

## MEDICINAL PRODUCTS FOR TREATMENT OF NEUROPATHIC PAIN - REGULATORY PROBLEMS IN ELDERLY

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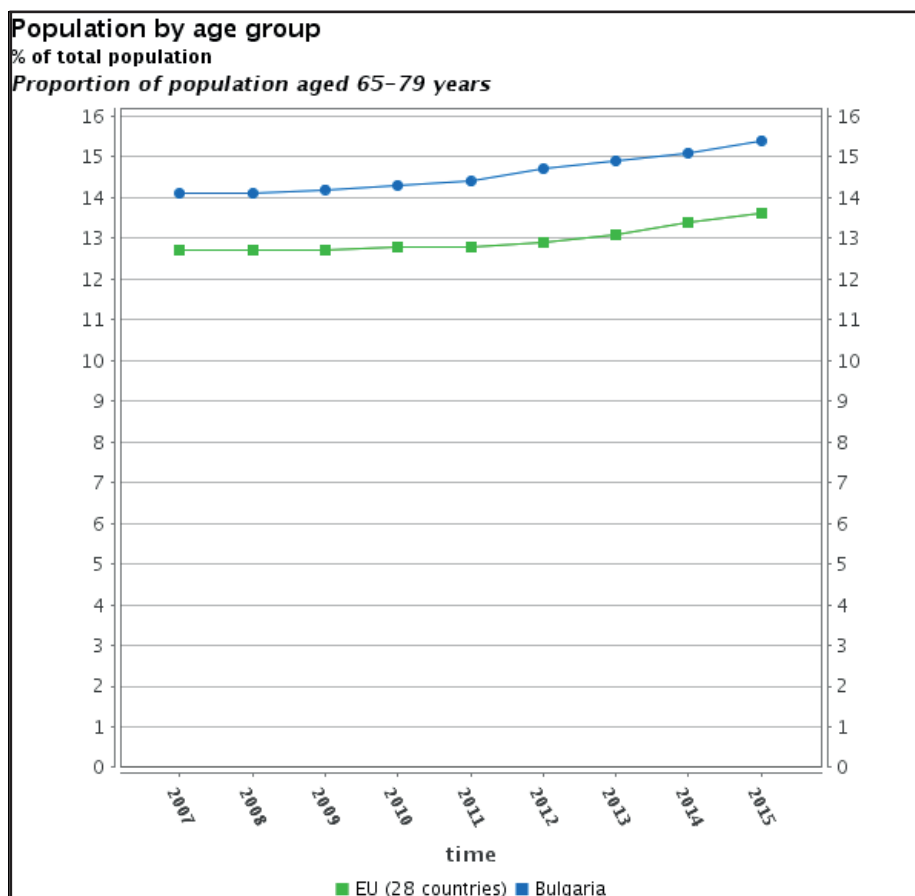
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**Abstract:** The group of people over 65 years old is growing not only in Bulgaria but in the whole EU. These patients experience changed physiological and biochemical characteristics. At the same time, they comprise a large part of the people who take pain-killers. The contemporary pharmaceutical regulation is taking first steps in implementing adequate requirements and recommendations for the use of drugs among this specific group of patients, as well as towards the clinical research during the development of new products. Our goal was to examine to what level the medicinal products intended for management of neuropathic pain authorized in Bulgaria comply with the requirements for medicinal products among elderly and fatigued patients. The results show that all "old" products, including the reference listed drugs that have received marketing authorization after a national procedure before 2007 require harmonization.

**Key words:** pharmaceutical legislation, elderly, neuropathic pain,

Among the general population, the rate of chronic pain in Europe and the US is approximately 20%. [1] Among the elderly population (over 65 years old) this condition affects an increasing number of people and reaches 40%. [2] According to data from Eurostat, the number

of people over the age of 65 is expected to increase from around 84 mln. in 2008 to around 141 millions in 2050. As a result, the elderly will represent a large population of patients, with the ones over 75 years of age being the fastest increasing group of patients. (Fig. 1) [3]

**Fig.1** EU Population by age group

Source of Data: Eurostat

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Hyperlink to the graph: <http://ec.europa.eu/eurostat/tgm/graph.do?pcode=tps00010&language=en>

The pain among the elderly patients is a special condition which drastically decreases the quality of life. To find the most appropriate therapeutic model during the past years, several scientific groups have developed various therapeutic guides that recommend a multidisciplinary approach. The therapeutic modalities are usually categorized in the following four therapeutic categories: pharmacotherapy, psychosocial therapy, physical rehabilitation and interventional methods.

Taking into consideration that along with the age-related changes in the body there is a change in the pharmacokinetics of the active substances, in many cases, there is a need for reconsideration of some therapeutic indications as well as in the dosage of medicinal products

and their interaction with other drugs.

Within the modern pharmaceutical regulation regarding the benefit/risk ratio among special groups of patients (pediatric; with impairment in certain functions and systems; elderly), there have been established a number of principles. Unlike the medicinal products intended for use during childhood, so far in Europe, there are no unified regulatory requirements towards the medicinal products intended for use among the elderly population (over 65 years old and fatigued patients). The only published and still, applicable document is the guideline by ICH – E7 Studies in Support of Special Population: Geriatrics. [4] On the other hand, although the usage of the main groups of medicinal products is the highest among patients over 75 years

old and they are relatively the largest users of medicinal products, there is a low percentage of participants in clinical research from this age group. This imbalance can be explained by the expansion of the criteria for exclusion from clinical research based on accompanying illnesses. [5] At the same time there is often a lack of regulatory instructions and guidelines on the inclusion of such patients in clinical or post-marketing research.

This is why there is an increase in the understanding that the collection of credible data about benefit/risk ratio among the target populations requires more than diligently balanced amount of participants in clinical research.

Based on best practices, the generic drugs need almost to mirror their information based on the information of the original products. This requirement has been enforced in Bulgaria since the beginning of the Stabilization and Association Process, meaning that the “old” products often do not comply or comply only partially.

With regard to the harmonization of application forms and documentation on the territory of the EU, the European Medicine Agency and its committees and working groups is developing regulatory and academic guidelines and instructions for the pharmaceutical companies, which are available on the web page <http://www.ema.europa.eu>

In the CHMP’s (Committee for Medicinal Products for Human Use) “Guideline on clinical trials for products intended for the treatment of neuropathic pain” [6] there are directions about the design of the clinical research, the selection of patients, methods for the assessment of efficacy, etc. All drugs that hold marketing authorization, with approved therapeutic indications “for the treatment of neuropathic pain” have been a subject to numerous clinical trials, whose purpose is to prove the indisputable efficacy, advantages and safety profile among the target group of patients, in accordance with the pain syndrome and/or separate forms of neuropathic pain. This is true for medicinal products holding marketing authorization after 2007.

This research shows the methodological approach for an assessment of the therapeutic indications, dosage, ways of use and safety profile of medical products which are widely used for the management of neuropathic pain.

### **Purpose:**

The purpose of our analysis is:

- To research and present the current state of the medicinal products for management of neuropathic pain holding marketing authorization in Bulgaria, and to what level they comply with the application guidelines for use in elderly patients.

- To research to what level manufacturing companies and state regulatory organs, in their assessment of the benefit/risk ratio of medicinal products, take into account the specific aspects of safety and efficacy related to elderly patients and to identify the potential regulatory gaps and to offer measures for their management.

The collected data should answer some fundamental questions such as:

What are the approved therapeutic indications for the medicinal products recommended by different international instructions/guidelines for the treatment of neuropathic pain and is the information [Summary of Product Characteristics (SPC)] of the different products harmonized with the information for the reference medicine?

Is there information about the dosage and usage/special warnings and precautions for usage by patients above the age of 65 years and is the information presented to the medical specialists and patients compliant with the clinical documentation that accompanies the marketing authorization.

### **Materials and methods**

The used materials are connected to the documentation that accompanies the procedures for marketing authorization of medicinal products on a national level which is regulated by the Legislation for the Medicinal Products in Humane Medicine and the related sub-legislative normative acts. A systematic view

took place during the research, which relied upon the available data in the register of the marketing authorized medicinal products and the released Summaries of Product Characteristics.

### Methods

In the current research, we included a follow-up research on the data of the published Summaries of Product Characteristics and the available clinical documentation on every marketing authorization of medicinal products.

The methodological approach that was chosen includes five consecutive stages:

1. Clarifying the registration status of the products that are recommended for the management of neuropathic pain, including the type of procedure that issued the marketing authorization.

2. Analysis of the approved therapeutic indications published in point 4.1 of the Short Characteristics of the Products.

3. Analysis of the recommended dosage among the special populations of patients, with a focus on elderly patients (point 4.2 of the SCP).

4. Analysis of the information such as special warnings and safety measures for usage

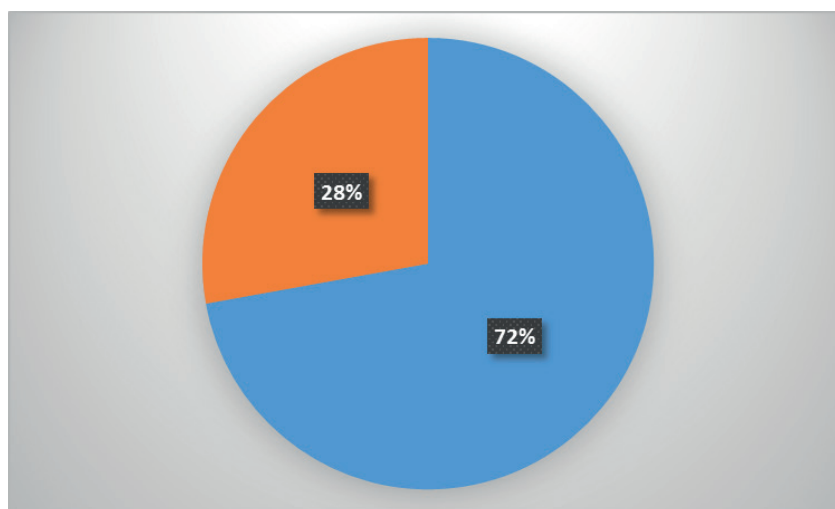
of the products by people over the age of 65 years, included in point 4.4 of the SCP

5. Analysis of the attached clinical documentation that supplements the marketing authorization (modules 2.5 and 5 from the dossier of the medicinal products).

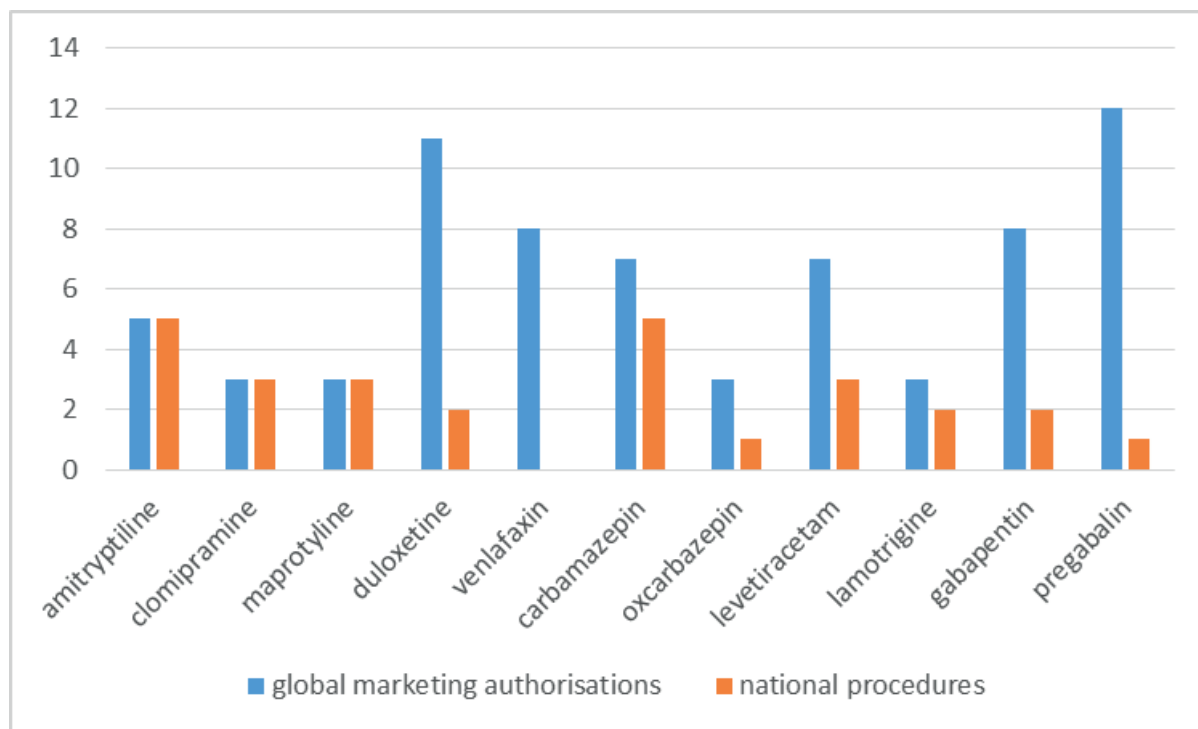
### Results and discussion

In accordance with what was discussed above, the documentation for 11 active substances, which are contained in 70 medicinal products, holding marketing authorizations in Bulgaria and/or other EU members, according to a national, decentralized and centralized procedure was reviewed. From them, 11 do not hold valid marketing authorization in Bulgaria, wherein for two products the procedure for marketing authorization has not yet finalised. Eight products have received marketing authorization by a national procedure, and 1 product has received marketing authorization by a centralized procedure (used as a reference medicine). (fig. 2 Distribution according to procedures - community procedures and national procedure) (fig. 3 Distribution according to active substances.)

**Fig. 2** Distribution according to type of procedure – community procedures (DCP/MRP) and national procedures



28% national procedures  
72% DCP/MRPs

**Fig.3** Distribution according to active substances

The obtained results are grouped according to active substances and their pharmaceutical class (in two main groups, as follows: those with confirmed full compliance and those that do not comply with contemporary requirements).

#### **Antidepressants:**

The antidepressants are recommended as a first line for the treatment of various occurrences of neuropathic pain. The therapeutic consensus and guidelines give advantage of the tricyclic antidepressants (TCA) and SNRI *venlafaxine* and *duloxetine*.

A reference to the Bulgarian Drug Agency's register of products that have received marketing authorization in the Republic of Bulgaria, [7] reveals that the following have received marketing authorization:

#### **Tricyclic antidepressants (TCA):**

**Amitriptyline:** Amitriptyline Meda 10 mg coated tablets. In Bulgaria, the following indication is approved: "Treatment of symptoms of depression, especially conditions that require a sedative effect." For comparison, in UK,

medicinal products that contain amitriptyline (4 trade names under various medicinal forms and quantity of active substance) have two approved therapeutic indications [8]: depressive conditions and enuresis nocturna in children over six years of age and adults, which is not caused by an organic impairment. The therapeutic indications vary in significant levels between the different products that have been nationally approved in different EU members, wherein there have been included bipolar disorder, insomnia and treatment of chronic pain (migraine, neuropathic pain with central or peripheral origin, fibromyalgia).

The identified differences in the SPC of medicinal products that contain amitriptyline also include dosage and posology, contraindications, adverse effects, warnings and precautions for the general population, as well as for the elderly group of patients. In the product information in Bulgaria there is no information about the following: predisposition towards adverse effects of the group of elderly patients, especially euphoria, states of confusion and orthostatic hypotony, syndrome of inadequate secretion of

the antidiuretic hormone and related hyponatremia, interaction with anticholinergics, which might lead to paralytic ileus, urine retention and acute glaucoma. There is no risk management plan submitted. SPC does not include information that is relevant with regard to the elderly patients.

**Clomipramine:** Anafranil 10 mg coated tablets (reference product). The approved indication in Bulgaria is: treatment of depressive conditions with diverse etiology and symptoms. For comparison, in France Anafranil is approved for treatment of painful diabetic neuropathy in adults. In a report from 2013, the Commission on Transparency determines that clomipramine is of significance for the treatment of this condition. [9] The indication is also approved for the generic of Anafranil products. In point 4.4 it is specified that the products must be used with caution in patients over 65 years of age, due to a risk of orthostatic hypotony, sedative effects, constipation and prostate hypertrophy. [10] These warnings **are not included in Anafranil's SPC in Bulgaria**. At the same time, the information for the product in Bulgaria suggests titration for elderly patients. Because the products have been on the Bulgarian market for more than 17 years (the marketing authorization was issued by the Law for The Medicines and Pharmacies in Humane Medicine in 1995), the documentation that supplements the marketing authorization is not preserved so it is not possible to assess to what level the information in SPC is in accordance with the data that supplements the marketing authorization.

In Belgium,[11] the information about the product is identical to the one in Bulgaria.

The identified differences in SPC of medicinal products that contain clomipramine relate mainly to the warnings and precautions mostly towards the population of elderly patients. The product information in Bulgaria does not include any data.

**Maprotiline:** Ludiomil 10 mg and Ludiomil 25 mg tablets. Medicinal products containing this active substance are approved nationally in several EU members, wherein we reviewed

*the products' SPCs in France and Bulgaria. There are no generics found. Ludiomil 10 mg and Ludiomil 25 mg tablets are approved for application in various depressive conditions, and they are not a subject of the current research.*

Despite being recommended as the first line in the treatment of various conditions that lead to neuropathic pain, the other representatives of the group of TCA, imipramine, nortriptyline and desipramine do not hold marketing authorization in Bulgaria.

**SNRIs:** (serotonin - norepinephrine reuptake inhibitors)

**Duloxetine:** Cymbalta – original product and ten generic drugs by a decentralized procedure and one marketing authorization by a national procedure.

Approved therapeutic indications in all medicinal products containing this active substance are: treatment of large depressive fits; treatment of peripheral diabetic neuropathic pain and treatment of generalized anxiety disorder [12]. They are harmonized with the ones that relate to the reference medicine. The dosage recommendations are identical for all products containing duloxetine in doses 30 mg or 60 mg.

The information included in the product's Summary of Product Characteristics and the risk management plans are completely harmonized with the reference medicine.

**Venlafaxine:** At the time of writing this publication, through a decentralized/national procedure there have been issued eight global (1 global marketing authorization includes all strengths with one trade name and one Marketing authorization holder [MAH]) marketing authorizations. Efectin ER, with HMA Pfizer Europe MA EEIG, UK is pointed as a reference medicine. All others are generic drugs.

All products have the same approved therapeutic indication: treatment of large depressive fits, for prevention of recurrence of large depressive fits, treatment of generalized anxiety disorder, treatment of social anxiety disorder, treatment of panic disorder with or without agoraphobia.

The information about the application of the products in elderly patients is included in the respective section, is identical for all generic drugs and is completely harmonized with the reference medicine.

### **Antiepileptics**

#### ***Carbamazepine***

In Bulgaria, there have been issued marketing authorizations for five medicinal products with this active substance. The reference medicine is Tegretol 200 mg tablets, MAH Novartis Pharma GmbH, Germany. The rest have market authorization as generic drugs.

The approved, in Bulgaria, indications are: idiopathic trigeminal neuralgia and trigeminal neuralgia, as a result of multiple sclerosis; idiopathic glossopharyngeal neuralgia, painful diabetic polyneuropathy. The information for the product has not been updated since 2013.

Approved therapeutic indications for the reference medicine in the UK are:

Generalized tonic-clonic and partial seizures in epileptic patients, paroxysmal pain in trigeminal neuralgia, prophylactic of manic-depressive psychosis in patients, who do not respond to lithium treatment.

Approved therapeutic indications for the reference medicine in France are:

Treatment of trigeminal and glossopharyngeal neuralgia; treatment of painful neuropathy in elderly patients.[10]

The established discrepancies concern not only the therapeutic indications but also the information about the dosage in patients above the age of 65 years; the warnings are not differentiated; in the dossier of the product for Bulgaria, there is no information about clinical research performed with elderly patients. The owner of the marketing authorization did not undertake the necessary regulatory actions for updating the product information.

The information included in the Summary of Product Characteristics and the risk management plan are not harmonized on the whole territory of the EU. There have been established discrepancies with the original product with

regard to the therapeutic indications for the generic drugs in Bulgaria - Neurotop, Finlepsin and Carbamazepine Actavis. The safety profile of the products is unified with the reference medicine.

#### ***Oxcarbazepine***

Three medicinal products hold marketing authorization, from which Trileptal is a reference medicine, and the rest are generic drugs.

Approved therapeutic indications: for treatment of partial seizures with or without secondary generalization; as mono-therapy or as additional therapy in elderly patients and children over six years old. The information is identical in the EU members.

The approved indications are identical in the EU members. The information included in the Summary of Product Characteristics and the risk management plans is completely harmonized with the reference medicine. The necessary warnings and directions for use in elderly patients are included.

#### ***Levetiracetam***

According to the register of marketing authorized medicinal products of the Bulgarian Drug Agency, during the time of research, there are seven valid global marketing authorizations of medicinal products containing this active substance. From them 1 DCP, 3 MRP, and three completely national marketing authorizations.

Approved therapeutic indications: for mono-therapy in the treatment of partial seizures with or without secondary generalization in patients over 16 years of age with newly diagnosed epilepsy.

The information included in the Summary of Product Characteristics and the risk management plans is entirely harmonized with the reference medicine. The necessary warning and directions for use in elderly patients are included.

#### ***Lamotrigine***

The documentation for marketing authorization and Summary of Product Characteristics

of 8 medicinal products was reviewed, from which, at the time of the research, three products hold a valid marketing authorization in Bulgaria.

Approved therapeutic indications: various forms of epilepsy and bipolar disorder.

Although all marketing authorized in Bulgaria medicinal products are generic drugs and are approved according to the Legislation for Medicinal Products and Pharmacies in Humane Medicine (in the period 2005 – 2007) by a national procedure, the information included in the Summary of Product Characteristics is entirely harmonized with the reference medicine. The necessary warnings and directions for use in elderly patients are included. The reference product does not have a risk management plan, hence, such is not needed for the generic drugs.

### ***Gabapentine***

In Bulgaria, there have been issued marketing authorizations for eight medicinal products containing this active substance. The reference medicine Neurotin holds marketing authorization by a national procedure. All generic medicinal products, except for one, hold marketing authorizations by a decentralized procedure.

Approved therapeutic indications: for treatment of epilepsy and peripheral neuropathy pain.

The reference medicine is Neurontin, holding a national marketing authorization, approved for treatment of neuropathy pain in patients at and over 18 years of age. The comparison, however, with the indications approved in other EU members shows a significant expansion of the indication. In UK, France, and Belgium the Neurontin's indications are for painful diabetic neuropathy and postherpetic neuralgia. The indications of the generic products registered in these countries are identical.

Also, it was determined that with the exception of Bulgaria, the information for all products in the EU included warnings about the need for adaptation towards the dosage in patients over the age of 65, as well as the potential risks with regard to the administration of

gabapentin in people in this age group.

SPCs of the generics are harmonized on the territory of the whole EU, with the exception of Bulgaria.

### ***Pregabalin***

The reference product Lyrica holds marketing authorization by a centralized procedure. At the time of the research, in Bulgaria, there have been issued marketing authorizations for 12 generic to Lyrica medicinal products, whereas only one of them holds marketing authorization by a national procedure.

Approved therapeutic indications: neuropathic pain: for treatment of peripheral and central neuropathic pain in elderly patients.

The information included in the SPC (indications, dosage, warnings and safety measures, undesirable drug interactions), as well as the risk management plans, are entirely harmonized with the reference product.

### ***Central acting opioid analgesic – Tramadol***

In Bulgaria, there have been issued four global marketing authorizations, from which three entirely national and one after a decentralized procedure. The approved indications are for treatment of moderate to moderately-severe pain. SPC are adapted to the reference medicine Tramal, and there is adequate information about the dosage in elderly patients.

A review of the dossiers of the cited drugs shows a clear and significant difference in the clinical documentation (Module 2.5, Module 5, SPC and patient leaflet) between the dossiers of all medicinal products that received marketing authorization before the Legislation on Medicinal Products and Pharmacies in Humane Medicine [LMPPHM] (2007) took effect and the dossiers of the products that received marketing authorization after Bulgaria joined the EU. The clinical documentation supplementing and supporting the marketing authorization (in Module 2.5 and Module 5 of the dossier) of the generic drugs that have received marketing authorization before LMPPHM (2007) took



effect is incomplete and does not meet the contemporary requirements: “When the applicant is able to prove that the product is generic (significantly improved) of a reference medicinal product that has received marketing authorization in member-state at least 8 years ago, the provision of results of own pre-clinical and clinical trials is not required”. [13] They are referred to the information about the reference medicine, and they only prove the pharmaceutical and bio-equivalency.

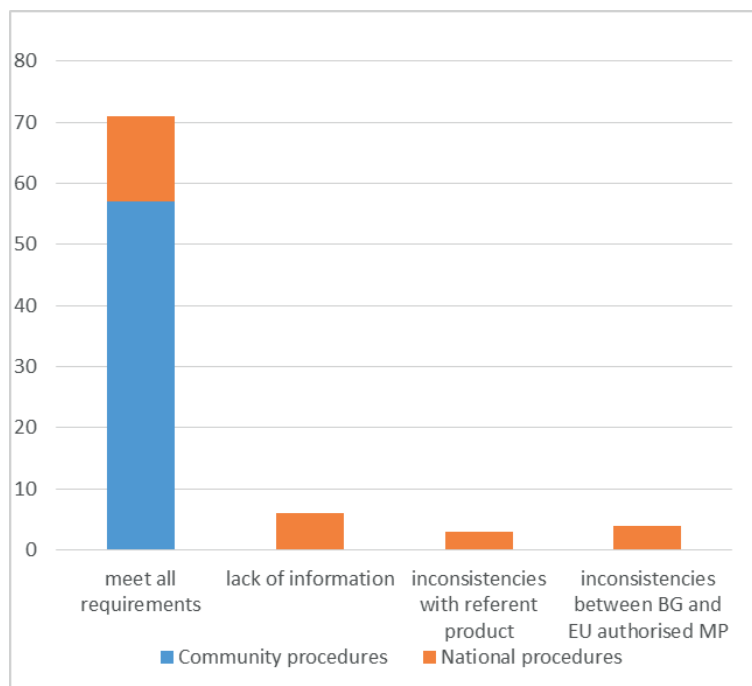
For the products that have received marketing authorization after Bulgaria joined the EU, that is, after the implementation of the contemporary regulatory norms in the Bulgarian pharmaceutical legislation, in the Bulgarian Drug Agency have been presented dossiers with the entire necessary documentation. From them, for only four active substances there have been presented research in elderly and/or fatigued patients. During the life cycle of the medicinal products, there have been presented and/or updated risk management plans for the same

products. This ascertainment, however, is not valid for products that have been on the market for decades. *All products that have received marketing authorization by the LMPPHM (Law for the Medicinal Products and Pharmacies in Humane Medicine from 1995) and the documentation that supplements the marketing authorization do not satisfy the contemporary regulatory requirements.*

### Conclusion:

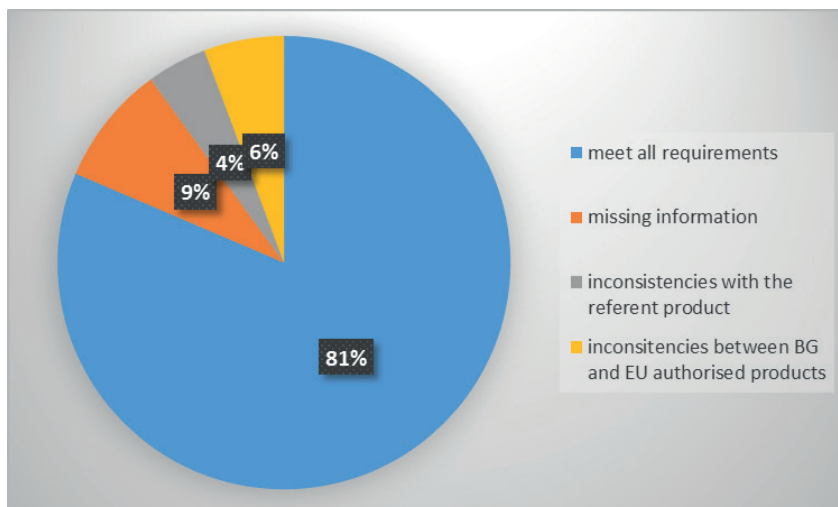
During the systematic review of the Summary of Product Characteristics of the medicinal products and the documentation that supplements the marketing authorizations, there were identified 2 big medicinal product groups as follows: the products that have received marketing authorization after 2007, paying attention to the contemporary regulation standards and especially those that have received marketing authorization by DCP/MRP correspond entirely with the standards and with the active substance’s reference product. (fig. 4)

**Fig.4** Inconsistencies found depending on the procedure and referent products



For medicinal products that have received marketing authorization decades ago by a national procedure, there have been established signifi-

cant absences in the information concerning elderly patients (>65 years of age) (fig. 5 and fig. 6).

**Fig.5** Inconsistencies and missing information for patients over 65 for all MPs reviewed**Fig.6** Discrepancies and missing information in SmPC and LP for elderly in MA via national procedures

The same is connected with missing or non-compliant with the requirements clinical data in Module 5 of the medicinal products' dossier. It is noted that in general, the number of research on the safety and efficacy of the medicinal products in elderly patients is very low. Usually, the information received from research in patients between the age 18-65 is extrapolated. The same is noticed in the research on pharmacokinetic features of the active substances.

The benefit/risk ratio for amitriptyline regarding the indication "for treatment of chronic pain" must be supported by a current overview of all available clinical evidence. Amitriptyline is a first-choice tool in several international and

national guidelines on the treatment of neuropathic pain. [14] At the same time, the only significant or serious cardiovascular undesired effects observed in patients without anamneses for cardiovascular diseases during intake of the determined therapeutic doses of tricycle antidepressants are orthostatic hypotony and tachycardia. These effects, however, can be especially concerning for patients over the age of 65.

Taking into account the continuously increasing population of patients in this age group, we believe that there is a high necessity for outlining concrete requirements towards the complete information about medicinal products with regard to their use in elderly people. The

contemporary guideline shows that for drugs used for the treatment of conditions which are observed in elderly patients, the inclusion of at least 100 participants in clinical research will allow the discovery of clinically significant differences. [4] For the approval of the product information (SPC and patient information leaflets) which hold marketing authorization by a national and/or decentralized (DCP and MRP) procedures, the responsibility rests entirely upon the national regulatory body of the respective country. Therefore, the regulatory authorities must determine and introduce concrete scientific and regulatory requirements towards the documentation for medicinal products. To initiate a procedure for a complete harmonization of the dossier/information of the products (Summary of Product Characteristics and Patient information leaflet) that hold marketing authorization before 2007 and to find an appropriate mechanism through which to encourage the holders of marketing authorizations for reference medicines to update the product information regularly. This is especially necessary since the LMPHM does not contain compulsory administrative measures in this direction.

### Bibliography

1. Breivik H, Collet B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. *European Journal of Pain* May 2006; 10(4):287–333.
2. Volkow ND, McLellan T. Opioid Abuse in Chronic Pain — Misconceptions and Mitigation Strategies. *N Engl J Med*, [online] 31 March 2016; 374(13), 1253-1263, <http://www.nejm.org/doi/full/10.1056/NEJM-ra1507771#t=article>
3. Eurostat, Eurographics, 13.01.2017
4. International Conference on Harmonisation, "Studies in support of Special Population: Geriatrics," 1993..
5. Cerreta G, Eichler H-G, Rasi G. Drug Policy for an Aging Population – The European Medicines Agency’s Geriatric Medicines Strategy *N Engl J Med* 2012; 1972-1974
6. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP) Guideline on Clinical investigation of medicinal products intended for treatment of neuropathic pain, London, 2007
7. Bulgarian Drug Agency, Register of the issued marketing authorizations , Sofia, 2016
8. Electronic medicines compendium, Datapharm, 2016.
9. COMMISSION DE LA TRANSPARENCE, "Avis 2," Direction de l'Evaluation Médicale, Economique et de Santé Publique, 2013.
10. <https://www.vidal.fr/Substance/clo-mipramine-6746.htm>
11. <http://bijsluiters.fagg-afmps.be/?localeValue=nl>
12. European medicines agency [online] Cymbalta EPAR 2004 [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/00572/WC500036781.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/00572/WC500036781.pdf)
13. Law on medicinal products in human medicine, 2007
14. Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen T, Nurmikko T. EFNS guidelines on the pharmacological treatment of neuropathic pain, *Eur J Neurol*. [online] 2010; 17(9): 1113-e88 <https://pdfs.semanticscholar.org/2793/20bfd69a057f4532cc8cb61405457061b209.pdf>

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