterol fumarate dihydrate	R03AL05	• Chronic obstructive pulmonary disease (COPD)	PASS	December 2014	Yes	Annex 1 (75%) and Annex 2 (100%)
15. Brineura[a]	cerliponase alfa	A16AB17	• Neuronal ceroid-lipofuscinoses	Authorized under exceptional circumstances, PASS	June 2017	No	-
16. Byfavo	remimazolam	N05CD14	• Conscious sedation	New active substance	April 2021	No	
17. Calcquence	acalabrutinib	L01EL02	• Chronic lymphocytic leukaemia	New active substance	November 2020	Yes	Annex 2 (100%)
18. Cerdelga[a]	eliglustat	A16AX10	• Gaucher disease	PASS	February 2015	Yes	Annex 1 (100%)
19. Belara	ethinylestradiol, chlormadinone acetate	G03AA15	• Contraception	PASS	June 2014	No	-
20. Comirnaty	COVID-19 mRNA vaccine	J07BN01	• COVID-19 virus infection	New active substance and new biological	January 2021	No	-
21. Duaklir Genuair	aclidinium bromide formoterol	R03AL05	• Chronic obstructive pulmonary disease (COPD)	PASS	December 2014	Yes	Annex 1 (75%) and Annex 2 (100%)
22. Drovelis	estetrol drospirenone	G03AA18	• Contraception	New active substance	June 2021	No	-
23. Elaprase	idursulfase	A16AB09	• Mucopolysaccharidosis II	Authorized under exceptional circumstances	April 2013	Yes	Annex 1(100%) and Annex 2 (100%)
24. Enhertu	trastuzumab deruxtecan	L01FD04	• Breast neoplasms • Non-small cell lung cancer • Gastric cancer	New active substance, CMA	January 2021	Yes	Annex 2 (100%)
25. Enspryng[a]	satralizumab	L04AC19	• Neuromyelitis Optica	New active substance and new biological	July 2021	Yes	Annex 1 (100%) and Annex 2 (100%)
26. Esperoct	turoctocog alfa pegol	B02BD02	• Hemophilia A	PASS	June 2019	Yes	Annex 1(100%) and Annex 2 (100%)
27. Evrenzo	roxadustat	B03XA05	• Anemia associated with chronic kidney failure	New active substance	September 2021	Yes	Annex 1(100%) and Annex 2 (100%)
28. Evrysdi	risdiplam	M09AX10	• Spinal muscular atrophy	New active substance, CMA	April 2021	Yes	Annex 1(100%) and Annex 2 (100%)
29. Exjade	deferasirox	V03AC03	• Iron overload • Beta-thalassemia	PASS	April 2013	Yes	Annex 1(100%) and Annex 2 (100%)

30. Gavreto	pralsetinib	L01EX23	• Carcinoma, Non-small-cell lung	New active substance, CMA	November 2021	Yes	Annex 2 (100%)
31. Glivec	imatinib	L01EA01	• Precursor cell lymphoblastic leukemia-lymphoma • Gastrointestinal stromal tumors • Dermatofibrosarcoma • Myelodysplastic-myeloproliferative diseases • Leukemia, Myelogenous, Chronic, BCR-ABL Positive • Hypereosinophilic syndrome	PASS	September 2014	No	-
32. Hukyndra[b]	adalimumab	L04AB04	• Arthritis, Psoriatic • Arthritis, Juvenile rheumatoid • Arthritis, Rheumatoid • Colitis, Ulcerative • Crohn Disease • Hidradenitis Suppurativa • Psoriasis • Spondylitis, Ankylosing • Uveitis	New biological	November 2021	Yes	Annex 1 (75%) and Annex 2 (100%)
33. Imnovid	pomalidomide	L04AX06	• Multiple Myeloma	PASS	September 2013	Yes	Annex 2 (100%)
34. Incruse Ellipta	umeclidinium bromide	R03BB07	• Chronic obstructive pulmonary disease (COPD)	PASS	May 2014	Yes	Annex 1 (75%), Annex 2 (100%)
35. Jyseleca	filgotinib	L04AA45	• Arthritis, Rheumatoid	New active substance	October 2020	Yes	Annex 1 (75%)
36. Kaftrio[a]	ivacaftor tezacaftor elexacaftor	R07AX32	• Cystic fibrosis	New active substance	August 2020	Yes	Annex 1 (100%)
37. Kerendia	finerenone	C03DA05	• Renal insufficiency, Chronic • Diabetes mellitus Type 2	New active substance	March 2022	Yes	Annex 1 (75%) and Annex 2 (100%)
38. Kesimpta	ofatumumab	L04AA52	• Multiple sclerosis	New biological	April 2021	Yes	Annex 1(100%) and Annex 2 (100%)
39. Lemtrada	alemtuzumab	L04AA34	• Multiple sclerosis	PASS	January 2020	Yes	Annex 1(100%) and Annex 2 (100%)
40. Leqvio	inclisiran	C10AX16	• Hypercholesterolemia • Dyslipidemias	New active substance	January 2021	Yes	Annex 1(100%) and Annex 2 (100%)
41. Libtayo	cemiplimab	L01XC33	• Cutaneous Squamous Cell Carcinoma • Basal Cell Carcinoma • Non-Small Cell Lung Cancer • Cervical Cancer	New active substance and new biological	July 2019	Yes	Annex 2 (100%)

42. Lorviqua	lorlatinib	L01ED05	• Carcinoma, Non-small-cell lung	New active substance, CMA	May 2019	Yes	Annex 2 (100%)
43. Lumykras	sotorasib	L01XX73	• Carcinoma, Non-small-cell lung	New active substance, CMA	January 2022	Yes	Annex 2 (100%)
44. Mayzent	siponimod	L04AA42	• Multiple Sclerosis, Relapsing-Remitting	New active substance	January 2020.	Yes	Annex 1(100%) and Annex 2 (100%)
45. MenQuadfi	meningococcal group A, C, W-135 and Y conjugate vaccine	J07AH08	• Meningitis	New biological	December 2020	No	-
46. Mysimba	naltrexone bupropion	A08AA62	• Obesity • Overweight	PASS	April 2015	No	-
47. Nubeqa	darolutamide	L02BB06	• Prostatic neoplasms, castration-resistant	New active substance	April 2020	Yes	Annex 2 (100%)
48. Oyavas[b]	bevacizumab	L01FG01	• Colorectal neoplasms • Breast neoplasms • Ovarian neoplasms • Fallopian tube neoplasms • Peritoneal neoplasms • Carcinoma, Non-small-cell lung • Carcinoma, Renal cell • Uterine cervical neoplasms	New biological	April 2021	Yes	Annex 2 (100%)
49. Palynziq[a]	pegvaliase	A16AB19	• Phenylketonurias	New active substance and new biological	May 2019	No	-
50. Paxlovid	nirmatrelvir ritonavir	J05AE30	• COVID-19 virus infection	New active substance	February 2022	Yes	Annex 1(100%) and Annex 2 (100%)
51. Phesgo	pertuzumab trastuzumab	L01XY02	• Breast neoplasms	New biological	January 2021	Yes	Annex 2 (100%)
52. Piqray	alpelisib	L01EM03	• Breast neoplasms	New active substance	August 2020	Yes	Annex 2 (100%)
53. Polivy[a]	polatuzumab vedotin	L01FX14	• Lymphoma, B-cell	New active substance and new biological	January 2020	Yes	Annex 2 (100%)
53. Ponvory	ponesimod	L04AA50	• Multiple Sclerosis	New active substance	June 2021	Yes	Annex 1(100%) and Annex 2 (100%)
55. Quinsair	levofloxacin	J01MA12	• Cystic fibrosis • Respiratory tract infections	PASS	April 2015	Yes	Annex 1 (100%) and Annex 2 (100%)
56. Reblozyl[a]	luspatercept	B03XA06	• Anemia • Myelodysplastic syndromes • Beta-thalassemia	New active substance	July 2020	Yes	Annex 1 (100%) and Annex 2 (100%)
57. Recarbrio	imipenem cilastatin relebactam	J01DH56	• Gram-negative bacterial infections	New active substance	February 2020	Yes	Annex 2 (100%)

58. Refixia	nonacog beta pegol	B02BD04	• Hemophilia B	PASS	June 2017	Yes	Annex 1 (100%) and Annex 2 (100%)
59. Rinvoq	upadacitinib	L04AA44	• Rheumatoid Arthritis	New active substance	January 2020	Yes	Annex 1 (75%)
60. Rozlytrek	entrectinib	L01EX14	• Cancer • Carcinoma, Non-small-cell lung	New active substance, CMA	August 2020.	Yes	Annex 2 (100%)
61. Ruxience[b]	rituximab	L01FA01	• Leukemia, Lymphocytic, Chronic, B-Cell • Arthritis, rheumatoid • Microscopic polyangiitis • Pemphigus	New biological	April 2020	Yes	Annex 1 (75%), Annex 2 (100%)
62. Rybelsus	semaglutide	A10BJ06	• Diabetes mellitus, Type 2	New biological	April 2020	Yes	Annex 1(100%) and Annex 2 (100%)
63. Ryego	relugolix estradiol norethisterone acetate	H01CC54	• Leiomyoma	New active substance	September 2021	Yes	Annex 1(100%)
64. Saphnelo	anifrolumab	L04AA51	• Lupus erythematosus	New active substance and new biological	February 2022	Yes	Annex 1(100%) and Annex 2 (100%)
65. Sarclisa	isatuximab	L01FC02	• Multiple myeloma	New active substance and new biological	June 2020	Yes	Annex 2 (100%)
66. Scemblix[a]	asciminib	L01EA06	• Chronic Myeloid Leukemia	New active substance	September 2022	Yes	Annex 2 (100%)
67. Sirturo[a]	bedaquiline	J04AK05	• Tuberculosis, Multidrug-resistant	CMA	March 2014	Yes	Annex 2 (100%) and Annex 3 (100%)
68. Spravato	esketamine	N06AX27	• Depressive disorder	Restrictions with regards to the safe and effective use of the medicinal product	January 2020	Yes	Annex 1 (50%) and Annex 2 (100%)
69. Strensiq[a]	asfotase alfa	A16AB13	• Hypophosphatasia	Authorized under exceptional circumstances	September 2015	Yes	Annex 1 (100%) and Annex 2 (100%)
70. Talzenna	talazoparib	L01XK04	• Breast cancer • Prostate cancer	New active substance	June 2019	Yes	Annex 2 (100%)
71. Tezspire	tezepelumab	R03DX11	• Asthma	New active substance and new biological	September 2022	Yes	Annex 1 (75%) and Annex 2 (100%)
72. Tibsovo[a]	ivosidenib	L01XX62	• Acute Myeloid Leukemia • Cholangiocarcinoma	New active substance	May 2023	No	-
73. Translarna[a]	ataluren	M09AX03	• Duchenne muscular dystrophy	CMA	September 2014	Yes	Annex 1 (100%)
74. Trodelvy	sacituzumab govitecan	L01FX17	• Triple-negative breast neoplasms	New active substance and new biological	December 2021	Yes	Annex 2 (100%)

75. Tukysa	tucatinib	L01EH03	• Breast neoplasms	New active substance	February 2021	Yes	Annex 2 (100%)
76. Vabysmo	faricimab	S01LA09	• Wet macular degeneration • Diabetic macular edema	New active substance and new biological	September 2022	Yes	Annex 1(75%) and Annex 2 (100%)
77. Valproate and related substances (sodium valproate and valproic acid, n = 11)	sodium valproate, valproic acid	N03AG01	• Epilepsy • Bipolar disorders • Migraine disorders	PASS	January 2015	Yes	Annex 1 (100%) and /or Annex 2 (100%)
78. Vaxneuvance	pneumococcal polysaccharide conjugate vaccine	J07AL02	• Pneumococcal infections	New active substance and new biological	January 2022	Yes	Annex 3 (100%)
79. Vegzelma[b]	bevacizumab	L01FG01	• Colorectal neoplasms • Breast neoplasms • Ovarian neoplasms • Fallopian tube neoplasms • Peritoneal neoplasms • Carcinoma, non-small-cell lung • Carcinoma, Renal Cell • Uterine cervical neoplasms	New biological	September 2022	Yes	Annex 2 (100%)
80. Veklury	remdesivir	J05AB	• COVID-19 virus infection	New active substance	July 2020	No	-
81. Verquvo	vericiguat	C01DX22	• Chronic Heart Failure	New active substance	July 2021	Yes	Annex 1 (75%) and Annex 2 (100%)
82. Vimizim[a]	elosulfase alfa	A16AB12	• Mucopolysaccharidosis IV	PASS	June 2014	Yes	Annex 1 (100%) and Annex 2 (100%)
83. Voxzogo[a]	vosoritide	M05BX07	• Achondroplasia	New active substance and new biological	September 2021	No	-
84. Vydura	rimegepant	N02CD06	• Migraine disorders	New active substance	May 2022	No	-
85. Vyndaqel[a]	tafamidis	N07XX08	• Amyloidosis	Authorized under exceptional circumstances	April 2013	Yes	Annex 1 (100%) and Annex 2 (100%)
86. Xofigo	radium Ra223 dichloride	V10XX03	• Prostatic neoplasms	PASS	December 2013	No	-
87. Xofluza	baloxavir marboxil	J05AX25	• Influenza	New active substance	January 2021	No	-

88. Xospata[a]	gilteritinib	L01EX13	• Acute myeloid leukemia	New active substance	November 2019	Yes	Annex 2 (100%)
89. Yuflyma[b]	adalimumab	L04AB04	• Rheumatoid arthritis • Juvenile idiopathic arthritis • Enthesitis-related arthritis • Axial spondyloarthritis • Psoriatic arthritis • Psoriasis • Hidradenitis suppurativa • Crohn's disease • Ulcerative colitis • Uveitis	New biological	March 2021	Yes	Annex 1 (75%) and Annex 2 (100%)
90. Zercepac[b]	trastuzumab	L01XC03	• Breast neoplasms • Stomach neoplasms	New active substance and new biological	August 2020	Yes	Annex 2 (100%)

AM: additional monitoring; ATC: anatomical therapeutic chemical; CMA: conditional marketing authorization; EMA: European Medicines Agency; INN: international non-proprietary name; PASS: post-authorization safety study; PDL: Positive Drug List
Note: [a] Orphan drug; [b] Biosimilar