Pursuant to the article 35 of the Law on Medicines ("Official Gazzette of the Republic of Montenegro", No 80/04 and "Official Gazzette of Montenegro", No 18/08), Ministry of Health passes

Rulebook on Detailed Content of Pharmacological-toxicological Study of Medicines

Rulebook is published in the "Official Gazette of Montenegro No 68/2009" from 13 October 2009

Article 1

This Rulebook determines in more details content of pharmacological-toxicological study of medicines and documentation for conducting of the pharmacological-toxicological study of medicines.

Article 2

Pharmacological-toxicological studies are conducted by known in vivo and in vitro validated methods or new experimental methods that are not standardly used.
If pharmacological-toxicological study is conducted by new methods, the results of it must be described in detail, as to allow it to be reproduced.
When planning processes of pharmacological-toxicological studies and results evaluations, it is necessary to use mathematical and statistical methods, if possible.
The results of pharmacological-toxicological studies must be evaluated in relation to the seriousness of the disease or condition which the study relates to, and the study results must be reliable and usable.

Article 3

Documentation on conducting of each pharmacological-toxicological study contains data on:
- legal person conducting the study;
- aim of the study;
- laboratory animals (species, gender, age, weight and other necessary data);
- medicine that is investigated (name, batch number, data on quality and other necessary data);
- experimental conditions of the study;
- study results

Article 4

Study results from the article 3 paragraph 1 indent 6 contain data on:
- subject and purpose of the study;
- plan of the study;
- both positive and negative obtained results;
- statistical analysis of results;
- objective discussion and conclusions on the toxicological and pharmacological properties of substances, the limits of safety and possible adverse, detrimental reactions, effective dose concentrations, as well as any possible adverse interactions;
- summary of the study;
- other data.

Article 5

Based on the documentation and study results from articles 3 and 4 of this Rulebook, following matters are determined:
- possible toxicities of a medicine, as well as any adverse toxic reactions that may occur in humans by the administration of a medicine in a proposed manner;
- pharmacological and pharmacodynamic and pharmacokinetic properties of a medicine;
- qualitative and quantitative evaluation of the proposed manner of administration in humans;
- data on possible therapeutic effect of a medicine in humans.

Article 6

Documentation on pharmacological-toxicological study of a medicine for certain groups of medicines, beside data from articles 4 and 5 of this Rulebook, also contain data on:
- systemic absorption and local action, as well as tolerance of medicine that is administered locally;
- possible occurrence and impact of antibodies when using immunological medicines (vaccines, sera, toxins, allergens, produsts derived from plasma or blood);
- exposure of organ/tissue to radiation and absorbed dose of radiation when using radiopharmaceuticals;
- pharmacokinetic and toxicological properties of the substance for the first time used in the pharmaceutical field ;
- where there is a possibility of significant degradation during storage of the medicinal product, the toxicology of degradation products must be considered.

Article 7

Pharmacodynamic study of a medicine is conducted in order to detect any change caused by investigated substance in **system functioning** in organism, regardless of whether changes on which therapeutic effect of a medicine is based or adverse reactions of the investigated substance are in question.
When the study from paragraph 1 of this article is in question, it is necessary to determine effects on different organ systems and evaluate them quantitatively.
It is necessary to determine pharmacodynamic profile of the investigated substance, if possible.
Pharmacodynamic studies are conducted with doses which are whithin and beyond envisaged therapeutic doses.
If the medicine contains a combination of several active substances in finished therapeutic form, it is necessary to examine the possibility of pharmacodynamic interactions and justification of combination designated for therapeutic use.

Article 8

Pharmacokinetic study of a medicine is conducted in order to examine the path of substance through organism, including examination of absorption, distribution, biotransformation and excretion of active substance.
Studies from paragraph 1 of this article are conducted by physical, chemical and biological methods as well as by comparison of pharmacodynamic effects of active substance.
Pharmacokinetic studies of a medicine are not required in case of new combinations of known substances, if previous studies show it or if active substances are proven to be safe for at least three years of treatment of humans, and no pharmacokinetic interactions were observed.
The protocol of pharmacokinetic study must be prepared in a manner that comparison and extrapolation of results in animals and humans are enabled.

Article 9

Acute toxicity studies are qualitative and quantitative studies of toxic reactions, which may be the result of single administration of active substance.
Medicines containing combination of active substances are investigated in order to determine whether known effects are more toxic or new toxic effects occur.
Acute toxicity study is conducted in accordance with the latest scientific and technological achievements and good laboratory practice.

Article 10

Repeated dose toxicity studies are intended to reveal any physiological and/or pathological changes induced by repeated administration of active substance, and to determine how these changes are related to dosage.
When conducting toxicity study from paragraph 1 of this article, autopsy of all animals from the study must be performed.
Repeated dose toxicity studies are conducted on two mammalian species, one of which shall be other than a rodent.
Toxicity in excipients for the first time used in the pharmaceutical field shall be tested as in active substance.

Article 11

Investigation of possible impairment of male or female reproductive function as well as harmful effects on progeny shall be performed by appropriate tests.
Embryo/foetal toxicity studies and perinatal toxicity detect toxic and teratogenic effects at all stages of development from conception to sexual maturity as well as latent effects, when the medicine has been administered to the female during pregnancy, and are normally conducted:
- on two mammalian species, one of which shall be other than a rodent;
- on at least one species when conducting perinatal toxicity studies.
Mutagenic action study is obligatory for every new substance and is conducted in order to detect changes in genetic material of individuals or cells caused by the use of that substance and which may cause the offspring to be permanently and inherently different to their ancestors.

Article 12

Pharmacological-toxicological studies aimed at detecting carcinogenic effects are required for substances which:
- are very similar to known carcinogenic and cocarcinogenic compounds;
- caused changes during long-term toxicology studies that indicate carcinogenicity;
- gave results in mutagenicity tests, or in other short-term tests for determining carcinogenicity and which indicate carcinogenicity;
- are intended for regular use in prolonged period.

Article 13

Pharmacological-toxicological tolerance studies are conducted in order to determine reactions of organism on the site of administration, as well as the range of systemic absorption, in accordance with proposed manner of clinical use (duration, frequency and route of administration, dosage).

In case that pharmacological-toxicological studies result in detection of local lesions, it is necessary to determine their reversibility.
During pharmacological-toxicological studies it is necessary to make difference between mechanic effects of administration, i.e. physicochemical and toxicological or pharmacodynamic effects of medicines.

Article 14

This Rulebook shall come into force on the 8th after being published the "Official Gazzette of Montenegro."
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Minister
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