PASS INFORMATION

Title	Multicenter prospective open-label non-interventional uncontrolled Post-Authorisation Safety Study (PASS) to evaluate the safety profile of Polyoxidonium in daily practice
Protocol identification No:	PETRO/2015-01
Protocol version identifier	Final version 1.1
Date of last version of protocol	3 February 2016
EU PAS register number	*to be specified*
Active substance	Azoximer bromide Pharmacotherapeutic group: other cytokines and immune modulators ATC code: L03AX
Medicinal product	POLYOXIDONIUM® 6 mg lyophilisate for solution for injection
Product reference	59/0220/02-S (national)
Procedure number	-
Marketing authorisation holder	MEDIGROUP s.r.o.
Sponsor:	NPO PETROVAXPHARM 1Sosnovaya St., Pokrov village, Podolsky district, Moscow region, 142143 Russia
Joint PASS	No
Research question and objectives	This PASS aims to collect data on the safety of Polyoxidonium in patients, for whom Polyoxidonium is prescribed in routine practice in accordance with the terms of the marketing authorisation (MA). The primary objective is: - to assess the frequency of adverse drug reactions - to estimate the proportion of subjects, who develop signs and symptoms of adverse renal effects associated with the use of Polyoxidonium. Secondary objective is to evaluate the clinical benefit of Polyoxidonium.
Country of study	Slovak Republic
Author	Andrius Bacevičius, MD, MSc, Medical Expert (CRO Biomapas)

MARKETING AUTHORISATION HOLDER

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POLYOXIDONIUM PASS PROTOCOL
PETRO/2015-01
Final version 1.1. 3 February 2016

PASS PROTOCOL APPROVAL FORM

MULTICENTER PROSPECTIVE OPEN-LABEL NON-INTERVENTIOANAL UNCONTROLLED POST-AUTHORISATION SAFETY STUDY (PASS) TO EVALUATE THE SAFETY PROFILE OF POLYOXIDONIUM IN DAILY PRACTICE

Protocol (study) identification No: PETRO/2015-01

Protocol Version and Date: Final version 1.1 3 February 2016

Sponsor's and MAHs representative(s):

NPO PETROVAXPHARM
Natalia V. Chirun, PhD, MD
Medical Director
Date: 05-Feb-2016
Signature:

MEDIGROUP s.r.o.
Peter Klembala
QPPV
Date: 05-Feb-2016
Signature:

CRO's Representative(s):

CRO Biotapas
Indrė Tutlytė
Project Director
Date: 08-Feb-2016
Signature:

ZM Company, Inc.
Yuri Zarotsky, MD
Medical Monitor
Date: 05-Feb-2016
Signature:

Confidential
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INVESTIGATOR SIGNATURE PAGE

MULTICENTER PROSPECTIVE OPEN-LABEL NON-INTERVENTIOANAL UNCONTROLLED POST-AUTHORISATION SAFETY STUDY (PASS) TO EVALUATE THE SAFETY PROFILE OF POLYOXIDONIUM IN DAILY PRACTICE

Protocol (study) identification No: PETRO/2015-01

Protocol Version and Date: Final version 1.1 3 February 2016

I, the undersigned, have read and understood the Post-Authorisation Safety Study Protocol, and agree with its contents. I declare that I will comply with all the Post-Authorisation Safety Study Protocol's requirements. The Post-Authorisation Safety Protocol, the Investigator's Agreement and any additional information provided by Sponsor will serve as a basis for cooperation in the study.

Name: Date: Signature:

Institution

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CRO	Contract Research Organisation
DM	Data Management
EC	Ethics Committee
eCRF	electronic Case Report Form
ECG	electrocardiogram
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
GPP	Good Pharmacoepidemiology Guidelines
ICD-10	International Classification of Disease, 10th rev.
ICD-9	International Classification of Disease, 9th rev.
ICF	informed consent form
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
PASS	Post authorization safety study
QPPV	qualified person in pharmacovigilance
RA	Regulatory Authorities
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOPs	Standard Operating Procedures
WBC	white blood cells

3. RESPONSIBLE PARTIES

This study will be conducted by qualified investigators under the sponsorship of NPO PETROVAXPHARM. CRO Biomapas will centrally manage the conduct of the study for the local Marketing Authorisation Holder (MAH).

Name	Address	Responsibilities	Contact person (s)
NPO PETROVAXPHARM	Krasnaya Presnya 22, Moscow, 123022, Russia	Sponsor	Natalia V. Chirun, PhD, MD Medical Director Tel.: +7(495) 730-75-45 ext. 125 e-mail:chirunnv@petrovax.ru
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CRO Biomapas	Savanoriu ave. 109 LT-44208 Kaunas, Lithuania	Project management Study planning Study monitoring Data management Data analysis Final report writing	Indrė Tutlytė, Project Director Tel.: +370 37 366307 e-mail: indre.tutlyte@biomapas.eu

List of investigators and study sites is presented as a stand-alone document and is available on request.

4. ABSTRACT

Title

Multicenter prospective open-label non-interventional uncontrolled Post-Authorisation Safety Study (PASS) to evaluate the safety profile of Polyoxidonium in daily practice.

Protocol version: final version 1.1 3 February 2016.

Protocol author: Andrius Bacevičius, MD, MSc, Medical Expert at CRO Biomapas.

Rationale and background

Data from Polyoxidonium acute and sub-acute toxicity studies in rodents and chronic toxicity in dogs showed the potential risk of renal toxicity.

Although no adverse effects on renal system were reported in Polyoxidonium clinical trials development programme and during routine post-authorisation pharmacovigilance activities, the potential renal effect cannot be ruled out.

The safety signal known from pre-clinical phase of development needs to be further investigated.

Research question and objectives

This PASS aims to collect data on the safety of Polyoxidonium in patients, for whom Polyoxidonium is prescribed in routine practice in accordance with the terms of the marketing authorisation (MA).

Primary objectives:
- to assess the frequency of adverse drug reactions;
- to estimate the proportion of subjects, who will develop signs or symptoms of adverse renal effects associated with the use of Polyoxidonium.

Secondary objective is to evaluate the clinical benefit of Polyoxidonium by evaluating the following variables:
- overall clinical improvement as assessed by investigators and subjects;
- mean duration of primary treatment of disease;
- mean number of days with fever >38°C and (or) disease symptoms;
- change in total and differential white blood cells (WBC) count (blood and urine) from baseline to the end of treatment (if data are available).

Study design: local, multicenter, prospective, open-label, non-interventional, uncontrolled study.

The decision to prescribe Polyoxidonium will be independent of the decision to enrol the subject into the study. Each subject will be observed for the duration of one cycle of Polyoxidonium treatment. In accordance with the SmPC, the treatment course consists of 5-10 injections depending on the disease. Thus, study duration for individual subject will take 7-23 days. There will be 5-10 study visits coinciding with routine visits to receive Polyoxidonium injections at the health care centre.

Actual assessments undertaken at each visit will be determined by clinical practice (see Study flow chart in Table 1). Subjects will not be administered any investigational medicinal products

and/or medical procedures neither undergo any laboratory evaluations, diagnostic or monitoring procedures specifically for the purposes of this study.

Population: The study will be conducted by immunologists or allergologists in primary or secondary care setting in Slovak Republic.

To be eligible for participation in this study, the patient must:

a) be male or female at least 18 years of age.
b) receive Polyoxidonium prescription in accordance to the SmPC currently approved in Slovakia, i.e., for the treatment of any of the following diseases or conditions accompanied by secondary immunodeficiency:
   - chronic recurrent bacterial infection;
   - chronic recurrent viral infection;
   - acute bacterial infection;
   - acute viral infection;
   - allergic disease (pollinosis, bronchial asthma, atopic dermatitis).
c) be informed about the study and provide written consent to participate.

The patient can't take part in the study if:

(a) Polyoxidonium is contraindicated as per SmPC:
(b) investigator deems necessary to prescribe more than 10 injections of Polyoxidonium per a single treatment course for the given patient.
(c) patient has any clinically significant underlying medical illness, condition or disorder that, in the judgment of the investigator, could interfere with the conduct of the study.
(d) patient is currently enrolled in any other investigational study or has participated in a interventional study within 4 weeks before enrolment.

Variables

Event of interest is signs or symptoms of adverse renal effects. In case of suspected adverse renal effect investigator will be encouraged to perform diagnostic workup and collect as much data as possible to confirm or reject the diagnosis of renal impairment. These data for each subject for whom adverse renal effect is suspected will be reviewed and adjudicated by and independent assessor. This final adjudicated conclusion will be qualified as event of interest (a case of adverse renal effect) or suspicion about renal toxicity will be rejected.

Safety variables include:

- proportion of subjects with adverse renal effect (as defined in Section 9.3.1)
- proportion of subjects, who experienced any AE;
- proportion of subjects with ADRs;
- proportion of subjects experiencing serious adverse events (SAEs);
- proportion of subjects with serious ADRs;
- severity of AEs;
- number of subjects who discontinued the study and the reasons for drop-outs;
- global assessment of tolerability by investigators: very good (no intolerance reactions), good (occasional intolerance reactions), moderate (frequent intolerance reactions), poor (intolerance reactions after every use);
- global assessment of tolerability by subjects: very good, good, moderate and poor

Clinical benefit assessment includes the following variables:

- global assessment of improvement by subjects score (0 to 4 scale: 0=much worse; 1= somewhat worse; 2=same; 3=somewhat improved; 4 = greatly improved)
- global assessment of improvement by investigators score (0 to 5 scale: 0 = worse; 1 = no appreciable improvement; 2 = slight improvement; 3 = moderate improvement; 4 = marked improvement; 5 = complete resolution)
- mean duration of primary treatment of disease (i.e., days with antibiotic use in case of infection or antiallergic medication in case of allergies),
- days with fever >38°C/days with symptoms,
- total and differential WBC count in blood and urine (if data are available).

Data sources

Data collection will be based on the review of medical records and routine examination of subjects. Regular medical records at study sites will serve as data sources.

Study size

Approximately 500 adult subjects

Data analysis

Descriptive and comparative statistical methods will be used.

A stratified analysis of main event of interest (i.e., adverse renal effect) will be performed by prior renal impairment and by use of concomitant nephrotoxic medicines to control confounders. Logistic regression will be employed to determine factors as possible predictors of adverse renal effect.

Stratified analysis by indication will be performed to investigate safety profile and clinical benefit in different subgroups of subjects.

Milestones

First eligible subject is planned to enrol on May 2016. Last subject last visit is expected to occur in November 2016.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Start of data collection	May 2016
End of data collection	December 2016
Registration in the EU PAS register	February 2016
Final report of study results	March 2017

7. RATIONALE AND BACKGROUND

7.1. Background

Immunodeficiency may occur both in the young and in the elderly, with immune responses beginning to decline at around 50 years of age due to gradual deterioration of the immune system. In developed countries, obesity, alcoholism, and drug use are common causes of poor immune function, whereas malnutrition is the most common cause of immunodeficiency in developing countries. Additionally, the loss of the thymus at an early age, chronic granulomatous disease, AIDS, some types of cancer (or cancer therapies) or other medical conditions can cause immunodeficiency.

Azoximer bromide, the active substance of Polyoxidonium, is a copolymer of N-oxidised 1,4-ethylenepiperazine and (N-carboxyethyl)-1,4-ethylenepiperazine bromide. Polyoxidonium influences certain immunogenic effects through the following mechanisms of actions:

- activates three major subpopulations of phagocytes: mobile tissue macrophages, circulating cells in blood, and fixed phagocytes in the reticulo-endothelial tissue. In particular, a migration of macrophages, as well their ability to phagocytize and to digest pathogenic bacteria, are activated. Furthermore, the adhesive activity of polymorphonuclear leukocytes increase, as well as their ability to produce reactive oxygen species upon contact with the opsonized fragments of microorganisms.
- Improves the interaction between T- and B-lymphocytes in the processes of antibody formation in response to foreign antigens. Polyoxidonium is distinguished from other mitogens, such as bacterial lipopolysaccharide and plant lectins, by its attributes of not inducing a polyclonal transformation of B-cell lymphocytes into cells that secrete immunoglobulins and not causing multiple cycles of cell division of B- and T-lymphocytes in the absence of antigenic stimulus.
- Increase the intensity of the antibody formation in response to antigens, in particular cellular corpuscular antigens (heterologous erythrocytes) after administration of the drug. Irrespective of the genetically determined ability of the organism to form the immune

response to any given antigen, the administration of Polyoxidonium stimulates antibody responses in both high- and low-reactive genotypes.

By stimulating the immune responses, Polyoxidonium does not alter the natural mechanisms of inhibition. In particular, the formation of T-suppressor cells, as well as the functioning of the already formed T-suppressor cells, stay unaffected after immunostimulatory dose of Polyoxidonium. By stimulating the immune system, Polyoxidonium does not deplete the reserve capacity of hematopoietic system. The quantity of hematopoietic stem cells in the bone marrow tissue, as well as the ability of these cells to proliferate and differentiate into specialized directions of development (erythroid, granulocytic, monocytic or megakaryocytic), had been shown to stay fully preserved after immunostimulatory dose of Polyoxidonium. Therefore, a single or multiple dose of Polyoxidonium intended to stimulate the immune responses in healthy organism with normal immune status does not affect the peripheral blood cells.

7.2. Rationale of this study

Polyoxidonium has been marketed for almost 20 years (it was first launched in 1996 in Russia). In Slovak Republic, Polyoxidonium is available since 2002. It is estimated that during the period from 1996 to 2013 (inclusive) the total number of approximately 1,025,000 patients worldwide have used Polyoxidonium. No adverse effects specifically affecting any of organ systems have been reported in clinical development programme and during routine post-authorisation pharmacovigilance activities.

Data from Polyoxidonium acute and sub-acute toxicity studies in rodents and chronic toxicity studies in dogs showed the potential risk of nephrotoxicity, which occurred at doses well above the therapeutically relevant dose range. Nephrotoxic effect was observed in dogs after 40 daily injections of Polyoxidonium at doses 10 times exceeding the maximum recommended human dose and in rats after 15 daily injections at doses as high as 100 times the maximum recommended human dose. Besides, Polyoxidonium is predominantly excreted by kidneys.

During chronic toxicity research in dogs, the administration of 10 times the therapeutic dose of Polyoxidonium intramuscularly daily for a period of three months did not affect the ECGs, peripheral blood cells, and protein, carbohydrate and lipid metabolism. At the same time, already after two months of administration of Polyoxidonium a moderate increase in transaminase activity, as well as an increase in the alkaline phosphatase, bilirubin, creatinine, and urea concentrations in the blood serum had been observed, all of which became more pronounced after three months of administration. Histopathological examination of internal organs, performed at the end of experiment, had shown that long-term daily administration of Polyoxidonium at 10 times the therapeutic dose (1 mg/kg) led to the development of glomerulitis, changes in renal tubular apparatus, and degeneration of protein and fatty hepatocytes in dogs. Based on the results obtained from the research of systemic toxicity of the drug Polyoxidonium (acute and sub-acute toxicity in rodents and chronic toxicity in dogs), it was possible to conclude that the kidneys are the only target organ of Polyoxidonium. Meanwhile, biochemical and histological studies in rats had shown no damaging effects on the kidneys after 3-month administration of the drug Polyoxidonium 100 times the maximum recommended dose (25 mg/kg) with intervals between injections. The intervals between injections significantly reduce the nephrotoxic effects of the drug Polyoxidonium, moreover there was no nephrotoxic effect was not observed when the drug was temporary withdrawn for up to 7 days.

Although no adverse effects on renal system have been reported in Polyoxidonium clinical development programme and during routine post-authorisation pharmacovigilance activities, the potential adverse renal effects need to be further investigated.

A non-interventional post-authorisation safety study will be undertaken to systematically collect safety information under real-life conditions in patients receiving Polyoxidonium therapy. The special focus of this PASS will be on signs or symptoms of potential adverse renal effects.

8. RESEARCH QUESTION AND OBJECTIVES

This PASS aims to collect data on the safety of Polyoxidonium in patients, for whom Polyoxidonium is prescribed in routine practice in accordance with the terms of the marketing authorisation (MA). This study is a part of a Risk Management Plan (RMP).

The primary objective is:

(a) to assess the frequency of adverse drug reactions

(b) to estimate the proportion of subjects, who develop signs and symptoms of adverse renal effects associated with the use of Polyoxidonium.

Secondary objective is to evaluate the clinical benefit of Polyoxidonium by evaluating the following variables:

(a) overall clinical improvement as assessed by investigators and subjects

(b) mean duration of primary treatment of disease

(c) mean number of days with fever >38°C and (or) disease symptoms

(d) change in total and differential white blood cells (WBC) count (blood and urine) from baseline to the end of treatment (if data are available).

9. RESEARCH METHODS

9.1. Study design

This PASS is a local, multicentre, prospective, open-label, non-interventional, uncontrolled study.

Patients for whom Polyoxidonium is prescribed as a part of routine clinical practice will be eligible for this study. The decision to prescribe Polyoxidonium will be independent of the decision to enroll the subject into the study.

Primary treatment of a disease, Polyoxidonium administration, diagnostic procedures and assessments as well as visits schedule will be left at the discretion of investigators, according to local guidelines and routine clinical practices.

The study is explorative in nature. It is undertaken to systematically collect safety information in a community-based sample of subjects receiving Polyoxidonium therapy in routine care setting, to quantify potential risks, investigate potential risk factors and effect modifiers, or to provide evidence about the absence of risks.

9.2. Setting

The study will be conducted by physicians in primary or secondary health care setting. These may be immunologists or allergologists. These specialists usually prescribe Polyoxidonium in Slovakia. Health care centres will be considered as investigative sites.

In order to ensure that data represent the source population, potential investigators will be randomly selected from the available list of Slovakian immunologists and allergologists and will be invited to participate in this study. Every assented physician will be evaluated for his (her) expertise in the care of patients with secondary immunodeficiency, the ability to appropriately perform the study and overall interest in participation. It is expected that the study will be conducted at 15 investigative sites.

The decision to prescribe Polyoxidonium will precede and will be independent of the decision to enrol the patient into the study. Upon prescription of Polyoxidonium, investigator will offer each eligible patient an option to take part in the study, will inform about study procedures, give the informed consent form to read and answer all patient's questions. If this patient does not meet inclusion criteria or meets exclusion criteria or declines to participate, the investigator will pursue with the next patient. Since inclusion and exclusion criteria are very limited, it is expected that enrolled subjects will represent the source population (i.e., target patients of Polyoxidonium therapy) in Slovakia. To document the number of patients invited and assess selection bias in subject recruitment, screening logs will be used.

9.2.1. Subject inclusion criteria

To be eligible for participation in this study, the patient must:

(a) be male or female at least 18 years of age.

(b) receive Polyoxidonium prescription in accordance to the SmPC currently approved in Slovakia, i.e., for the treatment of any of the following diseases or conditions accompanied by secondary immunodeficiency:
- chronic recurrent bacterial infection;
- chronic recurrent viral infection;
- acute bacterial infection;
- acute viral infection;
- allergic disease (pollinosis, bronchial asthma, atopic dermatitis).

(c) be informed about the study and provide written consent to participate.

9.2.2. Subject exclusion criteria

The patient can't take part in the study if:

(a) Polyoxidonium is contraindicated as per SmPC:
- if there is known hypersensitivity to azoximer bromide or any of the excipients of Polyoxidonium;
- if a woman is pregnant or breast-feeding;
- if a woman of childbearing potential doesn't use effective contraception method (acceptable methods of birth control are: intrauterine device (IUD), diaphragm

with spermicide, contraceptive sponge, condom, vasectomy, hormonal contraceptive).

(b) investigator deems necessary to prescribe more than 10 injections of Polyoxidonium per a single treatment course for the given patient.

(c) patient has any clinically significant underlying medical illness, condition or disorder that, in the judgment of the investigator, could interfere with the conduct of the study.

(d) patient is currently enrolled in any other investigational study or has participated in a interventional study within 4 weeks before enrolment.

9.2.3. Subject withdrawal criteria

Subject participation in the study must be prematurely discontinued for any of the following reasons:

- subject withdraws his/her consent;
- subject stops the treatment with Polyoxidonium;
- occurrence of AE or intercurrent condition that require discontinuation of treatment with Polyoxidonium;
- subject is lost to follow-up.
- subject has a confirmed positive serum or urine pregnancy test. Subjects with positive pregnancy tests will be followed to resolution (either miscarriage or normal birth, with or without complications). Refer to Section 11.5.

The reasons for study discontinuation must be recorded in a subject's medical records and eCRF.

A subject that discontinues from the study will not be replaced.

9.2.4. Study visits

It is planned to observe each subject for one cycle of treatment with Polyoxidonium. In accordance with the Summary of Product Characteristics (SmPC), the treatment course consists of 5-10 injections depending on the disease. Thus, study duration for individual subject will take 7-23 days. There will be 5-10 study visits coinciding with routine visits to receive Polyoxidonium injections at the health care centre (see Study flow chart in Table 1). If any visit (scheduled or unscheduled) occurs within 30 days after the last injection of Polyoxidonium as a part of routine practice, information on adverse events will be recorded.

Table 1. *Study flow chart*

	Study visits			
Study procedures	**First injection**	**Interim visits** *(3 to 8, depending on indication)*	**Last injection**	**Follow-up***
Day	**Day 1**		**Day 7 to 23**	
Inclusion/exclusion criteria	X			
Informed consent	X			
Demographic data	X			
Height and weight	X			
Medical history	X			
Physical examination**	X	X	X	
Information about relevant infection, allergic condition, etc.	X	X	X	
Vital signs (blood pressure, heart rate, body temperature)**	X	X	X	
Laboratory tests**	X	X	X	
ECG**	X	X	X	
Other diagnostic procedures**	X	X	X	
Polyoxidonium administration	X	X	X	
Concomitant medications	X	X	X	
Adverse events	X	X	X	X
Investigator's and subject's assessment of tolerability and improvement			X	

**any visit (scheduled or unscheduled) which occurs within 30 days after the last injection of Polyoxidonium as a part of routine clinical practice*
***if undertaken as a part of routine clinical practice. Results of laboratory tests, ECG examinations and other diagnostic procedures should be recorded only if performed within 3 days before subject's enrolment and (or) during the study period.*

9.2.5. Study procedures

At the first visit, an investigator will inform a subject about the study (refer to Section 10.2.). If the subject consents to take part in the study and signs the written informed consent form, correspondent entry will be recorded in subject's medical records.

Then, a subject will be assigned a unique identification code, consisting of 4 symbols:

- number of the centre (2 digits),
- number of the subject in the center, by chronological order of selection (2 digits).

The investigator will maintain a subjects' identification list as part of the study file.

Actual assessments undertaken at each visit will be determined by clinical practice (see Study flow chart in Table 1). Subjects will not be administered any investigational medicinal products and/or medical procedures neither undergo any laboratory evaluations, diagnostic or monitoring procedures specifically for the purposes of this study.

Concomitant therapies will be administered at discretion of the investigator in accordance to routine clinical practice. According to the SmPC, Polyoxidonium may be administered as monotherapy or concomitantly with antibiotics, antivirals, antifungals, and antihistamines, bronchiolytics, corticosteroids, beta agonists, and cytostatic agents.

At the last visit (i.e., last injection visit), investigators and subjects will rate the overall tolerance of Polyoxidonium treatment as well as improvement.

9.2.6. Dosage and method of administration of Polyoxidonium

Subjects will be treated with Polyoxidonium in accordance with the posology and method of administration as per current version of SmPC approved by State Institute for Drug Control of Slovakia. Depending on the disease, Polyoxidonium treatment regimen consists of 5-10 injections:

- Acute inflammatory diseases, complicated forms of allergic diseases: 6 mg daily for 3 days, then on alternate days, 5-10 injections totally.
- Chronic inflammatory diseases: five 6 mg injections every other day, then twice weekly, 10 injections totally.
- Urogenital inflammatory diseases: 6 mg every other day, 10 injections totally.
- Chronic recurrent herpes simplex: 6 mg every other day, 10 injections totally.
- Allergic diseases: 6 mg daily for 2 days, then on alternate days, 5 injections totally.

Polyoxidonium is given intramuscularly as a slow injection (15-20 sec) into the deltoid muscle of the upper limb or outer upper quadrant of the thigh.

9.3. Variables

Where assessments are undertaken as a part of routine clinical practice, the following data will be recorded into eCRF:

- demographic data (year of birth, gender),
- height, weight,
- vital signs (blood pressure, heart rate, and body temperature),

- therapeutic indication specific information (e.g., details on infections (type, primary treatment administered and duration, hospitalizations), allergic disease, etc.).
- reasons for prescribing Polyoxidonium therapy,
- current concomitant diseases or those which occurred within 5 years before this study,
- concomitant medications,
- abnormal findings at physical examination,
- results laboratory tests (blood chemistry, haematology, and urinalysis),
- ECG abnormalities,
- information about other diagnostic procedures, if any;
- Polyoxidonium injections (dates and doses),
- Polyoxidonium discontinuation and reasons of discontinuation,
- adverse events,
- subject's and investigator's assessment of clinical improvement and Polyoxidonium tolerability.

A full medical history will be obtained by the investigator or qualified designee. The investigator or qualified designee will record on the eCRF prior medication taken by the subject within 30 days or longer as appropriate prior to Visit 1. The identity of the therapy, the dose, route of administration, and regimen, the dates started and stopped (or notation of "continuing" if that is the case), and the reason for use must be recorded. The concomitant medications will be documented in the same manner all over the subject's participation in the study.

Results of laboratory tests, ECG examinations and other diagnostic procedures should be recorded only if performed within 3 days before subject's enrolment and (or) during the study period.

9.3.1. Definition of event of interest

In case of suspected adverse renal effect investigator will be encouraged to apply clinical judgement, to perform diagnostic workup and collect as much data as possible to confirm or reject the diagnosis of renal impairment. The signs and symptoms of renal toxicity, indicative of potential renal impairment include but are not limited to: increased blood concentrations of creatinine, potassium, blood urea nitrogen, urine protein levels, ECG changes, characteristic to elevated potassium levels; symptoms of intoxication, e.g. fatigue, nausea, vomiting.

These data for each subject for whom adverse renal effect is suspected will be reviewed and adjudicated by an independent assessor. This final adjudicated conclusion will be qualified as event of interest (a case of adverse renal effect) or suspicion about renal toxicity will be rejected.

9.3.2. Safety variables

Safety variables include:
- proportion of subjects with adverse renal effects (as defined in Section 9.3.1)
- proportion of subjects, who experienced any AE;
- proportion of subjects with ADRs;
- proportion of subjects experiencing serious adverse events (SAEs);
- proportion of subjects with serious ADRs;
- severity of AEs;

- number of subjects who discontinued the study and the reasons for drop-outs;
- global assessment of tolerability by investigators: very good (no intolerance reactions), good (occasional intolerance reactions), moderate (frequent intolerance reactions), poor (intolerance reactions after every use);
- global assessment of tolerability by subjects: very good, good, moderate and poor.

9.3.3. Clinical benefit variables

Clinical benefit assessment includes the following variables:
- global assessment of improvement by subjects score (0 to 4 scale: 0=much worse; 1= somewhat worse; 2=same; 3=somewhat improved; 4 = greatly improved)
- global assessment of improvement by investigators score (0 to 5 scale: 0 = worse; 1 = no appreciable improvement; 2 = slight improvement; 3 = moderate improvement; 4 = marked improvement; 5 = complete resolution)
- mean duration of primary treatment of disease (i.e., days with antibiotic use in case of infection or antiallergic medication in case of allergies),
- days with fever >38°C/days with symptoms,
- total and differential WBC count in blood and urine (if data are available).

9.4. Data sources

Subjects will attend the investigator site for regular visits during their treatment with Polyoxidonium according to local clinical practice. Data collection will be based on the review of medical records and routine examination of subjects. Regular medical records at study sites will serve as data sources. Relevant data will be entered into study database via eCRF by site personnel.

9.5. Study size

Due to the explorative character of the study and absence of the hypothesis to test, no formal attempt to calculate the sample size and power has been made.

A total of 500 subjects are expected to enter the study. It is assumed, that this number of subjects will allow to characterize the safety profile of Polyoxidonium and will be sufficient to identify, quantify and describe statistically the frequency of at least common (≥1/100, <1/10) and uncommon (≥1/1000, <1/100) adverse events and to allow for various subgroup analyses.

9.6. Data management

A Data Management (DM) vendor will be responsible for eCRF development and data management of this study, including data quality checking.

All required data for this study will be collected on the eCRF using the QCTMS EDC™ system. An appropriate internet access is required for data entry.

Sites will receive training and have access to a manual for appropriate eCRF completion. All eCRFs should be completed by authorized trained site staff, who will transcribe the collected subject data from paper source documents into the eCRF. eCRFs should be reviewed and electronically signed by the investigator.

For classification purposes, preferred terms will be assigned to the original terms entered on the eCRF, using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) terminology for adverse events and the International Non-proprietary Names (INN) for concomitant medicines.

An audit trail will maintain a record of initial entries and changes made, reasons for change, time and date of entry, and user name of person authorizing entry or change. The data will be transferred directly to the clinical database.

At the end of the study, the investigator will receive subject data for his/her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc will be required.

eCRFs are confidential documents and will only be available to Sponsor (including Sponsor vendors), the investigator and Regulatory Authorities.

9.7. Data analysis

This section provides specifications for preparation of Statistical Analysis Plan (SAP), which will be issued prior to database lock. The statistical analysis will be performed according to the nature of considered data. If the data situation does not allow for an adequate presentation of an envisaged parameter or stratification e.g. due to sparse data, the respective analysis will not be performed. Any differences compared to this statistical section should be identified and documented in final SAP.

Statistical analyses will be made after the approval of the SAP and the database lock.

9.7.1. Statistical methods

This study focuses primarily on the safety profile of Polyoxidonium and no statistical hypothesis testing is intended. Statistical analysis will be merely descriptive in nature.

Categorical data will be summarized in frequency tables. For continuous data, descriptive statistics (mean, median, minimum, maximum, standard deviation, 5% percentile, and 95% percentile) will be calculated. Comparative statistical analysis will be also performed. For statistical comparison of categorical data, the chi-square test will be used. Parametric Student t-test or nonparametric Wilcoxon rank sum test will be used for comparison of continuous data between two independent samples. Parametric paired Student t-test or nonparametric Wilcoxon signed-rank test will be used for comparison of continuous data between two dependent samples. Proportions of two dependent samples will be compared using McNemar's test. Statistical tests will be interpreted at the 5% significance level (two-sided).

A stratified analysis of main event of interest (i.e., adverse renal effect) will be performed by prior renal impairment and by use of concomitant nephrotoxic medicines to control confounders. Logistic regression will be employed to determine factors as possible predictors of adverse renal effects.

Stratified analysis by indication will be performed to investigate safety profile and clinical benefit in different subjects subgroups.

Data will be analyzed using SPSS software.

9.7.2. Safety evaluation

All subjects who receive at least one dose of Polyoxidonium will be subjected to the safety analysis.

Safety endpoints will be analysed per infusion and per subject at each individual study visit.

Safety endpoints are listed in Section 9.3.2.

9.7.3. Clinical benefit evaluation

All subjects who receive at least one dose of Polyoxidonium and for whom the clinical benefit variables are available at the end of study will be included in clinical benefit analyses.

Clinical benefit endpoints are listed in Section 9.3.3.

9.8. Quality control

9.8.1. Data quality assurance

Data entered manually will be collected via QCTMS EDC™ using eCRFs. Investigator will be responsible for data entry into the QCTMS EDC™ system. Data checks are embedded into the eCRF to remove data entry errors wherever possible. Data will be validated throughout the course of the study (raising queries in QCTMS EDC™ if necessary) according a Data Management Plan. In the event of discrepant data, data clarification will be requested from the sites, which the sites will resolve electronically in the QCTMS EDC™ system. eCRFs and correction documentation will be maintained in the QCTMS EDC™ system's audit trail.

9.8.2. Monitoring

Monitoring activities will be performed by the CRO, as defined in the Monitoring Plan. Each site will be visited at regular intervals by a monitor to ensure compliance with the study protocol and legal aspects. This will include on-site checking of eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters. In addition, the monitor will review remotely the data entered into the eCRFs on an ongoing basis.

The monitor will follow Standard Operating Procedures (SOPs) of the CRO. The monitor will prepare and submit a written report to the CRO after each study site visit or study-related communication.

9.8.3. Source data / source data verification

Study monitors will perform ongoing source data verification as defined in the Monitoring Plan to confirm that data entered by authorized site staff from source documents into the eCRFs are accurate.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the accuracy of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 9.8.4.

The investigators and institutions must provide the Sponsor's duly authorized personnel, the EC and applicable RAs to have direct access to source data which supports the data on the eCRFs. These personnel, bound by professional secrecy, must keep confidential all personal identity or personal medical information (according to confidentiality rules).

9.8.4. Source data handling and record keeping

The investigator is responsible for keeping all study-related documents (including but not limited to investigators file, source data, compact disc with subject data recorded during the study, signed ICFs, original subject identification list, EC, RA and sponsor correspondence pertaining to the study) in appropriate file folders. The study-related documents must be retained as strictly confidential at the investigator's site for at least 15 years after the completion or discontinuation of the study.

All data and documents shall be made available if requested by relevant Regulatory Authorities or Ethics Committees.

9.8.5. Sponsor audits and inspections by Regulatory Authorities (RA)

Representatives of the Sponsor's clinical quality assurance department may visit the site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. Similar auditing procedures may also be conducted by agents of any regulatory body.

The investigator agrees to allow the Sponsor auditors/RA inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the investigator is notified of a future inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the subjects should be respected during these inspections.

Any result and information arising from the inspections by the RA will be immediately communicated by the investigator to the Sponsor.

The investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

9.9. Limitations of the research methods

Due to limited data concerning the signal of outcome of interest no test hypothesis for this study has been formulated.

The limitations of this study are characteristic to other studies of a similar design (i.e., real life observational studies). Information concerning the potential confounders will be difficult to control.

Because of non-randomized design, absence of blinding and control group selection bias and information bias may occur. To mitigate this risk and ensure that study population represents the source population, investigators and study sites will be selected randomly from the available list of Slovakian immunologists and allergologists. The investigators will be trained and encouraged to enroll all eligible patients consecutively and keep screening logs to document the number of patients invited (refer to Section 9.2).

Some misclassification of outcome variables as well as confounders is possible. A validation is planned which will assess the rate of misclassification and correct the estimates accordingly. To mitigate the risk of information bias, investigators encouraged to collect as much data concerning the event of interest (adverse renal effects) as possible within the frame of routine practice. A set of available clinical data about the event of interest, presented in a standard format, will be adjudicated by an independent assessor.

Misclassification of exposure is not expected to happen. However due to nature of dosing regimen study population may be not homogenous in terms of duration of treatment and dosing schedule.

Since inclusion and exclusion criteria are very limited, it is expected that enrolled subjects will represent the source population (i.e., target patients of Polyoxidonium therapy) in Slovakia. To document the number of patients invited and assess selection bias in subject recruitment, screening logs will be used.

Subjects included in the study are expected to be representative of the source population (i.e., patients for whom Polyoxidonium is routinely prescribed in Slovakia) in terms of gender, age distribution, socio-economic class, indication, concomitant diseases.

Confounding by known and unknown covariates may happen:

- Patients with variety of diseases and medical conditions are planned to enroll in scope with Polyoxidonium approved indications. Study population will not be homogenous.
- Eligible subjects are likely to receive a concomitant treatment with nephrotoxic medicines, including some antibiotics. It may be impossible to estimate precisely the causative agent of observed adverse renal effects.

Regular medical records at study sites (i.e., primary or secondary health care institutions in Slovak Republic) will be used as data source. The potential for missing data for variables of interest in this setting is unknown, and implications for information bias are to be determined.

9.10. Other aspects

9.10.1. End of the study

The end of study is the date of the last visit of the last subject undergoing the study.

Early study termination decided by the Sponsor

The Sponsor reserves the right to prematurely stop or to interrupt the study at any time and for any reason; the decision will be communicated in writing to the investigator.

Early study termination decided by the RA/EC

The RA/EC may suspend or prohibit a study if it considers that the conditions of authorisation are not being met or has doubt about the safety or scientific validity of the study.

Early study termination decided by the investigator

The investigator must notify (30 days' prior notice) the Sponsor of his/her decision and give the reason in writing.

In all cases (decided by the Sponsor or by the investigator), the appropriate Regulatory Authorities and Ethics Committees should be informed.

Termination of the study in an individual case

Every subject has a right at any time and without indicating any reasons to withdraw his/her consent for further participation in the clinical study. Other possible reasons of subjects withdrawal from the study and procedures for discontinuation are described in Section 9.2.3.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Ethical principles

This study will be conducted in accordance with principles stated in the Declaration of Helsinki and subsequent amendments and in accordance with Guideline on Good Pharmacovigilance Practices (GVP) Module VIII-Post-authorisation safety studies [1], Good Pharmacoepidemiology Guidelines (GPP) [2] and Guide on Methodological Standards in Pharmacoepidemiology from The European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) [3].

Before initiating the study, this study protocol will be submitted to the Slovakia State Institute for Drug Control and relevant ethics committees.

The study will start only after obtaining written approvals from the corresponding institutions.

10.2. Informed consent

The investigator must obtain documented consent from each potential subject prior to participating in this study. Consent must be documented by the subject’s dated signature or by the subject’s legally acceptable representative’s dated signature on a consent form along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated informed consent form (ICF) should be given to the subject before participation in the study.

The initial informed consent form and any subsequent revised written informed consent form provided to the subject must receive the favorable opinion from the relevant ethics committee in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject’s willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject’s dated signature or by the subject’s legally acceptable representative’s dated signature.

10.3. Personal data protection

The subject's personal data and investigator's personal data which may be included in the Sponsor database will be treated in compliance with Directive 95/46/EC of the European Parliament and of the Council, other applicable laws and regulations.

When archiving or processing personal data pertaining to the investigator and/or to the subjects, the Sponsor will take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

The name of the subjects as well as other person-related data must not be forwarded by the investigator to the third party (with exception of regulatory inspectors or auditors or monitors for monitoring purposes). If it is necessary to identify the name of a subject during the course of the study due to medical reasons, the employees of the Sponsor and investigator taking part in the study conduct this under the observance of professional discretion. The investigator takes care that eCRF or other documents assigned to the sponsor do not include the name of the subject. The investigator handles a separate subjects' identification list which allows allocation of subject's identification code to his/her name.

Authorized persons can get access to the medical records in the context of monitoring, audit or inspection. This must be agreed and signed by the subject by signing Informed Consent Form.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Safety data will be processed and managed by CRO Biomapas. PcVmanager™ software will be used for this purpose. Serious ADRs will be reported to State Institute for Drug Control of Slovak Republic via EudraVigilance portal within required timelines. Research ethics committees will be notified according the applicable legislation.

Detailed information on the management and reporting of adverse events will be provided in Safety Management Plan.

11.1 Definitions

11.1.1 Adverse event

According to the ICH guideline for Good Clinical Practice, an adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the medicinal product.

Adverse events associated with the use of a medicinal product in humans, whether or not considered related, include the following:

- an adverse event occurring in the course of the use of a medicinal product in professional practice,
- an adverse event occurring from an overdose whether accidental or intentional,
- an adverse event occurring from medicinal product abuse,

- an adverse event occurring from medicinal product misuse,
- an adverse event occurring from medicinal product withdrawal,
- an adverse event occurring from medicinal product off-label use,
- an adverse event occurring from occupational exposure,
- an adverse events where there is a reasonable possibility that the event occurred purely as a result of the subjects participation in the study (e.g., adverse event or serious adverse event due to discontinuation of other medicinal products during wash-out phase) must also be reported as an adverse event even if it not related to the investigational product.

11.1.2 Special situations

In addition to AEs, the following special situations will be of interest, whether associated with AE or not:

- accidental or intentional overdose,
- medicinal product abuse or misuse,
- medication errors,
- medicinal product off-label use,
- pregnancy or breastfeeding exposure,
- lack of therapeutic efficacy,
- product quality complaints.

11.1.3 Serious adverse event

A serious adverse event (SAE) as defined by ICH as any untoward medical occurrence that at any dose meets any of the following conditions:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect, or
- is an important medical event.

Life-threatening: the term “life-threatening” in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.

Hospitalisation: any adverse event leading to hospitalisation (inpatient admission or overnight stay) or prolongation of hospitalisation will be considered as serious, UNLESS at least one of the following exceptions is met:

- the admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), OR
- the admission is not associated with an adverse event (e.g., social hospitalisation for purposes of respite care).

Important medical event: any adverse event may be considered serious based on medical and scientific judgment because it may jeopardise the subject and may require intervention to prevent one of the outcomes listed in the definition above. Any adverse event is considered a serious

adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

A suspected transmission of infectious agent via a medicinal product must also be considered as a serious adverse event.

11.2 Recording of adverse events

During the study subjects must be carefully monitored for adverse events or special situations and the investigator will be responsible for the determination and documentation of them. Adverse events should be assessed in terms of their seriousness, severity and relationship to Polyoxidonium.

Adverse events will be determined in one of the three ways:

- observed by the investigator;
- identified by general questions about any changes in subjects well-being, asked at all study visits;
- spontaneously reported by the subjects to the investigator.

The investigator is responsible for ensuring that all AEs, irrespective of its severity, intensity, and suspected relationship to Polyoxidonium, are recorded in the subject's medical record and on the eCRF.

For each AE recorded on the eCRF, the investigator will make an assessment of seriousness (see Section 11.1.3 for seriousness criteria), severity (see Section 11.2.1), and causality (see Section 11.2.2). All measures, taken to treat adverse event, must be described in medical documentation.

After informed consent has been obtained, all adverse events, regardless of relationship to Polyoxidonium, will be reported until study closure. Any AE that is still ongoing at the completion/discontinuation visit will have an outcome of „ongoing" in the eCRF, whereas the investigator will continue to follow up ongoing AEs and record information in the subjects medical documents. SAEs will be followed until the event resolves or the event or sequelae stabilise and this information will be reported to the Sponsor.

The investigator does not need to actively monitor subjects for adverse events once the study has ended. However, if becoming aware of any serious adverse events occurring to a subject within 30 calendar days after subject completed or withdrew the study, the investigator should report those to the Sponsor.

For all adverse events, a diagnosis (if known) should be recorded on the eCRF rather than individual signs and symptoms (e.g. record only liver failure or hepatitis rather than jaundice and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

11.2.1 Assessment of severity of adverse event

Severity of adverse events should be graded as follows:

- Mild – usually transient in nature and generally not interfering with patient's normal activities;
- Moderate – sufficiently discomforting to interfere with patient's normal activities;
- Severe – prevents patient's normal activities.

11.2.2 Assessment of relationship of adverse events to Polyoxidonium

Investigators should use their knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to Polyoxidonium.

An assessment of "Not related" would include:

- The existence of a clear alternative explanation, e.g., mechanical bleeding at surgical site, or
- Non-plausibility, e.g., the subject is struck by an automobile when there is no indication that Polyoxidonium caused disorientation that may have caused the event; or cancer developing a few days after the first Polyoxidonium administration.

An assessment of "Related" indicates that there is a reasonable suspicion that the adverse event is associated with the use of Polyoxidonium. Factors to be considered in assessing the relationship of the adverse event to Polyoxidonium include:

- The temporal sequence from Polyoxidonium administration: The event should occur after the Polyoxidonium is given. The length of time from Polyoxidonium exposure to event should be evaluated in the clinical context of the event.
- Recovery on discontinuation (de-challenge), recurrence on reintroduction (re-challenge): Subject's response after Polyoxidonium discontinuation (de-challenge) or subject's response after Polyoxidonium reintroduction (re-challenge) should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, inter-current diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other diseases the subject may have.
- Concomitant medication or treatment: The other medicinal products the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of Polyoxidonium: The pharmacokinetic properties (absorption, distribution, metabolism, and excretion) of Polyoxidonium, coupled with the individual subject's pharmacodynamics should be considered.

If an adverse event was assessed as "related" by the investigator, further it is considered as ADR.

11.3 Reporting of serious adverse events

All SAEs, including laboratory test abnormalities fulfilling the definition of serious, occurring during this study or brought to the attention of investigator within 30 days after subject completed or withdrew the study, must be reported to CRO Biomapas pharmacovigilance

department within 24 hours of the investigator's awareness. Information regarding serious AEs will be reported through QCTMS EDC™ using the Serious Adverse Event Form, which is incorporated into eCRF.

All serious AEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- the event resolves;
- the event stabilizes;
- the event returns to baseline, if a baseline value is available;
- the event can be attributed to agents other than Polyoxidonium or to factors unrelated to study conduct;
- it becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts).

The cause of death of a subject in the study, whether the event is expected or associated with Polyoxidonium, is considered a serious AE.

11.4 Reporting of serious adverse drug reactions to Health Authorities

All SAEs, including laboratory test abnormalities fulfilling the definition of serious, occurring during this study and assessed as "related" by the Investigator will be reported to State Institute for Drug Control of Slovak Republic. The reporting of serious ADRs is required as soon as possible, but in no case later than 15 calendar days after first knowledge by the MAH. This applies to initial and follow-up information. Where a case initially reported as serious becomes non-serious, based on new follow-up information, this information should still be reported within 15 calendar days. This will be assured by CRO Biomapas Pharmacovigilance department employees following applicable SOPs.

11.5. Management of pregnancy exposure cases

The investigator is expected to record pregnancy occurring in a subject [or a male subject's female partner] during the study using the Pregnancy Notification Form and submit it via QCTMS EDC™ to the CRO within 5 days after the being made aware of the pregnancy.

The CRO will forward the Pregnancy Notification Form to the Sponsor within 24 hours.

The investigator is requested to follow each case of pregnancy exposure until the outcome.

If the pregnancy results in an abnormal outcome during the study, this will be recorded in the eCRF as a SAE and managed as above described. After the end of study MAH/Sponsor is responsible for tracking and follow-up of the pregnancy in line with Good Pharmacovigilance Practice.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study protocol will be entered in the EU PAS register before the start of data collection. Updates of the study protocol in case of substantial amendments and the final study report will be also entered in the register.

The results of the study will be published in peer reviewed journals and presented at relevant events (e.g., scientific congresses or conferences).

13. REFERENCES

1. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies (Rev 1). 2013; EMA/813938/2011 Rev 1
2. ISPE Guidelines for Good Pharmacoepidemiology Practices (GPP). Revision 3: June 2015.
3. ENCePP. Guide on Methodological Standards in Pharmacoepidemiology (Revision 3). 2014; EMA/95098/2010

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

No	Document reference No	Date	Title
1	Version 1.0	02 Feb 2016	List of investigators and study sites*

**List of investigators and study sites is available on request*

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

To be inserted after it is completed

ANNEX 3. ADDITIONAL INFORMATION

List of nephrotoxic medications *(NOTE: this list is not exhaustive and is only provided for initial reference)***:**

ACE Inhibitors
Acetaminophen
Acyclovir
Adefovir
Allopurinol
Aminoglycosides
Amitriptyline
Amphotericin B
Angiotensin converting enzyme inhibitors
Anticoagulants
Aristocholic acid containing Chinese herbals
Arsenic
Aspirin
Bevacizumab
Bismuth
Carbon tetrachloride
Carboplatin
Carmustine
Celecoxib
Cephalosporins
Chloroquine
Cidofovir
Cimetidine
Ciprofloxacin
Cisplatin
Clopidogrel
Cocaine
Cyclosporine
Dilantin
Diphenhydramine
Diuretics
Doxepin
Doxylamine
Erythromycin
Esomeprazole
Fenofibrate
Fluoxetine
Foscarnet
Furosemide
Gemfibrozil
Gentamycin
Gold therapy
H1 antagonist
Heroin
Hydroxychloroquine
Ibuprofen
Ifosfamide
Indinavir
Infliximab
Interferon alpha
Interferons
Isoniazide
Ketamine
Lansoprazole
Laxative
Lead
Levofloxacin
Lithium
Lomustine
Mercury
Mesalamine
Methadone
Methamphetamine
Methicillin
Methotrexate
Mitomycin
Naproxen
Nitrosourea compounds
NSAIDs
Omeprazole
Pamidronate
Pantoprazole
Penicillins
Pentamidine
Propylthiouracil
Proton pump inhibitors
Quinine
Rabeprazole
Radiocontrast agents
Rifampin
Statins
Sulfonamides
Tacrolimus
Tenofovir
Tetracycline
Thiazides
Ticlopidine
Triamterene
Trimethadione
Vancomycin
Zoledronate

ANNEX 4. SUMMARY OF PRODUCT CHARACTERISTICS OF POLYOXIDONIUM

1. NAME OF THE MEDICINAL PRODUCT

POLYOXIDONIUM 6 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: each vial or ampoule contains azoximer bromide 6 mg.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilisate for solution for injections
Drug description: lyophilisate of yellowish to yellow colour and spongy consistence.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Polyoxidonium 6 mg is indicated in adults for therapy of disease, which are accompanied by secondary immonudeficiency:

- recurrent chronic bacterial infections
- recurrent chronic viral infections
- acute bacterial infections
- acute viral infections
- allergic disturbances (polynosis, bronchial asthma, atopic dermatitis)
- serious septic conditions
- post-surgical complications - purulent affections
- in patients with decreased cell immunity caused by primary therapy (cytostatics, X-ray)

4.2 Posology and method of administration

Polyoxidonium can be administered in form of either monotherapy or in complex therapy together with antibiotics, antivirotics, antimycotics or antihistaminics, broncholytics, corticosteroids, beta-agonists or cytostatics.

Posology

Polyoxidonium is administered to adults depending on the diagnosis and degree of the disease.

Acute inflammatory diseases, complicated forms of allergic disturbances: 6 mg daily for 3 days, then every second day; one cure comprises of 5-10 injections;

Chronic inflammatory diseases: five injections of 6 mg every second day, then twice a week; one cure comprises of 10 injections;

- urogenital diseases: 6 mg every second day, one cure comprises of 10 injections. Concomitant use of chemical drugs is recommended.

- chronic recurrent herpes simplex: 6 mg every second day, one cure comprises of 10 injections, concomitant use of drugs for treatment of herpes is recommended, interferons and interferone inductors.
- allergic disturbances: 6 mg during 2 days, then 6 mg every second day one cure comprises of 5 injections. The drug should be administered concomitantly with the antihistamine and other antiallergic drugs.
- oncological diseases: prior and after chemotherapy 6-12 mg every second day, one cure comprise of at least 10 injections.
- correction of immunodeficiency in patients with decreased cell immunity caused by primary therapy: 6 mg once to twice a week, 2-3 months to 1 year.

Experiences with the use in children are limited.

Method of administration
Dissolve the content of vial (ampoule) in 1.5 – 2 ml water for injections or isotonic saline solution.
The solution should be clear, without any mechanical impurities. Do not administer turbid solution.

The drug product should be administered intramuscularly, the slow application for 15-20 second is recommended. Intramuscular injection site should be deltoid muscle of upper limb or outer quadrant of thigh muscle.

4.3 Contraindications

Hypersensitivity to the azoximer bromide or to any of the excipients listed in section 6.1.
Polyoxidonium 6 mg is contraindicated during pregnancy and lactation. Women of childbearing potential must use effective contraception during treatment.

4.4 Special warnings and precautions for use

The drug is recommended to be administered slowly to reduce the local pain. Appropriate medical treatent and supervision should be always easy available after administration because of very rare anaphylactic reaction possibility.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Animal studies revealed reproductive toxicity (see section 5.3).
Polyoxidonium 6 mg is contraindicated during pregnancy and lactation. Women of childbearing potential must use effective contraception during treatment.
It is not known whether azoximer bromide and its metabolites are excreted into the breast milk.
Polyoxidonium 6 mg is contraindicated during lactation (see section 4.3)

4.7 Effects on ability to drive and use machines

Polyoxidonium 6 mg has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Polyoxidoium is generally very good tolerated.

Following frequencies are used for classifacation of undesirable effects:

Very common: ≥1/10
Common: ≥1/100 to <1/10
Uncommon: ≥1/1 000 to <1/100
Rare: ≥1/10 000 to <1/1 000
Very rare: <1/10 000 (including isolated cases)
Not known: (cannot be estimated from the available data)

General disorders and administration site conditions

- Uncommon: skin redness, induration.
- Very rare: elevation of the body temperature up to 37.3°C, slight restlessness, tremor during the first hour after drug administration.

Serious adverse reactions have not been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

4.9 Overdose

There has not been reported any case of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunopreparations, other cytokines and immune modulators
ATC code: L03AX

The active ingredient of medicinal product Polyoxidonium 6 mg is azoximer bromide (N-oxide of 1,4-ethylene piperazine and (N-carboxyethyl)-1,4-ethylene piperazinium bromide) with molecular weight of 100 kDa, which belongs to the group of water soluble derivate of hetero-chain aliphatic polyamines. This macromolecular compound provides

- immuno-stimulating effect associated with the ability of azoximer bromide to activate cells of mononuclear phagocyte system,
- detoxifying effects related with speciality of azoximer bromide chemical structure to adsorb different toxic compounds on its surface including substances of microbial origin,
- antioxidative and membrane-protective properties related with speciality of azoximer bromide chemical structure. Its ability of cells membrane recovery significantly decreases the sensitivity of cells against harmful effects of some drugs, especially imunosupressants.

5.2 Pharmacokinetic properties

Presence of N-oxid group in the main chain of azoximer bromide allows its degradation via free radicals mechanism. Degradation products are nontoxic oligomers of N-oxid with molecular weight of 1 – 2 kDa. High bioavailability 89 %; C_{max} in blood after intramuscular application is reached in 40 minutes and drug quickly is distributed into all organs and tissues. The drug is eliminated from body mainly via kidney in two phases. $T_{1/2}$ of fast phase is 25 minutes and $t_{1/2}$ of slow phase is 36,2 hours after i.m. administration.

45% of the drug is excreted into the urine during the first day. There has not been find any tissue cumulation of the drug.

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies but in animals at exposures similar to clinical with possible relevance to clinical use were as follows:

- single dose toxicity was studied on mice, rats, guinea pigs and rabbits when azoximer bormide was injected intraperitoneal. Azoximer bromide LD_{50} was 1417 mg/kg, 1450 mg/kg, 1150 mg/kg, 400 mg/kg and 500 mg/kg in mice males, mice females, rat females, guinea pigs and rabbit respectively. Based on the macro- and microscopic examination of organs i tis assumed the azoximer bromide in high doses affects transcapillar exchange and kidney are the main toxicityy organ.
- repeat dose toxicity was studied on rats after i.p. and s.c. administration. There has not been seen any toxic effects either after fifty-fold of therapeutic dose.
- administration of azoximer bromide to gravid rats led to reduction of survival index in neonatal period. There is resulting from stated, that azoximer bromide has embryotoxic effects.
- results of mutagenicity and carcinogenicity tests were negative.

Azoximer bromide has wide therapeutic index – 10 000. High safety degree is confirmed by results of preclinical tests. Azoximer bromide in dose of 50-folds of therapeutic one does not have pyrogenic, irritating, toxic or allergic properties.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, povidone, beta-carotene

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years
Reconstituted medicinal product should be applied immediately.

6.4 Special precautions for storage

Store in refrigerator (2°C – 8°C).
Store in the original package to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3

6.5 Nature and contents of container

Primary package:

- Vials made from neutral class I type glass of brown colour, closed rubber stopper and sealed with aluminium caps
- Brown glass ampoule

Outer package: cardbox

Pack size: 5 x 6 mg (vial)
5 x 6 mg (ampoule)

6.6 **Special precautions for disposal and other handling**

Dissolve the content of flask/vial in 1.5 – 2 ml water for injections or isotonic saline solution.
No longer required medicine and waste from it return to pharmacy.

7. MARKETING AUTHORISATION HOLDER
MEDIGROUP s.r.o., Bratislava, Slovak republic

8. MARKETING AUTHORISATION NUMBER
59/0220/02-S

9. DATE OF FIRST **AUTHORISATION/RENEWAL OF THE AUTHORISATION**
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10. DATE OF REVISION OF THE TEXT
August 2013