# ASSESSMENT OF THE EFFICACY OF COMBINATION THERAPY BUDESONIDE/FORMOTEROL FUMARATE (BUFOMIX EASYHALER® 160/4.5 MG OR 320/9.0 MG PER INHALATION) IN PATIENTS DIAGNOSED WITH ASTHMA

## PROTOCOL FOR AN OPEN-LABEL, MULTICENTRE, NON-INTERVENTIONAL, POST-AUTHORIZATION SAFETY STUDY

**STUDY NUMBER: ORN/AST/2016/004**

**Name of Marketing Authorization Holder:**
278 Grochowska St. apt. 31
03-841 Warsaw, Poland

Phone: +48 22 833 31 77
fax: +48 22 832 17 50

**Contact in case of adverse events:**
MBR Consulting
18 F Obrzeżna St.
02-691 Warszawa, Poland

e-mail: adr@mbrconsulting.com.pl
fax: +48 22 370 21 09

**Office of Study Organizer**
Europharma M. Rachtan Sp. z o.o.
6 Krzywa St.
40-121 Katowice, Poland

Phone: +48 32 771 14 60
fax: +48 32 731 50 32

**Name of Principal Investigator:**
Prof. MichałPirożyński MD., PhD

**Name of Coordinator:**
Prof. Jerzy Chudek MD.,PhD

**LEGAL NOTICE:**

This Protocol does not in any way constitute a basis for a decision on any diagnostic or therapeutic methods with respect to any participant of the study.

# SIGNATURES UNDER THE PROTOCOL

**Investigator Signature:**

I confirm that I have read the protocol for the open-label, multicenter, non-interventional, post-authorization efficacy study, entitled:

## ASSESSMENT OF THE EFFICACY OF COMBINATION THERAPY BUDESONIDE/FORMOTEROL FUMARATE (BUFOMIX EASYHALER® 160/4.5 MG OR 320/9.0 MG PER INHALATION) IN PATIENTS DIAGNOSED WITH ASTHMA

I am aware of the investigator's responsibilities imposed on me resulting from binding regulations and the Study Protocol. I agree to conduct this study in accordance with these guidelines and the guidelines on good pharmacovigilance practices (GVP).

NAME AND LAST NAME: _____ SIGNATURE: _____

POSITION: *Investigator*

ADDRESS OF THE MEDICAL CENTER: _____ DATE: _____

_____

_____

# PROTOCOL SUMMARY

| | |
|---|---|
| **PROJECT TITLE:** | **ASSESSMENT OF THE EFFICACY OF COMBINATION THERAPY BUDESONIDE/FORMOTEROL FUMARATE (BUFOMIX EASYHALER® 160/4.5 MG OR 320/9.0 MG PER INHALATION) IN PATIENTS DIAGNOSED WITH ASTHMA** |
| **STUDY AUTHORS:** | **Name of Principal Investigator:** Prof. MichałPirożyński MD., PhD<br><br>**Name of Coordinator:** Prof. Jerzy Chudek MD.,PhD |
| **MEDICINAL PRODUCT TO BE USED IN THE STUDY:** | **BUFOMIX EASYHALER®** powder inhalation contains budesonide/formoterol fumarate 160/4.5 or 320/9.0 micrograms at dose inhalation. **BUFOMIX EASYHALER®** is a drug in powder form for inhalation and is indicated in the treatment of asthma. |
| **RATIONAL AND BACKGROUND FOR THE STUDY:** | **The assessment of the** efficacy of asthma treatment with a combination therapy budesonide/formoterol fumarate (BufomixEasyhaler 160/4.5 $\mu$g or 320/9.0 $\mu$g per inhalation). |
| **RESEARCH QUESTION:** | **The role of the study** is to establish that combination therapy budesonide/formoterol fumarate (bufomixeasyhaler 160/4.5 $\mu$g or 320/9.0 $\mu$g) is efficacient and safe in treatment of patients diagnosed with asthma. |
| **THE AIMS:** | **The main aim of the study:** the assessment of the efficacy of combination therapy budesonide/formoterol fumarate (bufomixeasyhaler 160/4.5 $\mu$g or 320/9.0 $\mu$g) in patients diagnosed with asthma.<br>**Additional aim of the study:** the assessment patients compliance and the preferences of doctors in the treatment of asthma. |
| **PHASE OF THE STUDY:** | This is a non-interventional Post-Authorization Efficacy Study (PAES) with an Open-label, non-interventional study. The study has been imposed as volountary study by Marketing Authorization Holder in line with the requirements of EU. |
| **DESIGN OF THE STUDY:** | This is a prospective non-interventional observational study of patients receiving a combination therapy with **BUFOMIX EASYHALER®** - inhalation powder containing budesonide/formoterol fumarate - 160/4.5 $\mu$g or 320/9.0 $\mu$g per inhalation active substances for at least 14 days prior to study enrollment by allergist and pulmonologist . All study participants will be followed-up for at least 6 months. Data on the **BUFOMIX EASYHALER®** formulation efficacy will be recorded in Study Questionnaire (SQ) over three consecutive visits (planned according to the clinical needs of the patient), within a period of 6 months from the initiation of the use of **BUFOMIX EASYHALER®**. The efficacy will be assessed on the basis of ACT scale and the results of spirometry and compliance recommendations (MAQ). In addition, the preferences of doctors in the treatment of asthma well be assessed. |
| **STUDY POPULATION :** | The study population will consist of adult patients(≥18 years) diagnosed with asthma treated with medicinal product **BUFOMIX EASYHALER®** at last 14 days before enrollment to the study. |
| **ENDPOINTS:** | Primary endpoint: the efficacy of the treatment with **BUFOMIX EASYHALER®** on the basis of ACT scale and the results of spirometry.<br><br>Secondary endpoint is an assessment of patients compliance on the basis of the Medication Adherence Questionnaire (MAQ) and the preferences of doctors in the treatment of asthma.<br><br>Severe adverse events should be reported to MBR Consulting; ul. Obrzeżna 18 F;<br><br>02-691 Warszawa; e-mail: adr@mbrconsulting.com.pl; fax: 22 370 21 09 or UPRL or Study Organizer via website **www.dzialanianiepozadane.com.** |
| **STUDY SIZE:** | This is a non-interventional PAES study in which about 2500 patients was determined as an appropriate sample size, taking into account some practical limitations, and not on the basis of statistical analysis. Therefore, this study will not form the basis for the formulation of definitive conclusions about the efficacy and safety of the study drug. |
| **DATA ANALYSIS:** | The efficacy of used treatment will be assessed on the basis of the evaluation of ACT scale and the results of spirometry. The treatment tolerance will be assessed on the basis of the reported adverse events as well as on the basis of the Medication Adherence Questionnaire (MAQ). In addition, the preferences of doctors in the treatment of asthma will be assessed. |

# TABLE OF CONTENTS

# 1. INTRODUCTION

## 1.1. Information about asthma

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation(GINA 2015 definition). Asthma is a chronic inflammatory disease lower respiratory tract. In asthma pathogenesis participated numerous cells and the substances released by them. The chronic inflammation of bronchia is accompanied by bronchial hyperreactivity, leading to recurrent episodes of wheezing, breathlessness and tightness in the chest and coughing, occurring especially at night or in the morning.With these symptoms usually coexists diffuse, change of the restriction of airflow in the lungs, frequently resolved without treatment or after treatment. The cells involved in the development of inflammation in asthma are mast cells, eosinophils, T cells, neutrophils, and dendritic cells of the airway epithelium, bronchial smooth muscle and fibroblasts.

Among the phenotypes of asthma proposed by GINA in 2015 the key role play: allergic and non-allergic asthma.

Underlying mechanisms of allergic asthma are dependent on the class of immunoglobulin E (IgE) and immediate type reactions. The innate overproduction of IgE is named atopy. The disease usually starts in childhood and often is associated with other

atopic diseases (eg. atopic dermatitis). Contact with the allergen specific IgE on the surface of mast cells results in release of mediators of inflammation and the influx of inflammatory cells, mostly eosinophils (late phase), resulting in mucosal edema, smooth muscle contraction bronchial walls and mucus hypersecretion and, consequently, restriction of air flow through the respiratory tract.

Pathomechanism of non-allergic asthma is less known, and the main role of initiating the development of the disease is attributed to viral infections (eg. RS virus).The disease usually develops in adulthood, often is dominated by neutrophil type of airway inflammation, and response to treatment is generally worse than in the case of allergic asthma.

Observed in asthma, airway hyperresponsiveness is their excessive contractile response to various stimuli which not causing bronchoconstriction in normal subjects. This phenomenon increases with the intensity of inflammation, and usually decreases under the influence of applied anti-inflammatory treatment. In bronchial hyperresponsiveness important role is attributed to the neurogenic mechanisms taking place with the participation of the autonomic nervous system [1,2].

The reversibility of airflow obstruction in asthma is dependent on the severity of the disease and the treatment. The long duration of asthma, especially due to inappropriate treatment induces remodeling of the bronchi which results in fixation of obturation [1,2].

Asthma is one of the most common chronic diseases. The prevalence of asthma in Poland is estimated at nearly 10.57% of the population [1].

Direct and indirect costs of treatment of asthma in the European Union are estimated annually at more than 30 billion euros. Therefore, in many countries, there are national programs for early diagnosis and treatment of the disease curing asthma is impossible, however the available drugs allow gaining complete control of the disease and minimize its impact on the daily life of the patient [1,2].

The aims of effective treatment of asthma are:

1. achieving and maintaining control of symptoms,
2. maintaining normal activities, including the ability to undertake physical effort,
3. maintaining the efficiency of the respiratory system at as close as possible for the proper,
4. prevention of asthma exacerbations,
5. avoidance of adverse effects of drugs used in asthma treatment and
6. preventing death due to asthma.

Achieving these goals requires the development of a partnership between the patient and physician to identify risk factors for asthma exacerbations and the use of proper treatment ensures proper degree of control of the disease.

Drugs used in the treatment of asthma is divided into drugs to control the disease and rescue medication. Medications to control the disease are drugs taken regularly, every day, in order to obtain and maintain control of chronic asthma, mainly due to the anti-inflammatory effect. These included:

1. inhaled glucocorticoids (beclomethasone dipropionate, budesonide, ciclesonide, fluticasone, mometasone) - the most effective anti-inflammatory drugs for use in chronic asthma, medicines currently preferred,
2. leukotriene receptors antagonist CysLT1 (montelukast, zafirlukast)
3. long-acting beta2-adrenergic agonists – LABA (formoterol fumarate, salmeterol)
4. theophylline in a sustained release form - less effective than the above mentioned drugs and often causes significant adverse effects
5. cromones (cromolyn sodium, nedocromil sodium) - ineffective in adults
6. oral long-acting beta2-adrenergic agonists - slow-release formulations used exceptionally
7. anti-IgE (omalizumab) - currently indicated in severe allergic asthma with elevated serum IgE
8. long-acting antycholinergic drugs (tiotropium)
9. oral glucocorticoids (methylprednisolone, prednisolone, prednisone) - long-term use (ie.> 2 weeks) may be necessary in very poorly controlled asthma, but it is limited by the risk of serious adverse events.

Rescue medications are fast-acting bronchodilators, which counteract bronchoconstriction and its accompanying acute symptoms. These, increasing use especially during the day, signal deterioration in control of asthma and indicates the need to verify the treatment. These included:

1. inhaledfast-acting beta2-adrenergic agonists (eg. salbutamol, fenoterol, or formoterol) - preferred drugs
2. oral and intravenous glucocorticoids - play an important role in the treatment of severe asthma exacerbations
3. anticholinergics (ipratropium bromide) - less effective than inhaled fast-acting beta-2-agonists
4. theophylline - in the form of short-acting can be used in order to eliminate the symptoms of asthma, but its use in the treatment of acute exacerbations of asthma is controversial; theophylline in the form of short-acting preparation should not be given to patients chronically receiving sustained release theophylline, if there is no certainty that the concentration of theophylline in serum is small or when it cannot be monitored
5. oral fast-acting beta2-adrenergic agonists (eg. salbutamol in tablets) - rarely used when a patient cannot take inhaled medicines.

Administration of asthma drugs by inhalation is preferred, because drug reaches the airways directly where it can achieve a therapeutic concentration, with the risk of systemic adverse effects limited or completely eliminated [1].

According to current recommendations of GINA, inhaled corticosteroids (ICS) and long-acting β2 – agonists are essential for the treatment of asthma. Inhaled administration of these drugs provides their fast action, better therapeutic index making it possible to use their smaller doses at low risk of systemic adverse events. The advantage of this form of treatment is also relative ease of use [1,2].

The key impact on the effectiveness of asthma treatment is an appropriate cooperation of the patient and the doctor.

Factors influencing the active participation of the patient in the treatment process are: the attitude towards the disease (disease denial, underestimation of disease, exaggerating, adequate attitude), an idea about the disease, the importance of the disease for the patient and doctor-patient communication [3,4]. Observations conducted among patients with asthma indicate that recommended treatment regimens are used by less than 50% of patients. The level of implementation of the doctors' recommendations is dependent on such factors

as the degree of complexity of the therapy and concerns about side effects of drugs, knowledge regarding the nature of the disease and its complications.

perception of the disease and the priorities of life [4]. Improvement of the level of patient cooperation is enabled by the use of an easy-to-use inhaler enables single administration with its help of more than one product.

## 1.2. Information about the study drug

The **BUFOMIX EASYHALER®** medicinal product contains active substances of formoterol and budesonide, whose mechanism of action is different, and which have an additive effect in alleviating asthma exacerbations.

Budesonide is a corticosteroid, which is inhaled, exhibits a dose-dependent anti-inflammatory effects in the airways, leading to relief of symptoms and fewer exacerbations of asthma. Inhaled budesonide causes significantly less severe adverse effects than systemic corticosteroids. The exact mechanism responsible for the anti-inflammatory effect of glucocorticosteroids is unknown.

Formoterol is a selective β2-mimetic that upon administration by inhalation leads to a rapid and sustained relaxation of bronchial smooth muscle in patients with reversible obscuration.

Bronchodilator effect is dose-dependent, with the start action of the drug is observed within 1-3 minutes after inhalation. After a single dose, this effect persists for at least 12 hours.

Clinical trials in adults have shown that the addition of formoterol to budesonide relieves asthma symptoms and improves the lung activity, and reduces the frequency of exacerbations.

In two clinical trials in the 12-week follow-up evaluation of the effect of budesonide and formoterol, given in a single inhaler on lung function was identical to that observed after administration budesonide and formoterol separately and was stronger than occurring after the administration of budesonide alone. All therapeutic groups received extemporaneously short-acting β2-mimetic.

Studies conducted on populations of children (a total of 265 children aged 6-11 years) treated with a maintenance dose of budesonide and formoterol (80 micrograms + 4.5 micrograms) / dose 2 times per day) showed an improvement in lung function during 12 weeks observation period as compared to the use of an equivalent dose of budesonide alone, and treatment was well tolerated.

It has been shown that the medicinal products **BUFOMIX EASYHALER®** and Symbicort Turbuhaler, containing equivalent doses of budesonide and formoterol, are bioequivalent in terms of therapeutic levels obtained after administration by the inhalation route.

It has been shown the systemic effects of the Symbicort Turbuhaler medicinal product containing equivalent doses of budesonide and formoterol are bioequivalent to the observed respectively budezonidzie and formoterol administered separately.There was a small increase in the suppression of cortisol after the administration of a combination drugs compared to the ones administered separately in equivalent doses of simple products. However, it is believed, that this does not impact on clinical safety.

There is no evidence of adverse pharmacokinetic interactions between budesonide and formoterol.

Pharmacokinetic parameters formoterol and budesonide were comparable both when administered in the form of simple products, such as and complex product in an equivalent dose.In the case of budesonide AUC was significantly higher, absorption rate larger, and the maximal plasma concentration higher after administration of the complex drug.

In the case of formoterol maximum plasma concentration after administration of the complex drug was comparable to that achieved following administration of a simple equivalent dose. Budesonide, administered via inhalation is rapidly absorbed, with peak plasma concentration reached within 30 minutes after inhalation. According to data from the study, budesonide deposition in the lung tissue when inhaled from a dry powder inhaler ranged from 32% to 44% of the delivered dose and the systemic bioavailability is about 49% the delivered dose.

In children aged 6-16 pulmonary deposition of the drug is equivalent to that observed in adults, after administration of the same dose.

Plasma concentrations obtained was not determined.

Formoterol, administered via inhalation is rapidly absorbed, with peak plasma concentrations reached within 10 minutes after inhalation.

The average lung deposition of formoterol after inhalation of the powder inhaler is from 28% to 49% of the inhaled dose and systemic bioavailability is about 61% of the delivered dose.

About 50% of formoterol and 90% of budesonide binds with plasma proteins. The distribution volume is about 4 l / kg for formoterol and 3 l / kg for budesonide.

Formoterol is inactivated as a result of the conjugation reaction (formed are open metabolites O-demethylation and deformylated, which are considered inactive conjugates).

Budesonide is substantially (approximately 90%) biotransformed during its their first pass through the liver to metabolites with low activity.

Glucocorticoid activity characteristic of major metabolites, 6-beta-hydroxy-budesonide and 16-alpha-hydroxy-prednizolone represents less than 1% of budesonide.

There was no metabolic interactions or displacement reaction between formoterol and budesonide.

Formoterol is in mostly transformed by liver metabolism, followed by elimination of the drug by the kidneys.After inhalation, 8% to 13% of the delivered dose of formoterol is secreted as a non-metabolized in the urine. Formoterol is characterized by high systemic clearance (approximately 1.4 L / min), and the terminal half-life of elimination is 17 hours.

Budesonide is eliminated through metabolism mainly catalysed by the enzyme CYP3A4.The metabolites of budesonide are eliminated in the urine as such or in the form of a conjugate. Trace amounts of budesonide in unchanged form are detected in the urine. Budesonide has a high systemic clearance (about 1.2 l / min) and a terminal half-life of elimination after intravenous administration is four hours.

The pharmacokinetics of formoterol has not been studied in children.

The pharmacokinetics of budesonide or formoterol in patients with renal impairment is unknown.

Concentration of systemic budesonide and formoterol may be increased in patients with liver disease.

In animal studies adverse effects of budesonide and formoterol administered concomitantly or alone were observed. In studies of reproduction in animals it has demonstrated that corticosteroids such as budesonide, can cause malformations (cleft palate, skeletal anomalies).However, the results of animal studies seem to have no clinical relevance to the situation of administration of recommended doses in humans. Studies on the effect of formoterol on animal reproduction studies have shown a slight reduction in fertility in male rats at high systemic exposure and problems the implantation of embryos, and reduced postnatal survival and birth weight at systemic exposures significantly higher than those achieved during clinical use. In summary, the results of animal studies do not seem to have significance for the safety of these drugs in humans.

**BUFOMIX EASYHALER®** is indicated for use in adults and adolescents aged from 12 to 17 years in regular treatment of asthma, when a combination therapy (inhaled corticosteroid and longacting β2-mimetic) is necessary to control the disease: in Patients with inhaled corticosteroids, along with relevant extemporaneously β2-agonist do not provide adequate asthma control or - in patients where sufficient control providing both inhaled corticosteroids and long-acting β2-agonists.

**How to use BUFOMIX EASYHALER®**

Use medicinal product **BUFOMIX EASYHALER®** as a drug to start treatment of asthma is not recommended. Dosage components of medicinal product **BUFOMIX EASYHALER®** is determined individually and appropriately modified depending on the symptoms of the disease. If in an individual patient, it is necessary to use a different dose of medicinal products than available in the inhaler containing a complex medicinal product the appropriate doses of β2-mimetków and (or) corticosteroids in separate inhalers should be prescribed.

Recommended doses:

Adults (over 18 years): one inhalation twice daily. In selected patients to achieve disease control the increase of the dose to two inhalations twice a day may be necessary.

Children and adolescents

Adolescents (aged 12 to 17 years): one inhalation twice daily.

Medicinal product **BUFOMIX EASYHALER®** is not recommended for children under the age of 12 years.

The degree of asthma control should be regulary assessed to determine the optimum dose of the medicinal product **BUFOMIX EASYHALER®**. After obtaining a long-term control of the disease the minimum effective maintenance dose of the drug should be determined. In clinical practice, it usually means reducing the dosage to the one inhalation per day or by an formulation consisting of a lower dose glucocorticoid. The withdrawal of long-acting treatment with beta2-agonist is currently not recommended. Increased use of symptomatic drugs indicates insufficient degree of asthma control and should lead to the revision of the used pharmacotherapy. A lower dose of the medicinal product (160 micrograms + 4.5 micrograms / inhalation dose can be used in long-term maintenance treatment, and at the same time as a supporting and symptomatic drug grade 3 treatment according to GINA 2015). **BUFOMIX EASYHALER®** (320 micrograms + 9 micrograms) / inhalation dose should be used only in the long-term maintenance treatment.

**Contraindications to the use of Budesonide and formoterol fumarateinclude:** -hypersensitivity to active substance or to excipient (lactose, which contains small quantities of milk protein).

**Special warnings and precautions for use of BUFOMIX EASYHALER® :**

Treatment should not be stopped suddenly, a gradual reduction of dose is recommend. If the patient reports that treatment is ineffective and currently is taking the highest recommended dose of medicinal product **BUFOMIX EASYHALER®** they should urgently consult a doctor. Increasing use of fast-acting bronchodilators indicates insufficient degree of asthma control, and warrants a revision of therapy. Sudden and progressive deterioration in control of symptoms known as exacerbation requires treatment modification. In the case of mild exacerbations increase of the dose of inhaled corticosteroids and drugs used extemporaneously is recommended. If such action is unsuccessful, use additional oral glucocorticoids is recommended and the patient should immediately seek medical attention.

In the case of exacerbations of more severe course, the patient should urgently seek medical consultation, as it can potentially be life-threatening. Patients should be advised to always be in the possession of a rescue medication..

Patients should be reminded of the need for regular use of the product **BUFOMIX EASYHALER®** in accordance with doctor recommendation, even during the period when symptoms are not present.

After obtaining the control of asthma symptoms, usually after about 3 months of therapy, gradually reducing the dose of medicinal product **BUFOMIX EASYHALER®** may be considered.

The regular monitoring of patients during the dose reduction is important. Use the lowest effective dose of the medicinal product **BUFOMIX EASYHALER®** is recommended.Do not reduce doses during infection, pregnancy and dust. During therapy with the medicinal product **BUFOMIX EASYHALER®** side effects associated with the treatment or asthma exacerbations may occur. Patients should be advised to seek medical attention.Similarly to other inhaled drugs after inhalation of a medicinal product **BUFOMIX EASYHALER®** may occur paradoxical bronchospasm resulting in shortness of breath may occur. If a patient develops a paradoxical bronchospasm, the therapy with the medicinal product **BUFOMIX EASYHALER®** should be discontinued immediately, the patient should undergo a medical examination and - if desired – use the alternative treatment. Paradoxical bronchospasm occurs usually after the rapid-acting inhaled bronchodilator, which must then be adopted without delay.

Systemic side effects may occur with all inhaled corticosteroids, especially with the use of high doses for a long time. The probability of their occurrence in the case of inhalation glucocorticoids is much smaller than in the case of oral corticosteroids. Possible systemic side effects of corticosteroids include Cushing's syndrome, the symptoms of Cushing's syndrome, suppression of the adrenal glands, growth inhibition in children and adolescents, decrease in bone mineral density, cataract and glaucoma and more rarely a range of adverse effects of psychological and behavioral (eg. psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression, especially in children).

The potential negative impact on bone mineral density should be considered particularly in patients receiving high doses of inhaled glucocorticoids for long periods, which coexist with risk factors for osteoporosis. Long-term observational studies on the use of inhaled budesonide in children taking daily dose 400 micrograms of drug, or the group of adults taking a daily dose of 800 micrograms showed no significant effect on bone mineral density. There are no data on the effect of higher doses of budesonide on bone mineral density.

Adequate to the degree of control of asthma inhaled budesonide therapy usually minimizes the need for oral steroids.

Please note that patients treated for a long time with oral corticosteroid may be characterized by decreased adrenal reserve, which creates a potential risk of adrenal insufficiency when changing the way of glucocorticoid administration. In such situations, you should regularly monitor the function of the hypothalamic-pituitary-adrenal (HPA). During periods of an increased need for endogens glucocorticoids, eg. severe infections, planned surgery, childbirth use of additional systemic corticosteroids (usually hydrocortisone) should be considered.

Too fast reduction in the dose of oral corticosteroids can cause acute adrenal cortex insufficiency- adrenal crisis. The most common symptoms are: hypotension, hypoglycemia, anorexia, abdominal pain, weight loss, fatigue, headache, nausea, vomiting, decreased the level of consciousness or seizures.

Do not suddenly stop taking corticosteroids, both systemic and inhaled budesonide.

During the conversion oral glucocorticoid treatment for inhalation therapy medicinal product **BUFOMIX EASYHALER®** mild systemic symptoms associated with deficient endogenousglucocorticoid, eg. rhinitis, eczema and muscle and joint pain may occur. If it is accompanied by other symptoms such as tiredness, pain, headache, nausea and vomiting, a temporary increase in the dose of oral corticosteroids is necessary.

The most common mild side effect of inhaled corticosteroids is candidiasis of the mucous membranes of the mouth and throat. To minimize the risk of its occurrence Patients should be advised the need to rinse the mouth with water after inhaling the drug.

Avoid simultaneous treatment with itraconazole, ritonavir or other potent CYP3A4 inhibitors. If this is not possible, the longest possible interval between the doses of drugs causing interaction should be exercised..

Medicinal product **BUFOMIX EASYHALER®** should be used with caution in patients with thyrotoxicosis, pheochromocytoma, diabetes mellitus, untreated hypokalaemia, hypertrophic cardiomyopathy, obstructive of the left ventricle, idiopathic subaortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disease, for example.

ischemic heart disease, tachyarrhythmia or severe heart failure.

Caution should be exercised when treating patients with a prolonged QT interval. Formoterol may cause QT prolongation.

In patients with active or quiescent pulmonary tuberculosis and fungal and viral infections of the respiratory tract verify the indications for use and the dose of inhaled corticosteroids.

Large doses of β2-agonists may lead to severe hypokalemia, and this phenomenon increases the simultaneous treatment with drugs such as methylxanthines, steroids or diuretics, intensifying their hypokalemic effect or cause hypokalemia per se.

Particular caution is recommended in case of coexistence of severe asthma, which is characterized by high consumption inhaled bronchodilators and unstable angina, when the likelihood of hypokalaemia is increased, and its effects exacerbated by hypoxia of the heart muscle.

Monitoring serum potassium levels is recommended.

As in the case of all β2-agonists in patients with diabetes additional determination of the concentration of blood glucose should be considered due to the risk of hypoglycemia.

Medicinal product **BUFOMIX EASYHALER®** contains approximately 8 mg of lactose attributable to a single inhalation. This amount usually does not cause symptoms in patients with lactose intolerance.

The excipient lactose contains small amounts of milk proteins, which may cause allergic reactions.

The regular monitoring of growth in children receiving long-term inhaled corticosteroids is recommended.

If growth slowdown is detected, the used therapy should be revised and if possible, usage of the lowest dose of inhaled glucocorticoid necessary for effective control of asthma should be exercised.

Benefits of corticosteroid therapy and the potential risk of growth inhibition should be assessed. Referring the patient to a specialist pulmonologist children should also be considered.

Limited data from long-term observational studies suggest that most children and adolescents treated with inhaled budesonide ultimately achieve the target growth in adulthood. However, a slight and temporary limiting the growth (about 1 cm), usually in the first year of budesonide therapy was observed.

Sufficient clinical data on the safety of the medicinal product

**BUFOMIX EASYHALER®** during pregnancy are not available. There are no adequate data from the use of formoterol in pregnant women. In animal studies, formoterol exerted adverse effects on reproduction at systemic exposure of its very high concentrations.

Safe use during pregnancy short acting beta-2 agonist - salbutamol, however, allows to assume that treatment with long-acting beta-2 agonist, due to a similar mechanism of action, also is not associated with an increase in risk to the fetus.

Studies in animals have shown that glucocorticoids can cause malformations. However, this problem probably does not apply to people treated with the recommended dose.

Scientific data on the course of 2 000 pregnancies, do not confirm the teratogenic effect of inhaled budesonide. In animal studies, it is argued that the excess use of corticosteroids prenatally may be associated with an increased risk of intrauterine growth, the development of cardiovascular disease in adulthood and permanent changes in glucocorticoid receptor density.

However, from a clinical point of view, decisively greater risk to the fetus is uncontrolled asthma. Therefore, during pregnancy, a medicinal product **BUFOMIX EASYHALER®** should be used only if the potential benefit outweigh the risks. Use the lowest effective dose of budesonide needed to ensure proper asthma control.

Budesonide and its metabolites are excreted in human milk. Product **BUFOMIX EASYHALER®** is used at the recommended doses seems to have no effect on the body of children breast-fed. It is not known whether formoterol passes into human breast milk. In rats, a small amount of formoterol was detected in breast milk. When deciding whether to discontinue breast-feeding during treatment **BUFOMIX EASYHALER®**, the risk of asthma control deterioration in the mother should be considered .

There are no available data on the effects of budesonide on fertility. Studies on the effect of formoterol on reproduction in animals showed a slight reduction in fertility in male rats at high systemic exposure.

**BUFOMIX EASYHALER®** has no or negligible influence on the ability to drive and use machines.

**Interaction with other medication products and other form of interaction**

Strong CYP3A4 inhibitors (eg. ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telytromycyna, nefazodone and HIV protease inhibitors) can significantly increase the concentration of budesonide in plasma and their simultaneously application should be avoided. If this is not possible, keep the longest interval between doses of the inhibitor and budesonide. In patients taking potent inhibitors of CYP3A4 maintenance and symptoms mitigation therapy is not recommended.

A potent inhibitor of CYP3A4, ketoconazole at a daily dose of 200 mg increased the average concentration the plasma-administered oral budesonide (3 mg single dose) six times. When ketoconazole was administered 12 hours after the budesonidzie, the concentration is increased approximately 3-fold, which demonstrates that the individual administration of these drugs can reduce the levels budesonide in the plasma.

Limited data for this type of interaction with high doses of budesonide indicate that significant increases in plasma concentrations (approximately 4-fold) may develop after administration of itraconazole, 200 mg once a day, at the same time of inhaled budesonide (single dose of 1 000 µg.

Non-selective beta-blockers can weaken or inhibit the effect of formoterol. Therefore, medicinal product **BUFOMIX EASYHALER®** should not be used together with beta-blockers (including eye drops), unless it is justified clinically.

Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine), and tricyclic antidepressants may lead to QT prolongation, and increase the risk of ventricular arrhythmias.

In addition, L-Dopa, L-thyroxine, oxytocin and alcohol can increase susceptibility to cardiac β2-sympathomimetics.

Concomitant treatment with monoamine oxidase inhibitors, including drugs with properties similar to furazolidone and procarbazine, may aggravate allergic reactions.

In patients anaesthetized generally at fluorinated hydrocarbon there is an increased risk of arrhythmias.

Concomitant use of other beta-agonists and anticholinergics produces an additive effect on bronchi extension.

Hypokalemia may increase the risk of arrhythmias in patients treated with digitalis.

There was no interaction of budesonide and formoterol with other medicines used in asthma treatment.

Interaction studies have been performed in adults, only.

**The adverse events related to use of BUFOMIX EASYHALER® formulation, include:**

Very common(1/10): none

Common (≥1 / 100 and <1/10): candidiasis of the mouth and throat, headache, tremor, palpitations, mild throat irritation, coughing, hoarseness

Uncommon (≥1 / 1000 and <1/100): aggression, psychomotor hyperactivity, anxiety, sleep disorders, dizziness, tachycardia, nausea, bruising, muscle spasms

Very rare (<10 000): Cushing's syndrome, adrenal suppression, growth inhibition, decreased bone mineral density, hyperglycaemia, depression, behavioral changes (especially in children), cataract, glaucoma, angina pectoris, QT prolongation, fluctuations in blood pressure

Unknown: none.

Candidiasis of the oral cavity and pharynx is the result of drug deposition on the mucosa during inhalation. The risk of its development can be minimized, recommending the patient to rinse the mouth after each inhalation. Candidiasis of the mouth and throat occurs usually after topical antifungal therapy without interrupting therapy with inhaled corticosteroids. As with other inhaled therapies paradoxical bronchospasm may occur. The phenomenon affects less than 1 in 10 000 people and is characterized by shortness of breath immediately after inhalation. Paradoxical bronchospasm persists after the rapid-acting inhaled bronchodilator, which should be used immediately after the occurrence of symptoms.

Use of the product **BUFOMIX EASYHALER®** must be discontinued immediately and the patient be retested and, if necessary, alternative treatment should be implemented.

Inhaled corticosteroids can exert systemic effects, particularly at high doses taken by the

long time.

The probability of their occurrence is much smaller than in the case of oral corticosteroids.

To the possible systemic side effects include Cushing's syndrome, the symptoms of Cushing's syndrome, adrenal suppression, suppression of growth in children and adolescents, decrease in bone mineral density, cataract and glaucoma.

Increased susceptibility to infections and disturbance of adaptation to stressful stimuli may also occur.

Side effects may be dependent on the dose, the exposure time, simultaneous or prior systemic steroids administration and the individual patient sensitivity.

Treatment with β2-agonists may lead to elevated plasma concentrations of insulin, free fatty acid, glycerol in the blood, ketones in the urine.

The regular monitoring of growth in children receiving long-term therapy with inhaled corticosteroids is recommended.

**Overdosage**

An overdose of formoterol may lead to side effects typical of β2-agonists:tremor, headache and palpitations. The symptoms observed in individual cases were: tachycardia, hyperglycemia, hypokalemia, prolonged QT interval, arrhythmia, nausea and vomiting.

The maximum safe dose of formoterol in patients with severe airway obstruction is 90 micrograms given within three hours.

Acute overdosage with budesonide, even at very high doses, should not present a hazard.

In case of chronic use of very high doses systemic influence of glucocorticoids may occur, eg. an underactive adrenal cortex.

If the therapy with the medicinal product **BUFOMIX EASYHALER®** is interrupted due to an overdose of formoterol, the continuation of corticosteroid therapy in the equivalent dose should be ensured.

## 1.3. The clinical reason for conducting this open-label, non-randomized, multicenter, post authorization efficacy study

The medicinal product **BUFOMIX EASYHALER®** contains active ingredients formoterol and budesonide, whose mechanism of action is different and which show an additive effect in alleviating asthma exacerbations.

Budesonide is a inhaled glucocorticosteroid, which, exhibits a dose-dependent anti-inflammatory effects in the airways, leading to symptoms alleviate and fewer exacerbations of asthma. Inhaled budesonide causes less severe side effects than systemic corticosteroids. The exact mechanism responsible for the anti-inflammatory effect of glucocorticoids is unknown.

In Poland, a medicinal product **BUFOMIX EASYHALER®** containing formoterol and budesonide in the form of powder inhalation was registered in May 2014. Hence, the study the efficacy of the medicinal product in patients with a diagnosis of asthma is particularly important to obtain data from the Polish population. The data will be used for the purposes of planned marketing campaigns, training staff and doctors.

The planned study medicinal product **BUFOMIX EASYHALER®** can be carried out only on the trade name, as the subject of research interest is the specific medicinal product dministered in the form of inhalable powder.

# 2. THE AIM OF THE STUDY

The main aim of the study is to assess the efficacy of **BUFOMIX EASYHALER®** (budesonide / formoterol fumarate 160 / 4.5 micrograms or 320 / 9.0 micrograms dose inhalation) in the form of powder for inhalation in patients with asthma. The additional aim of the study is to assess the patient compliance as well as the preferences of physicians in the treatment of asthma.

## 2.1. The main aim of the study

The assessment of the efficacy of **BUFOMIX EASYHALER®** (budesonide/formoterol fumarate 160/4.5 micrograms or 320/9.0 micrograms dose inhalation) in the form of powder for inhalation in patients with asthma.

## 2.2. The additional aim of the study

Assessment of the patient compliance as well as the preferences of physicians in the treatment of asthma.

# 3. STUDY DESIGN

## 3.1. Basic information

This is an open-label, multicenter, non-interventional, post-authorization efficacy study. Data will be collected on the efficacy of medicinal product **BUFOMIX EASYHALER®** (budesonide/formoterol fumarate 160/4.5 micrograms or 320/9.0 micrograms dose inhalation) in the form of powder for inhalation in patients with asthma. The medicinal product will be prescribed in the usual manner in accordance with the terms of the marketing authorization in the manner specified in the Summary of Product Characteristics.

Patient inclusion into the study is independent of the previous decision regarding treatment with **BUFOMIX EASYHALER®**. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current clinical practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures will be applied to the patients and epidemiological methods will be used for the analysis of the collected data.

### *3.1.1.Characteristics of the study population*

The study population will be adult patients (aged 18 years and over) of both sexes, diagnosed with asthma on the basis ICD-10 and who are not excluded from participating in the study. The subjects should be using **BUFOMIX EASYHALER®** for at least 14 days before enrollment.

### *3.1.2. Study design*

This study is an open-label, multicenter, non-interventional, post-authorization efficacy study.

## 3.2. Endpoints

Primary endpoint: the efficacy of the treatment with **BUFOMIX EASYHALER®** on the basis of ACT scale and spirometry results (if performed).

The secondary endpoint is the assessment of the patient compliance as well as the preferences of physicians in the treatment of asthma.

Severe adverse events should be reported to MBR Consulting or UPRL or Study Organizer via website **www.dzialanianiepozadane.com.**

## 3.3. Substantiation of the study construction

The study is a non-interventional observation study for assessment efficacy treatment with medicinal product **BUFOMIX EASYHALER®** and patient compliance and the preferences of physicians in the treatment of asthma that will be conducted in multiple medical centers in Poland. The follow-up of study subjects during three visits does not require any additional diagnostic and monitoring procedures. Study subjects will be monitored by completion of a questionnaire during their routine visits to the medical centers.

The aim of the study is the collection of data concerning efficacy of the treatment with medicinal products **BUFOMIX EASYHALER®** on the basis of ACT scale and spirometry results (if performed) in which the medicinal product **BUFOMIX EASYHALER®** is used in routine therapy as indicated and in accordance other information contained in the Summary of Product Characteristics.

Collection of such data in the population of Polish patients is very important from the scientific and practical point of view as the medicinal product **BUFOMIX EASYHALER®** containing budesonide and formoterol fumarate in the form of inhalation obtained permission of the marketing authorization in 2014. The data will be used for the needs of planned marketing campaigns, training staff and doctors.

The study will be conducted in 2500 patients with diagnosis of asthma treated with **BUFOMIX EASYHALER®** as a part of the routine therapy. Observation of efficacy from one patient will continue up to months (including the period of application of the drug before the first assessment), due to the chronic nature of therapy. During this time, centers collect data on the efficacy of the treatment, which will be recorded in the observational sheet. The observational sheet will also be recording data on the patient compliance. In addition, doctors fill in a questionnaire containing socio-demographic data and their preferences for the treatment of asthma. Observations sheet will then be returned to the Office Organizing the Study in aim to develop the report.

#### *3.3.1. Duration of the study*

Observation of patients during the study will take up to six months from the date of first assessment. Number of assessments will not affect or the number of visits or changes in the application of therapy in accordance with the criteria the Summary of Product Characteristics.

# 4. COMPLIANCE WITH TERMS OF GOOD CLINICAL PRACTICE, ETHICAL ISSUES AND INFORMED CONSENT TO PARTICIPATE IN THE STUDY

## 4.1. Compliance with terms of good clinical practice, and ethical issues

This is a non-interventional study, thus is not subject to the provisions of the Clinical Trial Directive, Directive 2001/20/EC of the European Parliament and of the Council of Europe of 4 April 2001.

The study will be conducted in accordance with current EU pharmaceutical legislation, the requirements laid down in EU Good Vigilance Practice (GVP Module VIII) and all applicable provisions of the local law.

## 4.2. Informed consent to participate in the study

The study is a non-interventional observation study which is being conducted with **BUFOMIX EASYHALER®** which is a medicinal product that has an existing marketing authorization in Poland. As this study is non-interventional, there is no requirement to acquire formal informed consent from study subjects under the current EU regulations and guidance regarding non-interventional post-authorization efficacy studies (PAES). However, study participants should give their agreement for information to be collected about their experience during the use of **BUFOMIX EASYHALER®**.

# 5. STUDY POPULATION

## 5.1 Records of participants in the study

Each Investigator will be required to keep a list of patients included in the study. The list should include the patient number and name, initials and date of birth, and must be kept confidentially at the study center.

The study is planned to include 2500 patients treated in Poland by 250 allergist and pulmonologist or doctors currently in course of obtaining these specializations. Each physician participating in the study should focus at at least 10 patients. Finally, the size of the study group will amount to 2500 patients.

**The selection of doctors:**

- Current license to practice
- Allergist or pulmonologist or doctors currently in course of obtaining these specializations leading treatment for an adequate number of patients meeting the eligibility criteria for testing under conditions of ambulatory health care.

Recruitment to participate in the study project is done by filling in and submitting the Application Form for study on the basis of which the qualification follows. Due to the limited number of investigators Europharma Maciej Rachtan Sp. J. stipulates that the inclusion in the study will be conducted on the first come, first served basis..

After the original research questionnaires along with the report are transferred to the organizer of the study - in special cases justified by the research need and if the investigator shows readiness to continue of the study (investigator will have a group of

patients who met the inclusion criteria) - the study may be continued by the researcher from the receipt of the original surveys from the Organizer of study.

## 5.2 Inclusion criteria

Each study participant must meet the following criteria:

- Adults patients of both sexes
- The diagnosis of asthma.
- The use of a novel combination therapy of budesonide/formoterol fumarate (**BUFOMIX EASYHALER®** 160 / 4.5 micrograms or 320 / 9.0 micrograms) at least 14 days before enrollment into the study.

The inclusion all participants in the study must be separated from the decision to prescribe treatment with medicinal product **BUFOMIX EASYHALER®** .

## 5.3. Exclusion criteria

Patients meeting the following criteria (partially in line with Summary of Product Characteristics) will not be included in the study:

1. Hypersensitivity to budesonide or formoterol or lactose.
2. The participation in other study.
3. Pregnancy, breast-feeding.
4. Unstable asthma defined as the use of oral steroids 3 times during the last year or hospitalization due to asthma in the last 6 months
5. Use of the combination budesonide / formoterol fumarate (**BUFOMIX EASYHALER®** 160 / 4.5 or 320 mg / 9.0 ug), less than 14 days before enrollment.
6. Patients of both sexes under the age of 18 years.

## 5.4. Procedures for treatment discontinuation or if the patient withdraws from the study

If the patient is excluded from the Study, the main reason for discontinuation will be recorded in the Study Questionnaire(SQ). Discontinuation from the study because of adverse effects must be adequately described in the patient records.

The investigator provides patients excluded from the study with adequate further treatment - personally or by another doctor with the existing documentation of the disease course.

# 6. METHODOLOGY

## 6.1. Schedule of the study

A summary of observations and assessments that will be conducted during the study is presented in the following table.

**Table1. Schedule of the project**

| Procedures for particular visits | visit 1 | visit 2* | visit 3* |
|---|---|---|---|
| Demographic data | X | | |
| Suitability of the patient for participating in the observational study (inclusion criteria) | X | | |
| History concerning co morbidities and their treatments | X | | |
| Comorbidities and their treatments | | X | X |
| History concerning course of primary disease treatment before using **BUFOMIX EASYHALER®** medicinal product | X | | |
| The dose of **BUFOMIX EASYHALER®** medicinal product used. | X | | |

| | | | |
|---|---|---|---|
| The evaluation of the efficacy treatment with **BUFOMIX EASYHALER®** on the basis of ACT scale and spirometry results (if performed). | X | X | X |
| Reporting adverse events related to **BUFOMIX EASYHALER®** use | X | X | X |
| The assessment of patients compliance on the basis of MAQ questionnaire | X | X | X |

*The visit will take place only if it is planned as a part of routine observation of the patient.

## 6.2. Visits in a specialist clinic under the study

### *6.2.1. Initial visit (Visit 1)*

The form filled in on this visit will be consist of two parts:

**A destined for the Doctor:**

- Doctor socio-demographic data: specialization, work experience, place of work and city in which they work
- Doctor preferences for the treatment of asthma

**B przeznaczonej dla Pacjentów:**

B destined for the Patient:

All patients that have been prescribed **BUFOMIX EASYHALER®** in accordance with the decision of the treating physician and in line with the conditions contained in the Summary of Product Characteristics, are eligible for inclusion in the study. In these patients the following information well be recorded in a Study Questionnaire (SQ):

- patient number
- patient initials
- demographic data
- concomitant diseases on the basis of medical records
- data regarding the duration of the disease, asthma control, pharmacotherapy scheme used previously and currently, duration of current pharmacotherapy
- data on pharmacotherapy of concomitant diseases
- determination of the inclusion and exclusion criteria
- data on the time when **BUFOMIX EASYHALER®** was used as well as its dose prior to enrollment
- assessment of the efficacy of the treatment
- data on adverse events related to treatment with **BUFOMIX EASYHALER®**
- assessment of the patient compliance on the basis of medication adherence questionnaire (MAQ).

### *6.2.2. Control assessments 2 and 3 (after 3 months from the previous assessment in accordance with the deadline resulting from the clinical needs of the patient)*

The assessments will take place as a part of the routine observation of the patient within the period of 6 months from the initiation of therapy with **BUFOMIX EASYHALER®** .

Patients data will be collected during two control visits. These assessments will be conducted in accordance with the plan as part of routine follow-up of the Patient and timed according to the individual clinical needs. During these assessments, the Investigators will collect and record in the IOF information on efficacy of treatment with **BUFOMIX EASYHALER®** on the basis of ACT scale and spirometry results (if performed), on the changes in pharmacotherapy

used in concomitant diseases treatment, and on the reported adverse events which are thought to be related to treatment with **BUFOMIX EASYHALER®** .

Obserwacja Pacjenta będzie trwała około 6 miesięcy.

# 7. ASSESMENT PERFORMED IN THE STUDY

Study project assumes assessing the efficacy of treatment with **BUFOMIX EASYHALER®** .

## 7.1. Endpoints and methods its evaluation

### *7.1.1. Efficacy*

Data on the current clinical status of the patient will be collected during the entire period of observation on the basis of research results.

The efficacy will be assessed on the basis of evaluation of changes in ACT scale and spirometry results (if performed).

### *7.1.2. Compliance*

On the basis of medication adherence questionnaire (MAQ).

# 8. STUDY DRUG

## 8.1. Administration of the drug

The drugs will be used based on a recommendation from the treating doctor, after the prescription is filed at the publicly pharmacy.

**Study drug**

Is a preparation containing active substances called budesonide and formoterol fumarate.

**CODE IN THE STUDY: BUFOMIX EASYHALER®**

Pharmaceutical form: inhalation powder of white to yellowish colour in a metered inhaler (Easyhaler).

Potency: 160 $\mu$g + 4,5 $\mu$g or 320 $\mu$g + 9 $\mu$g at an inhalable dose

Excipients: monohydrate lactose containing milk's protein

**Name and address of the manufacturer responsible for batch release:**

The company manufacturing pharmaceutical Orion Corporation, Orionintie 1, FI-02200 Espoo, Finland

**Description:** Multidose dry powder inhaler comprising seven plastic parts and springs made of stainless steel. Plastics used for the production of the inhaler include polybutylene, LDPE, polycarbonate, styrene-butadiene, polypropylene. The inhaler is sealed in the laminated bag and packed with or without protective packaging (polypropylene and thermoplastic elastomer) in a cardboard box.

**Packaging: BUFOMIX EASYHALER®**, (160 micrograms + 4.5 micrograms or 320 micrograms + 9 micrograms) / inhalation dose) powder for inhalation:

1 inhaler with 60 doses, 1 inhaler with 60 doses with the protective package 3 inhalers with 60 doses.

## 8.2. Identifications of patients

Throughout the duration of the study all of the included patients must be identifiable. The investigator will lead the list of the numbers of patients as well as their names and surnames, so that the records can be reached in the future, if necessary. Records of patients in the study must be stored on a confidential data at the site of examination.

Patient number will be assigned during the first assessment in accordance with the chronological order of inclusion in the study in the resort. Patients in the course of this study will be identified using a unique identification number. Patient number and center number will be recorded in the observation sheet.

Patients qualified for the study are not covered by randomization.

### 8.3 Drug delivery

Not applicable.

### 8.4 Concomitant medication

Data on other drugs used concomitantly with **BUFOMIX EASYHALER®** will be recorded in the Study Questionnaire(SQ) on every visit.

## 9. REPORTING RELATED ADVERSE EVENT

Reporting of related adverse events will be in accordance with applicable local legal regulations.

If there is a related adverse event the DRUG RELATED ADVERSE EVENT REPORT should be filled and sent to the MBR Consulting company or Study Organizer via website **www.dzialanianiepozadane.com**.

or

Department for Monitoring Adverse Action Medicines Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (URPL), Al. Jerozolimskie 181C, 02-222 Warszawa, tel.: + 48 22 49 21 301, faks: + 48 22 49 21 309, e-mail: ndl@urpl.gov.pl

Or Europharma

The procedure for reporting ADR will be carried out in accordance with the standards of GVP.

Reporting of adverse reactions associated with the use of **BUFOMIX EASYHALER®** will be carried out in accordance with the provisions of the Pharmaceutical Law in particular with art. 45 of the Act on professions of physician and dentist.

## 10. STATISTICAL CONSIDERATIONS

### 10.1. Patient classification and definition

Treated Patient: Patient who received at least one dose of the study drug.

### 10.2. Analysis, population, definition

The efficacy analyses on the basis ACT scale and spirometry results (if performed) will be performed in patients who participated in all assessments provided in study protocol.

### 10.3.The method of determining the sample size

This is anon-interventional PAES study in which about 2500 patients was determined as an appropriate sample size, taking into account some practical limitations, and not on the basis of statistical analysis. Therefore, this study will not form the basis for the formulation of definitive conclusions about the efficacy and safety of the study drug.

### 10.4. Statistical analysis

On the basis of evaluation of changes in the ACT scale and spirometry results (if performed) the efficacy of the used treatment will be assessed. Treatment tolerance will be assessed on the basis of reported adverse events.

Statistical analysis of the collected data will be carried out in accordance with the standards of the EU GCP / ICH.

Generally, all data will be summarized and presented using descriptive statistical methods. For analysis of changes in estimated parameters appropriate statistical tests will be applied depending on the distribution of the variables and their type (continuous, categorized).

#### *10.4.1. Demographic data and other basic characteristics*

Descriptive summary statistics (n, mean, standard deviation (SD), median, minimum, maximum) or frequency for demographic and basic characteristics data (medical history, co-morbidities, the primary disease diagnosis, previous treatment) will be presented.

### *10.4.2. Distribution of patients and cases of exclusion from the study*

The number of patients treated, the number of patients who discontinued treatment with the study drug, and the number of patients who participated in all of the study visits will be presented in the form of tables. The main reasons for patients' discontinuation from participation in the study will be presented in the form of tables.

### *10.4.3. The efficacy assessment*

Will be carried out on the basis of evaluation of changes in the ACT scale and spirometry results (if performed).

### *10.4.4. The safety assessment*

All adverse events will be coded in accordance with Medical Dictionary for Regulatory Activities (MedDRA).

All safety data will be included in the summaries of data on individual patients. Analyses and summary tables will be based on data from the study population taking into account the duration of exposure to the medicinal product under investigation.

The prevalence of all reported adverse events and serious adverse events occurring during the study will be presented in the form of tables. In addition, summary tables will be presented, that will include data on severity, relationship to the study drug administration and related data on adverse events, and patients who discontinued treatment with the study drug for any reason.

All adverse events occurring during the use of the study drug will be noted in the tables of adverse events. Other medications used to treat concomitant diseases will be summarized with the number and percentage of patients receiving concomitant medications and these patients will be grouped according to the pharmacological class of the medicine and International Non-proprietary Name (INN) of the drug.

**DEFINITIONS:**

By related side effect occurring during the study of the drug considered are any adverse events that occur Of the drug considered are during an active study phase if:

- it was not present prior to the first dose of study medication

or

- it was present prior to receiving the first dose of study drug, but its severity has been increasing during the observation.

The differences between the adverse event (AE) and adverse drug reaction (ADR) in accordance with the definitions of the Textbook of Pharmacoepidemiology 2013

Adverse event (AE) is defined as any untoward medical occurrence in a patient after drug administration, which does not necessarily have a causal relationship to treatment.

Adverse Drug Reaction (ADR) is defined as all harmful and unintended reactions to medicinal product occurring during his administration regardless of the dose. In the case of adverse drug reactions cause and effect relationship must be at least suspected by a physician.

### *10.5. Factors which may affect statistical analysis and modify the results of the study*

- failing to submit the patient to control assess,
- the discontinuation of study drug use for reasons other than adverse events,
- use other drugs during observation,
- omission by the investigator to answer some of the questions included in the survey,
- the lack of information about the fate of the patient in the event of failure to report on the control assessment.

### *10.6. Factors limiting the study*

Limitations result from the observation period (the length of exposure) for the investigational medicinal product.

Security analysis allows to evaluate the incidence of adverse drug reactions occurring in more than 1/1000 (very frequent, frequent and infrequent).

The obtained data will not allow a reliable assessment of rare and very rare adverse drug reactions. This does not exclude observable adverse drug reactions that occur with unknown frequency.

# 11. MONITORING PROCEDURES

The Investigator is responsible for the validation of all data collected in the center.

In this study patients should not be subjected to any additional diagnostic procedures and monitoring.

Completeness of the Study Questionnaire(SQ) will be checked at the Office of the Study Organizer and any missing or inconsistent data will be clarified with the Investigator by the people involved in data management.

# 12. MANAGEMENT OF THE STUDY

## 12.1. Inspections and audits

Not applicable.

## 12.2. The scope of the data collected

The investigator is required to record all the data relating to the procedures detailed in the Study Protocol, including use of the study drug in the SQ provided for the purpose of this study.

The Investigator is required to sign the page of the SQ relating to the completion of study and a certificate of study completion to prove that all entered data is accurate and complete.

Any corrections in the SQ and source documents must be placed in such a way that the original entries were still legible (strike-through single thin line). If the reason for the change is not obvious, this should be clearly stated.

## 12.3.Verification of source data

Not applicable.

## 12.4. Verification of data quality

The Study Questionnaires (SQ) will be transferred from the Study centers to the **Office of the Study Organizer** will be analyzed in terms of completeness, consistency, clarity and compliance with the Protocol.

If data elements are missing from the SQ, the Investigator should state the reason for the missing data or other deviations from the Protocol. The **Office of the Study Organizer** will communicate to the Investigator any questions regarding the processing of data and the points that have not been sufficiently explained, for the purpose of clarification or improvement. The Investigator must ensure that all requests for clarification of data are immediately addressed. The Investigator is obliged to keep copies of all data, including a record of all changes and clarifications with SQ.

## 12.5 Data management

Data management will be conducted by the Office of the Study Organizer.
All the procedures of data processing will be carried out in accordance with standard operating procedures of the Office of the-Study Organizer.
The Office of Study Organizer have an obligation to ensure that appropriate input methods (e.g. double data entry) are applied, and that all inquiries on missing or inconsistent data are addressed.
In addition, during the formation of the database will be included the rules for creating a database allowing to avoid mistakes during the statistical analysis, such as:

1. Entering data as numerical variables in all cases where this is possible.
2. Variable names are clearly described, so as not to raise questions during their use in statistical analysis.
3. One variable will be assigned to one column.

4. The data of each study subjects are entered in the same order as the recording method missing data will be consistent.
5. Each respondent will be given its own unique identification number.
6. The data of all respondents will be entered into a database.
7. The source will be introduced qualitative variables.
8. The project database prior to their introduction has been consulted with biostatistics.
9. The data will be made by one person, and then verified by a second.

The MAH and investigators should follow all relevant national legislation and guidance of those Member States where the study is being conducted [DIR Art 107m(2)]. The legislation on data protection should be followed in accordance with Directive 95/46/EC of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data.
All study information should be handled and stored so as to allow for accurate reporting, interpretation and verification of that information. The MAH shall ensure that the confidentiality of the records of the study subjects remains protected[DIRArt 36].

### 12.6. Committee for study management

Not applicable.

### 12.7. Archiving and storage of databases

The data will be stored for the period of availability of medicinal products **BUFOMIX EASYHALER®** on the Polish market + 5 years.

## 13. ADMINISTRATIVE PROCEDURES

### 13.1. Consent of the relevant authorities to carry out this study

In accordance with paragraph 36u of the Act No. 2 of 6 September 2001 r. on Pharmaceuticals and on Amendments to Some Related Acts (the Act on Pharmaceuticals), published in Journal of Laws 2001 No. 126, item 1381, The Study Protocol does not require approval from President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products and consent for conducting the study.

Ethics Committee approval is not needed for this study because it is a non-interventional study. Due to the same reason formal patient consent is not needed. However, the patient should be informed about the purpose of the study and agree to complete the questionnaire.

### 13.2. Study registration

The Study Organizer will request inclusion of the study information in the EU electronic register of post-authorization studies (EU PAS Register) maintained by the EMA and accessible through the European medicines web-portal (http:/encepp.eu/encepp_studies/indexRegister.shtml.

The study protocol will be entered in the register..

### 13.3. Rules on publication

No applicable.

### 13.4. The report on the study

The report on the study well be prepared by the Office of the Study Organizer.

### 13.5. Details concerning contracts and financing

Contracts with the Investigators will be concluded by the Office of the Study Organizer.

A list of all collaborating institutions and investigators will be made available to the Agency and national competent authorities upon request. Payments to healthcare professionals for participating in the study will be restricted to compensation for time and expenses incurred [DIR Art 107m(4)].

### 13.6. The insurance, taking responsibility and compensation

These will be in accordance with the provisions of applicable local law.

## 14. AMENDMENTS TO THE PROTOCOL

Amendments can be made by the Office of the Study Organizer in consultation with the Main Investigator and all substantial protocol amendments must be accompanied by a justification for the amendment and the impact on the PAES study subjects. The amendments should be approved by sponsor.

## 15. REFERENCES

1. Global strategy for asthma management and prevention. www.ginaasthma.com
2. Smoliński B, Sybilski AJ, Raciborski F, i wsp. Występowanie astmy oskrzelowej u dzieci, młodzieży i młodych dorosłych w Polsce w świetle badania ECAP. Alergia AstmaImmunologia 2009; 14: 27-34.
3. Clark NM, Cabana MD, Nan B, Gong ZM , Slish KK, Birk NA, Kaciroti N. The clinician-patient partnership paradigm: outcomes associated with physician communication behavior. ClinPediatr (Phila) 2008; 47: 49-57.
4. Hesselink AE, Penninx BW, Wijnhoven HA, et al. Determinants of an incorrect inhalation technique in patients with asthma orCOPD. Scand J Prim Health Care 2001; 19: 255-260.