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Review Article

INNs granted with specific storage requirements in Bulgarian pharmacies. Part 1: Medicines acting on cardiovascular and nervous system

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Abstract

Some medicines require special storage in Bulgarian pharmacies due to serious adverse reactions that may be even life-threatening. They are listed in Appendix № 9 to Art. 17, para. 1 of Ordinance № 28 of 9th December 2008, issued by the Minister of Health. The appendix includes 70 medicines from different pharmacotherapeutic groups and with various pharmacological effects. The performed documentary data analysis showed that a major part of these medicines are not registered for use by the Bulgarian Drug Agency to date. In addition, there are a number of medications that have a marketing authorization for use in Bulgaria but are not listed in this specific Appendix, although they belong to the same pharmacotherapeutic group and exert the same pharmacologic action as some included medicines. In conclusion, due to these inconsistencies, it remains unclear whether the Appendix is up to date or needs to be updated.

Keywords

appendix № 9, cardiovascular, medicine, nervous, special storage

Introduction

The main normative acts governing healthcare in the Republic of Bulgaria and in particular the use of medicinal products are: Medicinal Products in Human Medicine Act (MPHMA), Narcotic Substances and Precursors Control Act (NSPCA), Health Act (HA), Health Insurance Act (HIA) and Medical-Treatment Facilities Act (MTFA) (Ministry of Health). According to the MPHMA, the discharge of medicinal products on the Bulgarian pharma market is carried out only after obtaining a marketing authorization or a registration certificate issued by the Bulgarian Drug Agency (BDA). Another option is marketing authorization to be granted under the centralized procedure defined in the Regulation (EC) № 726/2004 of the European Parliament and of the Council (Ministry of Health 2022).

In Bulgaria, the processes of prescribing and dispensing of medicines are regulated by a special Ordinance № 4/4.3.2009, issued by the Minister of Health (Ministry of Health 2018). Work organization in Bulgarian pharmacies is particularly determined by an Ordinance № 28/9.12.2008.

This important document specifies all the requirements for the premises, equipment and furniture in this kind of healthcare facilities, work organization in community and hospital pharmacies, internet sale of medicinal products without a prescription, pharmacy documentation, as well as the rules for storage and preparation of medicinal products in the pharmacy (Ministry of Health 2010).

Proper storage of medicines is of great importance to ensure their quality, efficacy and safety. One of the main factors that determines the place of drugs keeping in the pharmacy is the temperature of the premises. The repository of all medicinal products must be carried out in accordance with the requirements set out in the summary of product characteristics. Most medicines require a storage temperature below 25 °C. Nonprescription drugs (Over-The-Counter, OTC) can be stored on open shelves while prescription drugs must be placed in spaces with limited visual patients' access. Thermolabile medicines usually require storage temperature between 2–8 °C and must be stored in a refrigerator to prevent destruction, decomposition or change in their chemical structure (Ministry of Health 2010, 2018).

The stowage of medicinal products in the community pharmacy is determined also by their safety considerations. Therefore, combustible and flammable medicinal products are stored in a metal cabinet or hopper in the warehouse premise of the pharmacy. Medicinal products that do not comply with the requirements relating to quality, safety, and efficacy, with damaged primary or secondary packaging, as well as expired medicinal products shall be stored separately from other medicines in a designated place with an appropriate indication that they are blocked and should not be dispensed (Ministry of Health 2010, 2018). Some medicines require special storage - in metal boxes or cabinets with a secret lock, mainly due to the content of narcotic substances or due to their safety profile. Pharmacies that have a license for retail trade, storage and dispensing of medicinal products containing narcotic substances must store them in a fixed and locked metal safe (for drugs containing narcotic substances, listed in Schedule № 2 of the Regulation for the order of classifying plants and substances as narcotic) or in a locked metal cabinet (for drugs containing narcotic substances, listed in Schedule № 3 of the same Regulation). The key to the metal safe is kept by the head of the pharmacy or by a master of pharmacy appointed by him (Ministry of Health 2013). Medicinal products included in Appendix № 9 to Art. 17, para. 1 of Ordinance № 28/9.12.2008 are stored in a separate locked cabinet that may be situated in different storage place, in regard to the type of the pharmacy. In the community pharmacy the separate locked cabinet is located in the reception area, assistant or warehouse premises whereas in the hospital pharmacies under art. 222, para. 4 of MPHMA, the cabinet is placed in the assistant or warehouse premises. Thermolabile medicines included in Appendix № 9 are stored in a refrigerator (Ministry of Health 2010).

The aim of the present study is to assess the specificity and particularity of the drugs listed in Appendix № 9 to Art. 17, para. 1 of Ordinance № 28/9.12.2008, issued by the Minister of Health.

Methods

For the purpose of the study, it was conducted a thorough review of the available official documentation as well as scientific databases about the medicinal products included in Appendix № 9 of Ordinance № 28/9.12.2008, especially drugs affecting cardiovascular and nervous system. The data collected were analyzed and summarized in order to assess the relevance of the list and to clarify the reasons why specific storage conditions are required for these drugs.

Results and discussion

Appendix № 9 to Art. 17, para. 1 of Ordinance № 28/9.12.2008 includes 70 drugs that belong to different pharmacotherapeutic groups according to the Anatomical Therapeutic Chemical (ATC) classification. According to the regulation these medicines must be kept in a securely locked cabinet. The requirements for special storage are associated probably with a low therapeutic index of the drugs, serious adverse drug reactions, incl. life-threatening events, toxic effects related to the mechanism of action, etc. The medicinal products included in Appendix № 9 are shown in Table 1 by their international nonproprietary name (INN). For convenience, drugs listed in the Appendix are divided into several groups according to their pharmacological action.

Drugs acting on Cardiovascular system and blood coagulation included in Appendix № 9 to Art. 17, para. 1 of Ordinance № 28/9.12.2008.

Appendix № 9 contains 7 medicines that acts on cardiovascular system and blood coagulation. Five of them are from the group of cardiac glycosides while the other are coumarin anticoagulant drugs.

Cardiac glycosides are natural compounds isolated from various plants such as *Digitalis lanata*, *Digitalis purpurea*, *Strophantus spp*., *Nerium oleander*, etc. They are composed of a sugar moiety, a steroid and a lactone ring. Cardiac glycosides have a complex mechanism of action and exert a positive inotropic and bathmotropic effects as well as a negative chrono- and dromotropic effects. The positive inotropic effect is associated with inhibition of Na^+/K^+-ATPase in cardiomyocytes (Botelho et al. 2019). Cardiac glycosides are characterized by a low therapeutic index and a long plasma half-life (digoxin has a half-life of 36–48 hours) resulting in an increased risk of cumulation and digitalis intoxication. Patients with renal disease are more susceptible to toxic effects because cardiac glycosides are excreted in urine mainly unchanged. In addition, many drugs as well as electrolyte disorders may increase their toxicity. Digitalis intoxication is manifested by nausea, vomiting, weakness, impaired color vision, atrioventricular (AV) block, ventricular arrhythmias which can be life-threatening (Pita-Fernández et al. 2011; Rehman and Hao 2023).

Table 1. Medicines included in Appendix № 9 that require storage in a locked cabinet (Ministry of Health 2010).

Drugs acting on cardiovascular system and blood coagulation	Drugs acting on peripheral and central nervous system	Antineoplastic and immunomodulating agents		Anabolic steroids
Acenocoumarol	Alcuronium	Amsacrine	Idarubicin	Metandienone
Acetyldigoxin	Ambenonium	Asparaginase	Ifosfamide	Nandrolone
beta-Methyldigoxin	Atracurium	Azathioprine	Irinotecan	Oxymetholone
Digitoxin	Atropine	Bleomycin	Lomustine	
Digoxin	Biperiden	Busulfan	Melphalan	
Ethyl biscoumacetate	Butylscopolamine	Carmustine	Mercaptopurine	
Lanatoside C	Ergotamine	Chlorambucil	Methotrexate	
	Galantamine	Ciclosporin	Mitobronitol	
	Mevacurium chloride	Cisplatin	Mitolactol	
	Nalorphine	Cyclophosphamide	Mitomycin	
	Naloxone	Cytarabine	Mitoxantrone	
	Neostigmine	Dacarbazine	Paclitaxel	
	Pancuronium	Daunorubicin	Procarbazine	
	Pilocarpine	Doxorubicin	Tegafur	
	Pipecuronium bromide	Epirubicin	Teniposide	
	Pyridostigmine	Estramustine	Tioguanine	
	Rocuronium bromide	Etoposide	Vinblastine	
	Scopolamine	Fluorouracil	Vincristine	
	Suxametonium	Fotemustine	Vinorelbine	
	Tetracaine	Hydroxycarbamide		
	Tubocurarine			

Oral anticoagulants (acenocoumarol and ethyl biscoumacetate) are derivatives of coumarin which has a natural origin. Coumarin anticoagulants are vitamin K antagonists. They block the enzyme vitamin K epoxide reductase (VKOR) which inhibits the synthesis of vitamin K-dependent coagulation factors [II, VII, IX, X] and disrupts the coagulation process (Liu et al. 2021). The most serious problem that can occur with coumarin anticoagulant treatment is bleeding which may be potentially fatal in some cases. Regular laboratory tests (monitoring and maintenance of the INR value in the optimal therapeutic range) are required in order to ensure adequate coagulation and prevent bleeding (Holbrook et al. 2012).

Table 2 shows the pharmacotherapeutic group, therapeutic indications and serious adverse reactions for each drug as well as the defined daily dose (DDD) according to the World Health Organization (WHO). The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (WHO 2023h). Table 3 summarizes the information for the prescribing and dispensing of the medicines in this group, availability of marketing authorization in Bulgaria and the trade name of the authorized products.

From the performed review of the available regulatory documentation, it is clear that only 3 of the listed INNs (metildigoxin, digoxin and acenocoumarol) are authorized in Bulgaria. In addition, other antithrombotic agents (new oral antithrombotic agents) are widely prescribed in recent years but are not included in Appendix № 9. It remains unclear whether this is due to the better safety profile of these drugs or because the list has not been updated recently (Sikka and Bindra 2010).

Table 2. Cardiac glycosides and coumarin anticoagulants included in Appendix № 9 (WHO, Cardiac glycosides; Kanji and MacLean 2012; Di Minno 2017; Askari 2019; WHO 2023q).

INN / ATC code	Pharmacotherapeutic group	Therapeutic indications	Undesirable effects	DDD/ Administration route *
Acetyldigoxin C01AA02	Cardiac glycosides, Digitalis glycosides	Heart failure; Atrial fibrillation	Nausea, vomiting, headache, visual disturbance, irregular heartbeat; narrow therapeutic index, risk of accumulation and intoxication	0.5 mg / O
Digitoxin C01AA04				0.1 mg / O 0.1 mg / P
Digoxin C01AA05				0.25 mg / O 0.25 mg / P
Lanatoside C C01AA06				1 mg / O 1 mg / P
Methyldigoxin C01AA08				0.2 mg / O 0.2 mg / P
Acenocoumarol B01AA07	Antithrombotic agents, Vitamin K antagonists	Treatment and prevention of thromboembolic diseases	Bleeding, including severe intracerebral bleeding	5 mg / O
Ethyl biscoumacetate B01AA08				0.6 g / O

* O = Oral; P = Parenteral.

Table 3. Access to cardiac glycosides and coumarin anticoagulants included in Appendix № 9 in Bulgaria (BDA 2017).

INN	Prescription Drugs (Rx)	Over-the-Counter (OTC) Drugs	Marketing authorization for use in Bulgaria	Brand name, dose, dosage form
Cardiac glycosides				
Acetyldigoxin	✓			
beta-Metildigoxin (incl. Metildigoxin)	✓		✓	Lanitop 0,1 mg tabl.
Digitoxin	✓			
Digoxin	✓		✓	Digoxin Sopharma 0,25 mg tabl. or 0,25 mg/ml sol. for inj./inf.
Lanatoside C	✓			
Vitamin K antagonists				
Acenocoumarol	✓		✓	Sintrom 4 mg tabl.
Ethyl biscoumacetate	✓			

Drugs acting on Peripheral and Central nervous system included in Appendix № 9 to Art. 17, para. 1 of Ordinance № 28/9.12.2008.

Drugs acting on peripheral and central nervous system that are included in Appendix № 9 belong to different pharmacotherapeutic groups (peripherally acting muscle relaxants, parasympathomimetics, parasympatholytics, etc.) and have various indications for use. Peripherally acting muscle relaxants are used during surgical procedures to provide muscle relaxation, which is achieved by blocking the transmission of nerve impulses at neuromuscular synapses. Most clinically used neuromuscular blocking drugs are quaternary ammonium compounds (tubocurarine, atracurium, pancuronium, etc.) and belong to the non-depolarizing neuromuscular blocking agents. They are competitive antagonists of N_2-cholinergic receptors in skeletal muscle cells and prevent the interaction of acetylcholine with N_2-cholinergic receptors, resulting in muscle relaxation (D'Souza et al. 2023). Suxamethonium has a different mechanism of action and is classified as depolarizing neuromuscular blocking agent. It acts as an agonist of N_2-cholinergic receptors, but causes prolonged depolarization in contrast to acetylcholine, which also leads to blockade of neuromuscular transmission and skeletal muscle relaxation (Hovgaard and Juhl-Olsen 2021). Both groups of neuromuscular blocking agents have specific adverse reactions that are listed in Table 4. Some of them may be potentially fatal, such as idiosyncratic reactions (malignant hyperthermia) after suxamethonium application. Furthermore, the use of suxamethonium in patients with genetically determined pseudocholinesterase deficiency that is responsible for its metabolism can lead to markedly prolonged paralysis. Neuromuscular blockers are administered intravenously to achieve general anesthesia, usually in combination with general anesthetics, M-cholinoblockers, etc., so there is a significant risk of drug interactions (Lee 2009). Information for the use of neuromuscular blockers in Bulgaria is given in Table 5. In this group DDDs have not been established because the doses used vary substantially.

In general, in Appendix № 9 are included 7 non-depolarizing neuromuscular blocking agents but only 3 of them are with granted marketing authorization in Bulgaria.

Parasympathomimetics mimic the effects of acetylcholine as a result of activation of the parasympathetic nervous system. They can be divided into 3 subgroups - cholinomimetics acting on muscarinic and nicotinic receptors (directly and indirectly acting), muscarinic agonists and nicotinic agonists. Most cholinomimetics are agonists of cholinergic receptors, in contrast to indirectly-acting cholinomimetic, also known as anticholinesterase drugs. They act by inhibiting acetylcholine esterase activity, the main enzyme that is responsible for the breakdown of acetylcholine. The result is accumulation of endogenous acetylcholine in the synapses and activation of the parasympathetic nervous system (Forrester et al. 2016). In Appendix № 9 are included acetylcholinesterase inhibitors (galantamine, neostigmine, pyridostigmine, ambenonium) and muscarinic agonists (pilocarpine). Main pharmacological effects

Table 4. Neuromuscular blocking agents included in Appendix № 9 (Lee 2009; Clar and Liu 2022; WHO 2023f, g, n).

INN / ATC code	Pharmacotherapeutic group	Therapeutic indications	Undesirable effects
Non-depolarizing neuromuscular blocking agents			
Alcuronium M03AA01	Muscle relaxants, Peripherally acting agents, Curare alkaloids	An adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation	Increased release of histamine (hypotension, tachycardia, bronchospasm, urticaria); Anaphylactic reactions; Residual paralysis, including paralysis of the respiratory muscles (curare-like effect)
Tubocurarine M03AA02			
Pancuronium M03AC01	Muscle relaxants, Peripherally acting agents, Other quaternary ammonium compounds		
Atracurium M03AC04			
Pipecuronium bromide M03AC06			
Rocuronium bromide M03AC09			
Mivacurium chloride M03AC10			
Depolarizing neuromuscular blocking agents			
Suxamethonium M03AB01	Muscle relaxants, Peripherally acting agents, Choline derivatives	An adjunct to general anesthesia, to facilitate rapid endotracheal intubation and to provide short skeletal muscle relaxation during surgery or mechanical ventilation	Malignant hyperthermia; Prolonged neuromuscular block in patients with deficient or inactivated plasma cholinesterase; Cardiac arrhythmia and cardiac arrest; Myalgia; Hyperkaliemia

of cholinomimetics are stimulating of gastrointestinal and bladder motility, miosis, excessive salivation, sweating, urinary urgency, bronchoconstriction and increased bronchial secretion, improvement of nerve impulse transmission in skeletal muscle cells, while some improve acetylcholine neurotransmission mostly in the central nervous system. Adverse reactions of parasympathomimetics are related to the mechanism of action and are due to overactivation of the parasympathetic nervous system (Singh and Sadiq 2023). The therapeutic indications and adverse drug reactions of cholinomimetics included in Appendix № 9 are presented in Table 6.

Table 5. Access to neuromuscular blocking agents included in Appendix № 9 in Bulgaria (BDA 2017).

INN	Prescription Drugs	Over-the-Counter (OTC) Drugs	Marketing authorization for use in Bulgaria	Brand name, dose, dosage form
Non-depolarizing neuromuscular blocking agents				
Alcuronium	✓			
Tubocurarine	✓			
Pancuronium	✓			
Atracurium	✓		✓	Tracrium 10 mg/ml sol. for inj.
Pipecuronium bromide	✓		✓	Arduan 4 mg powder and solvent for sol. for inj.
Rocuronium bromide	✓		✓	Esmeron 10 mg/ml sol. for inj.; Rocuronium B.Braun 10 mg/ml sol. for inj./inf.
Mivacurium chloride	✓			
Depolarizing neuromuscular blocking agents				
Suxametonium	✓		✓	Lysthenon 10 mg/ml or 20 mg/ml sol. for inj.

Table 6. Cholinomimetics and anticholinergics included in Appendix № 9 (Panarese and Moshirfar 2022; Ghossein et al. 2023; Singh and Sadiq 2023; WHO 2023b, c, e, m, o, p).

INN / ATC code	Pharmacotherapeutic group	Therapeutic indications	Undesirable effects	DDD/ Administration route *
Parasympathomimetic drugs				
Galantamine N06DA04	Anti-dementia drugs, Anticholinesterases	Alzheimer's disease; Polyneuropathy; Myasthenia gravis; Muscular dystrophy; Cerebral paralysis	SLUDGE syndrome (Salivation, Lacrimation, Urination, Diaphoresis, Gastrointestinal upset, Emesis); Miosis; Bradycardia, AV block; Bronchoconstriction; Severe respiratory depression; Muscle fibrillation, fasciculations, and paralysis; Seizures; Retinal detachment	16 mg / O
Neostigmine 1. N07AA01	1. Parasympathomimetics, Anticholinesterases	To reverse the effects of nondepolarizing muscle agents; Myasthenia gravis Paralytic ileus; Urinary retention		1. 60 mg / O
				2 mg / P
2. S01EB06	2. Antiglaucoma preparations and miotics, Parasympathomimetics			2. 0.4 ml
				40 mg / oint.
Pyridostigmine N07AA02	Parasympathomimetics, Anticholinesterases	Myasthenia gravis; Paralytic ileus; Urinary retention		0.18 g / O
				10 mg / P
Ambenonium N07AA30	Parasympathomimetics, Anticholinesterases	Myasthenia gravis		60 mg / O
Pilocarpine 1. N07AX01	1. Parasympathomimetics, Other parasympathomimetics	1. Xerostomia		1. 15 mg / O 10 mg / P
2. S01EB01	2. Antiglaucoma preparations and miotics, Parasympathomimetics	2. Glaucoma		2. 0.4 ml 0.285 / lamella 40 mg / oint.
Anticholinergic agents				
Atropine 1. A03BA01	1. Belladonna and derivatives, plain, Belladonna alkaloids, tertiary amines	1.Bradycardia; AV block; To reduce salivation and bronchial secretions before surgery; As an antidote for overdose of cholinergic drugs or mushroom poisoning; Stomach and intestinal spasms, spasms of the urinary tract and the gallbladder;	Mydriasis, Xerostomia Tachycardia, Blurred vision, Urinary retention, Constipation, Lack of sweating, Hyperthermia, Flushing, Arrhythmias, Increased intraocular pressure, Pyloric obstruction, Neurological symptoms, including delirium, agitation, and hallucinations (intoxication)	1. 1.5 mg / O 1.5 mg / P
2. S01FA01	2. Mydriatics and cycloplegics, Anticholinergics	2.To dilate pupil		2. –
Scopolamine 1. A04AD01	1. Antiemetics and antinauseants, Other antiemetics	1. Motion sickness; Postoperative nausea and vomiting		1. –
2. N05CM05	2. Hypnotics and sedatives, Other hypnotics and sedatives	2. As a premedication, in surgery (to reduce respiratory tract secretions)		2. 0.9 mg / O 0.9 mg / P
3. S01FA02	3. Mydriatics and cycloplegics, Anticholinergics	3. Mydriasis, Eye inflammation		3. –
Butylscopolamine A03BB01	Belladonna and derivatives, Plain; Belladonna alkaloids, semisynthetic, quaternary ammonium compounds	Stomach and intestinal spasms, spasms of the urinary tract and the gallbladder		60 mg / O
				60 mg / P
				60 mg / R
Biperiden N04AA02	Anti-Parkinson drugs; Anticholinergic agents; Tertiary amines	Parkinson's disease; Extrapyramidal disorders secondary to neuroleptic drug therapy		10 mg / O
				10 mg / P

* O = Oral; P = Parenteral; R = Rectal.

Anticholinergic drugs are competitive antagonists of M-cholinergic receptors that suppress the effects of acetylcholine and reduce the activity of the parasympathetic nervous system. Pharmacological effects of parasympatholytic agents are spasmolytic and broncholytic effects, mydriasis, increased heart rate, urinary retention, etc. Anticholinergic drugs included in Appendix № 9 are 4 and belong to different pharmacotherapeutic groups (Table 6). Intoxication with anticholinergics causes the so-called atropine-like effects - xerostomia, mydriasis, tachycardia, dizziness, fatigue, constipation, urinary retention, dry skin due to suppression of sweating, fever, etc. It's often used the memory aid "red as a beet, dry as a bone, blind as a bat, mad as a hatter, hot as a hare, full as a flask' to remember the common symptoms of anticholinergic toxicity (Ghossein et al. 2023). In Table 7 is summarized the information on the use of parasympathomimetics and anticholinergic drugs included in Appendix № 9 in Bulgaria.

In conclusion, two of the listed parasympathomimetic drugs that are cholinesterase inhibitors and one anticholinergic agent are not authorized in Bulgaria. However, there is cholinesterase inhibitors that have marketing authorization in Bulgaria but are not included in the Appendix.

The other drugs acting on the Nervous system are ergotamine, nalorphine, naloxone and tetracaine. They have different mechanism of action and indications. Ergotamine is an ergot alkaloid. It selectively binds and activates serotonin $(5\text{-HT})_{1B}$ and $(5\text{-HT})_{1D}$ receptors located on intracranial blood vessels, resulting in vasoconstriction and reduction in cerebral blood flow that may relieve some types of headaches (Silberstein and McCrory 2003). Nalorphine and naloxone are competitive antagonist of opioid receptors. Unlike naloxone, nalorphine has agonistic effect at the kappa opioid receptors (KOP) (Theriot et al. 2023). Tetracaine is a local anesthetic from the amino-esters class. It's a membrane-stabilizing drug which reversibly blocks the voltage-gated sodium channels in the neuronal cell membrane (Adeleve 2020). Indications and side effects of these drugs are shown in Table 8. In Bulgaria tetracaine is used only in combination with other drugs (Table 9).

Table 7. Access to cholinomimetics and anticholinergics included in Appendix № 9 in Bulgaria (BDA 2017).

INN	Prescription Drugs	Over-the-Counter (OTC) Drugs	Marketing Authorization for use in Bulgaria	Brand name, dose, dosage form
Parasympathomimetic drugs				
Neostigmine	✓			
Pyridostigmine	✓		✓	Kalymin 60 mg tabl.; Mestinon 60 mg tabl.;
Ambenonium	✓			
Pilocarpine	✓		✓	Pilocarpin Vision 20 mg/ml eye drops, sol.
Galantamine	✓		✓	Nivalin 5mg or 10 mg tabl.; Nivalin 1 mg/ml, 2.5 mg/ml, 5 mg/ml or 10 mg/ml sol. for inj.; Galantamine DS 1 mg/ml or 5 mg/ml sol. for inj.; Galsya SR 8 mg, 16 mg or 24 mg caps.
Anticholinergic agents				
Atropine	✓		✓	Atropine Sopharma 1 mg/ml sol. for inj.; Atropine Vision 10 mg/ml eye drops, sol.
Scopolamine	✓			
Butylscopolamine	✓	✓	✓	Buscolysin 10 mg tabl.; Buscolysin 20 mg/ml sol. for inj. Buscopan 10 mg tabl.; Buscopamine 20 mg/ml sol. for inj.; Scopolamine butylbromide Kalceks 20 mg/ml sol. for inj.;
Biperiden	✓		✓	Akineton 2 mg tabl.; Akineton 5 mg/ml sol. for inj.; Akineton SR 4 mg tabl.; Akinestat 2 mg tabl.; Mendilex 2 mg tabl.;

Table 8. Other drugs affecting on nervous system (Adeleve 2020; Ngo and Tadi 2022; Theriot et al. 2023; WHO 2023d, j, k).

INN / ATC code	Pharmacotherapeutic group	Therapeutic indications	Undesirable effects	DDD*/ Administration route **
Ergotamine 1. N02CA02	Analgesics, Antimigraine preparations, Ergot alkaloids	Migraine and cluster headache attacks	Nausea, Vomiting, Life-threatening peripheral or cerebral ischemia, arterial hypertonia when administered with CYP3A4 inhibitors, Overuse headache, Ergotism	1. 4 mg / Inhal 4 mg / O 4 mg / P
2. N02CA72				4 mg / R
				4 mg / SL
				2. 4 mg / O
Nalorphine V03AB02	Antidotes	Opioid overdose	Withdrawal symptoms; Dysphoria, anxiety, confusion, hallucinations due to activation of the KOR	–
Naloxone V03AB15			Withdrawal symptoms (restlessness, agitation, nausea, vomiting, tachycardia, sweating)	–
Tetracaine N01BA03 N01BA53	Anesthetics, local, Esters of aminobenzoic acid	Spinal anesthesia; to produce local anesthesia in the eye, ear and nose	Systemic reactions – central nervous system toxicity (numbness, tinnitus, blurry vision, dizziness)	–

* For some of the drugs DDDs have not been established. ** O = Oral; P = Parenteral; R = Rectal; Inhal = Inhalation; SL = Sublingual/buccal/oromucosal.

Ergotamine and nalorphine are not authorized in Bulgaria although they are listed in Appendix № 9. Surprisingly, another opioid antagonist – naltrexone has marketing authorization in Bulgaria but is not listed in Appendix № 9. In addition, other local anesthetic from the class of amino-esters (procaine) is available in Bulgaria but is not included in the Appendix. Furthermore, local anesthetics from the amino-amides class (lidocaine, mepivacaine, bupivacaine, etc.) that are authorized in Bulgaria are not listed in Appendix № 9 too.

Anabolic steroids included in Appendix № 9 to Art. 17, para. 1 of Ordinance № 28/ 9.12.2008.

Appendix № 9 includes 3 medicinal products related to anabolic steroids (Ministry of Health 2010). They are synthetic derivatives of testosterone that have anabolic and androgenic effects due to activation of intracellular androgen receptors and influencing the expression of glucocorticoid receptors. Anabolic effects are the stimulation of protein synthesis in skeletal muscle cells, stimulation of red blood cells production, improvement of athletic performance, etc., while androgenic effects are associated with a number of hormonal changes that in most cases are undesirable. Anabolic and androgenic effects cannot be completely separated and are common to all anabolic steroids, although some of the synthetic steroids (nandrolone, oxymetholone, metandienone) show predominant anabolic effects. Myotrophic–androgenic index is used for evaluation of anabolic and androgenic effects of the anabolic steroids (Kicman 2008). Therapeutic indications and adverse reactions for the anabolic steroids, included in Appendix № 9 are shown in Table 10. Anabolic steroids are prescription-only medicines although they are sometimes used to increase muscle mass and physical endurance without medical consultation. Long-term use of anabolic steroids is associated with serious adverse effects and should be avoided (Farzam 2021). None of the anabolic steroids included in Appendix № 9 is authorized for use in Bulgaria (BDA 2017).

In the present study we analyzed and summarized the available information about the medicinal products included in Appendix № 9 to Art. 17, para. 1 of Ordinance № 28/9.12.2008, issued by the Minister of Health. The list includes 70 drugs and all of them, except butylscopolamine (INN is in the OTC list) for oral administration are available only by prescription. Most medicines listed in Appendix № 9 may be potentially dangerous even when taken in therapeutic doses. These drugs belong to different pharmacotherapeutic groups and have a variety of indications for use. For a better presentation of the information, the medicines were divided into four groups – Medicines acting on peripheral and central nervous system, Medicines acting on cardiovascular system and blood coagulation, Antineoplastic and immunomodulating agents and Anabolic steroids.

In the first part of this article, we reviewed the available information about the medications acting on cardiovascular system, nervous system and anabolic steroids. A total of 31 drugs are included in these groups but we established that half of them (16 drugs) are not registered for use by the Bulgarian Drug Agency (BDA) to date and are not used in clinical practice in Bulgaria. On the other hand, in Bulgaria there are some medicinal products that have a marketing authorization granted by the BDA or are authorized for use under a centralized procedure under Regulation (EC) №726 / 2004 of the European Parliament and of the Council of 31 March 2004 but are not included in the Appendix although they belong to the same pharmacologic and pharmacotherapeutic group with medicines listed in Appendix № 9. The information is summarized in Table 11. These medicines have identical mechanism of action and similar therapeutic indications but have not been added to the list

Table 9. Access to ergotamine, nalorphine, naloxone and tetracaine in Bulgaria (BDA 2017).

INN	Prescription Drugs	Over-the-Counter (OTC) Drugs	Marketing authorization for use in Bulgaria	Brand name, dose, dosage form
Ergotamine	✓			
Nalorphine	✓			
Naloxone	✓		✓	Naloxon WZF 0.4 mg/ml sol. for inj; Forvel 0.4 mg/ml sol. for inj.
Tetracaine	✓		✓	Furotalgin 2,5 mg/31,25 mg/87,5 mg/ml ear drops, sol.

Table 10. Anabolic steroids included in Appendix № 9 (Frati et al. 2015; WHO 2023a, l).

INN / ATC code	Pharmacotherapeutic group	Therapeutic indications	Undesirable effects	DDD/ Administration route *
Metandienone A14AA03	Anabolic steroids, Androstane derivatives	Androgen replacement therapy for the treatment of hypogonadism in men	Cardiotoxicity, Hepatotoxicity, hepatocellular neoplasms; Metabolic and Endocrine disorders	5 mg / O
Oxymetholone A14AA05		Anemias caused by deficient red cell production; aplastic anemia, congenital aplastic anemia, myelofibrosis and hypoplastic anemias due to the administration of myelotoxic drugs		0.25 g / O
Nandrolone A14AB01	Anabolic steroids, Estren derivatives	Senile and postmenopausal osteoporosis. Palliative treatment of certain cases of disseminated breast cancer. Additional specific therapy in pathological conditions with negative nitrogen balance.		2 mg / P

* O = Oral; P = Parenteral.

Table 11. Medicines with a marketing authorization in Bulgaria that are not included in Appendix № 9 (Ministry of Health 2010; BDA 2017).

Pharmacotherapeutic group	INN		
	Included in Appendix № 9 with marketing authorisation in Bulgaria*	Included in Appendix № 9 without marketing authorization in Bulgaria*	Not included in Appendix № 9, but have marketing authorization in Bulgaria*
Acetylcholinesterase inhibitors	Pyridostigmine, Galantamine	Neostigmine, Ambenonium	Rivastigmine, Donepezil, Ipidacrine
Opioid antagonists	Naloxone	Nalorphine	Naltrexone
Local anesthetics	Tetracaine	–	Procaine

* by the BDA or under a centralized procedure.

with medications that must be stored in a locked cabinet. The presented information about drugs authorization in Bulgaria is up-to-date as of June 2023 (BDA 2017).

The question remains whether these drugs, shown in Table 11 have better safety profile or there is a different reason they are not included in the Appendix. Furthermore, it remains unclear when the list of medicines in Appendix 9 was last updated, as well as the criteria for inclusion of drugs in it. It would be useful to present detailed and up-to-date information on the medicinal products listed in Appendix № 9 during the professional trainings organized by the Bulgarian Pharmaceutical Union.

Conclusion

In conclusion, many of the listed INNs are not presently available on the Bulgarian market. Therefore, it is necessary to periodically update the list of medicinal products included in Appendix № 9 and to optimize the storage of medicinal products containing potentially dangerous active substances. Also, it is necessary to develop clear and precise criteria for the inclusion of medicines in this special Appendix and to ensure their storage in a locked cabinet in the hospital and retail pharmacies. Increasing the pharmacists' knowledge and awareness about the toxicity of these medicinal products would lead to increased caution when dispensing them to the patients. Thus, the pharmacist will be able to recognize the side effects of the therapy and can provide more adequate pharmaceutical care.

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