CLINICAL TRIAL PROTOCOL

LDP0114

Study title:	Multicenter open-label randomized clinical trial of the efficacy and safety of Levopront® syrup 30 mg/5 ml in comparison with Libexin® 100 mg tablets in patients suffering from dry non-productive cough caused by acute upper respiratory infection
Study number:	LDP0114
Phase:	3
Study drug:	Levopront® (levodropropizine)
Indication:	Cough
Sponsor:	Dompé farmaceutici S.p.A.
Contact person:	Mauro P. Ferrari Via San Martino 12-12a 20122 Milano, Italy Tel +39 02 58383271
Protocol Version:	**2.0**
Amendment 1 date:	September 14, 2017
Prevail Version:	In the event of any inconsistencies between Russian and English version, the English version shall prevail

Protocol Version	Modification	Date
1.0	Final Version	*09-MAR-2016 (*as amended on *06-MAY2017)*
2.0	**Amendment 1:** to provide justification of the increasing of the patients number based on the results of the analysis, that showed lack of power due to lower efficacy rate in both treatment groups than had been projected initially**.** For this reason this analysis are considered interim analysis and an interim report will be issued to show these results. The full final report will be issued at the end of the study with the inclusion of the results of all patients.	*14-SEP-2017*

PAGE OF THE PROTOCOL APPROVAL

Signature _____ Date September 14, 2017
Mauro P. Ferrari, Early Clinical Development Manager
Dompé farmaceutici S.p.A.

Signature _____ Date 14 Sep 2017
Marcello Allegretti, ChemD – Chief Scientific Officer
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Signature _____ Date SEPTEMBER 14, 2017
Saibene Federico, MD – Dompé Medical Expert
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Signature _____ Date 21 Sep 2017
Natalia Vostokova, Chief Operating Officer
IPHARMA LLC

Signature _____ Date 21 Sep 2017
Julia Trakhtenberg, Medical Director
IPHARMA LLC

STATEMENT OF THE PRINCIPAL INVESTIGATOR

Site n° ☐☐	
Full name:	
I, the undersigned, hereby certify that I have read and understood the protocol. I agree to follow protocol LDP0114: "Multicenter open-label randomized clinical trial to assess the efficacy and safety of Levopront® syrup 30 mg/5 ml in comparison with Libexin® 100 mg tablets in patients suffering from dry non-productive cough caused by acute upper respiratory infection". I undertake to conduct the study in accordance with the requirements of Good Clinical Practice Guidelines of International Conference on Harmonization (ICH GCP) and Eurasian Economic Union (EAEU), principles outlined in the Declaration of Helsinki, and applicable regulations of Russian Federation.	
Date:	**Signature:**

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	Site 04: State Autonomous Healthcare Institution of Yaroslavl Region «Clinical Hospital of Emergency care n.a. N.V. Solovyev»	11, Zagorodny sad str., Yaroslavl, 150003, Russia
	Site 06: The Laboratory of Pulmonology, State Budgetary Educational Institution of Higher Professional Education «Moscow State Medical-Stomatological University n.a. A.I. Evdokimov» under Ministry of Health of the Russian Federation (Clinical base of state budget health care institution "City polyclinic № 62 Moscow Health Department" Branch number 5)	Legal address: 20/1 Delegatskaya str., Moscow, 127473, Russia Actual Address: 37 Ul. Planetarnaya, Russia

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	Site 09: State Budgetary Educational Institution of Higher Professional Education "Ryazan' State Medical University n.a. academician I.P. Pavlov" under Ministry of Health of the Russian Federation	9 Vysokovoltnaya str., Ryazan, 390026 Russia
	Site 10: «Institute of Medical Research» LLC	liter «A» 25, Koli Tomchaka str., Saint-Petersburg, 196084, Russia
	Site 14: LLC Treatment-and-prophylactic institution on the «Smolensk clinic»	Legal address: 39, 15th district, Smolensk region, Roslavl, Russia Actual address:1 Novoseltsi, str. Yubileynaya, Smolensk, 214016, Russia

SYNOPSIS

Sponsor:

Dompe farmaceutici S.p.A., Italy

Name of the investigated medicine:

Levopront®

Active Substance:

Levodropropizine

Trial Title:

Multicenter open-label randomized clinical trial to assess the efficacy and safety of Levopront® syrup 30 mg/5 ml in comparison with Libexin® 100 mg tablets in patients suffering from dry non-productive cough caused by acute upper respiratory infection

Trial ID:

LDP0114

Development phase: 3

Primary objective:

To assess the efficacy of Levopront® in comparison with Libexin® based on daytime cough resolution rate by Day 8.

The daytime cough symptoms resolution corresponds to 0 or 1 points on the "Six-point daytime and nighttime cough assessment scale".

Secondary objectives:

Treatment effect assessment in terms of the following efficacy and safety parameters:

- To assess the efficacy of Levopront® in comparison with Libexin® based on nighttime cough resolution rate by Day 8.
- Daytime and nighttime cough symptoms resolution according to "Six-point daytime and nighttime cough assessment scale" by Day 4.
- Change in severity and frequency of daytime and nighttime cough according to "Six-point daytime and nighttime cough assessment scale" on Day 4 and Day 8 from baseline on Day 1.
- Cough intensity change according to the visual-analogue scale on Day 4 and Day 8 from baseline on Day 1.
- Change of FEV1 on Day 8 from baseline values on Day 1.
- Rate of Adverse events (AE) and Serious Adverse Events (SAE) of the various severity according to subjective complaints, laboratory test results, physical examination, vital signs and spirometry

Rationale:

Levopront® is a medicinal product of Dompe farmaceutici S.p.A., Italy, authorized in European Union, and established within the past two decades as a reliable and safe cough treatment drug. The active ingredient (Levodropropizine) is a levorotary isomer of the dropropizine racemic mixture and it is registered as a non-narcotic anti-cough agent of predominantly peripheral action. Levodropropizine suppresses coughing by inhibiting the

stimulation of peripheral sensorial nerves and modulations of the neuropeptides involved in the coughing reflex. At the same time, it does not modify the spirometry parameters, the rheology of the bronchial secretion and the ciliary activity of the bronchial epithelium. Levodropropizine does not bind to beta-adrenergic, muscarine and opioid receptors, it does not have the affinity to H1-histamine and alpha-adrenergic receptors. The drug has less pronounced effect on the central nervous system, it has no effects on cardiovascular system and respiratory functional parameters, nor does it promote the development of drug dependence. The sedative effect of the drug is mild.

This Phase 3 clinical trial is designed to assess of the efficacy and safety of Levopront® (Levodropropizine) in a form of 30 mg/5 ml syrup in patients with non-productive cough caused by acute upper respiratory tract infection.

Study design:

The present study is a multicenter open-label randomized comparative Phase 3 clinical trial in parallel groups. The study will be conducted at 8 Russian sites.

A total expected number of enrolled patients is 184 (92 per each group).

Screening and randomization

At Visit 1, Day 1 after signing the Informed Consent Form, the patients will be screened for assessment of inclusion/exclusion criteria. Demography, medical history, and information on concomitant medications will be collected; physical examination, vital signs, weight and height measurements will be performed; blood and urine samples for laboratory tests will be collected; the cough severity and frequency rate will be assessed using the "Six-point daytime and nighttime cough assessment scale"; cough intensity will be assessed using the visual-analogue scale; ECG and spirometry will be performed (pre- and post-bronchodilator) along with the chest x-ray or fluorography. Women of childbearing potential will take the pregnancy test before conducting the chest x-ray or fluorography.

The patients who meet all inclusion/exclusion criteria will be randomized into two groups (in 1:1 ratio)

- Levopront® syrup 30 mg/5 ml — 10 ml t.i.d. for 7 days
- Libexin® 100 mg tablets — 1 tablet t.i.d. for 7 days

Study treatment period

The study drugs will be taken t.i.d. (with the interval of not less than 6 hours, between meals) during 7 days. The first study drug administration will be performed at the clinical site on the day of randomization; the last study drug administration will be performed in the evening before Day 8 (±1).

During the study treatment period, the patients will maintain a diary on a daily basis and fill in the daytime and nighttime cough severity frequency data, and intensity data, study drug dosing, concomitant medications and adverse events. The patients will be recommended to measure the body temperature twice per day: in the morning after waking up and in the evening before retiring to bed.

Patients will visit the clinical site on Days 4 and 8 for assessment of efficacy and safety parameters. Patients should bring the completed Diary and the unused study drug at each visit. During the visits, physical examination will be performed, vital signs will be assessed, cough severity and frequency assessment will be performed using the "Six-point daytime and nighttime cough assessment scale", and also cough intensity assessment will be performed using the visual-analogue scale. On Day 8, blood and urine samples for laboratory tests will be

collected, spirometry (without bronchodilator) will be conducted, and then the study treatment period will be completed. If necessary, the patients will continue treatment according to the local standards of medical care.

Follow-up period

On Day 10, patients will be contacted by the Investigator via the telephone to follow-up for possible adverse events. After that, the patient's participation in the study will be over.

Study population:

Patients from 18 to 65 years old with dry non-productive cough caused by acute upper respiratory infection.

The main inclusion/exclusion criteria:

Inclusion criteria:

1. Signed Informed Consent Form
2. Male or female aged from 18 to 65 (inclusive)
3. Dry non-productive cough as a symptom of acute upper respiratory infection (IDC codes J00-J06)
4. Daytime cough symptom score ≥ 3 points according to the "Six-point daytime and nighttime cough assessment scale"
5. Pre-bronchodilator FEV1 ≥ 70% of the predicted values, post-bronchodilator FEV1 increase of ≤ 12% or ≤ 200 ml compared to the baseline, FEV1/FVC (Tiffeneau index) ≥ 0.7
6. Patient's consent to follow the protocol procedures, including the completion of the patient's diary
7. Patient's consent to use the adequate contraception methods throughout the study period. The adequate contraception methods are the following:
   - Oral or transdermal contraceptives
   - Condoms or diaphragms (barrier method) with spermicide
   - Intrauterine contraceptive devices

Exclusion criteria:

1. Hypersensitivity or individual contraindications to Levodropropizine, Prenoxdiazine or additives of the study drug
2. Hereditary fructose intolerance, glucose-lactose malabsorption, lactase deficiency, sucrose-isomaltose deficiency
3. Tuberculosis, bronchial asthma, malignant tumors of lungs or bronchi, COPD, severe respiratory failure (cyanosis, need for respiratory support) or other lung pathology at screening or in history
4. Inhalation anesthesia within 3 months before screening
5. Smoking history of more than 10 pack-years
6. Previous use of cough medicines, ACE inhibitors or amiodarone within 30 days before screening. Concomitant use of sedative drugs in particularly sensitive individuals.
7. Contraindications or inability to perform spirometry

8. Necessity (in the Investigator's opinion) of prescribing mucolytic agents, expectorants, antibiotics or other medications prohibited by the protocol during the study
9. Excessive mucous excretion which (in the Investigator's opinion) could be a contraindication to prescribing anti-cough medicines; decreased mucociliary function (Kartagener's syndrome, ciliary dyskinesia)
10. Malignant tumors in the past 5 years (except for the basal cell carcinoma)
11. Serious cardiovascular disease at the moment or within 12 months prior to screening, including: Chronic heart failure class III or IV (according to the classification of the New York Heart Association), severe arrhythmias requiring treatment with antiarrhythmic drugs class Ia, Ib, Ic or III, unstable angina, myocardial infarction, heart surgery and coronary arteries, serious valvular heart disease, transient ischemic attack or stroke, uncontrolled hypertension with systolic blood pressure > 180 mmHg and diastolic blood pressure > 110 mmHg, pulmonary embolism or deep vein thrombosis
12. Gastric or duodenal ulcers, gastroesophageal reflux disease within a period of 12 months before screening
13. Systemic autoimmune disorders and connective tissue diseases that require (currently or previously) administration of systemic glucocorticosteroids, cytostatic medications or penicillamine
14. Signs of intensive non-controlled concurrent disease, including disorders of the nervous system, endocrine system, kidneys, liver or gastrointestinal tract, which (in the Investigator's opinion) could prevent the patient's participation in the study
15. History of alcohol or drug abuse at screening or in the past, which results in the inability of the patient to participate in the study at the Investigator's discretion
16. Taking part in another clinical trial or use of study drug within 30 days before screening
17. Pregnant or breast-feeding women or women planning pregnancy during the clinical trial; women of childbearing potential (including not sterilized operatively and in postmenopausal period of less than 2 years), not using appropriate methods of contraception
18. Inability to read or write; unwillingness to understand and follow the procedures of the study protocol; violation of the drug administration regimen or procedure execution that, at the discretion of the Investigator, can impact he results of the study or safety of the patient and interfere his further participation in the study; any other concomitant medical or serious mental conditions that make the patient unsuitable for participation in the clinical study, limit the validity of receiving an informed consent or may affect the patient's ability to participate in the study

Patient's withdrawal

The randomization procedure will be performed before the laboratory test results are available. In case of detecting significant abnormalities that in the Investigator's opinion interfere the patient's participation in the study, the patient should be withdrawn from the study.

Study drug, dosing and mode of administration:

1. Study drug: Levopront®

Active substance: Levodropropizine

Pharmacological class: peripheral cough suppressant

Pharmaceutical form: syrup 30 mg/5 ml

Dosing: orally 10 ml (60 mg) t.i.d. with intervals of not less than 6 hours (between the meals)

Package 220 ml brown glass bottle containing 200 ml of solution and closed with an HDPE child-proof cap, complete with an LDPE seal and a PP measuring cap.

Manufacturer: Dompe Farmaceutici S.p.A. (Italy)

2. Comparator product: Libexin®

Active substance: Prenoxdiazine

Pharmacological class: peripheral cough suppressant

Pharmaceutical form: 100 mg tablets

Dosing: orally 1 tablet (100 mg) t.i.d., no chewing

Package: 20 tablets in a blister, one blister per 1 carton

Manufacturer: Chinoin Pharmaceutical and Chemical Works Private CJSC (Hungary)

Concomitant and prohibited medications:

Patients may receive symptomatic treatment of the main disease.

For symptomatic treatment are permitted antipyretics - NSAIDs: Paracetamol (maximum single dose of 2 g, the maximum daily dose of 4 g); ibuprofen (200 mg 3-4 times a day), acetylsalicylic acid (a single dose of 0.5-1 g, maximum single dose of 1 g, the intervals between doses of the drug for at least 4 hours, the maximum daily dose of 3 g). To improve nasal breathing may be used vasoconstrictor nasal drops and sprays. In case of appearing of any symptoms of laryngotracheitis it is permitted to use local antiseptics.

The decision on the appointment of concomitant therapy in each case takes the Investigator.

The patients will take the etiotropic and pathogenetic therapy of the main disease.

Patients will not take antibiotics, mucolytics and expectorants, antiviral drugs (except Arbidol®); combined "anti-commoncold" drugs; antihistamines; drugs that have a sedative effect and reinforcing the depressive effect on the central nervous system, as well as other cough suppressants, except for the study drugs.

Duration of the study:

Each patient's study participation will last for approximately 10 days and include the following stages: screening and randomization (Day 1), study treatment period (7 days), follow-up period (2 days).

The first part of the study started on 09 November 2016 (First Visit First Patient) and it has been completed on 27 April 2017 (Last Visit Last Patient). For the second part of the study, the start of patient enrollment is expected in November, 2017 and the completion of the study visits in February 2018.

Efficacy Endpoints

The primary efficacy endpoint is the rate of patients responded to the treatment — daytime cough symptoms resolution — by Day 8. The daytime cough symptoms resolution corresponds to 0 or 1 point according to the "Six-point daytime and nighttime cough assessment scale".

The secondary efficacy endpoints include:

- Rate of patients responded to the treatment — nighttime cough symptoms resolution — by Day 8.
- Rate of responders with daytime and nighttime cough symptoms resolution according to the "Six-point daytime and nighttime cough assessment scale" by Day 4.
- Mean change in cough severity and frequency according to the "Six-point daytime and nighttime cough assessment scale" on Day 4 and 8 from baseline on Day 1.
- Mean change in cough intensity according to the visual-analogue scale on Day 4 and 8 from baseline on Day 1.
- Mean change of FEV1 on Day 8 from baseline on Day 1.

Safety assessment

The safety will be evaluated based on the rate of AE and SAE of different severity according to the data from subjective complaints, laboratory testing results, physical examination, vital signs and spirometry.

Statistic methods:

Efficacy analysis

Per-protocol population analysis (PP) includes all randomized patients completing treatment with the study drug, having primary efficacy analysis assessment done and considered to be compliant. PP population will be the primary population for efficacy analysis[22].

The primary objective is to demonstrate the "non-inferiority" of Levopront® comparing to Libexin® with regards to the primary endpoint. For this purpose, the 97,5% one-sided Confidence Interval (CI) will be calculated for the two proportions difference — the rate of patients who responded to treatment by Day 8 in the study treatment group and in the control group with a non-inferiority margin of $\delta = 20\%$. The null hypothesis (H_0) that in the study treatment group the rate of treatment responders is less than in the control group, will be declined if the lower bound of the 97,5% one-sided CI for the two proportions difference is located to the right of the -0.20, with the final conclusion of non-inferiority of Levopront® versus Libexin®.

For the secondary efficacy endpoints analysis, the descriptive statistic methods will be used along with calculating the 95% CI and independence testing. To compare the dynamic changes of the parameters obtained for the study groups, independent samples T-test will be used.

Safety analysis:

All patients who receive at least one dose of the study drug will be included into the safety population.

The number and percentage of the patients with AE and SAE for every treatment group (along with the total numbers) will be summarized in tables by system organ class and preferred term, relationship to the study drug and severity; the laboratory results will be summarized in tables with change from baseline. The vital signs, laboratory and spirometry results will be summarized by means of descriptive statistics.

Distribution of patients, demographic and baseline characteristics:

Distribution of patients, demographic and baseline characteristics will be presented using descriptive statistics. Number and percent of patients taking concomitant medications will be presented in frequency tables by the therapeutic class and name of active substance. Number of patients with preceding medical conditions will be presented. Information about dosing, including daily dose, exposure period and total dose will be presented descriptively in each treatment group.

Sample size:

The sample size is calculated for the primary efficacy endpoint - the proportion of patients with response to therapy (daily cough symptoms permission to visit Day 8), and the non-inferiority hypothesis to the efficacy.

The sample size estimation in the protocol amendment is based on the results of the study interim analysis that showed approximately 70% efficacy in both groups vs. 80% efficacy that had been projected initially. Thus the interim analysis at $\alpha = 0.05$ (one-sided) showed lack of power for the hypothesis testing (< 80%).

In order to achieve power 80%, with corrected $\alpha = 0.025$ (one-sided)[20,21], expected efficacy rate of 70% in both groups, non-inferiority margin $\delta = 20\%$, and ED rate not exceeding 10%, 184 patients should be enrolled in the study at 1:1 ration (92 patients per treatment group).

Assuming the screen-failure rate of about 20%, up to 230 patients will be screened in the study.

Randomization:

Patients will be randomly assigned into two equal groups (at 1:1 ratio). Randomization will be conducted with the use of Interactive Web Response System (IWRS).

Number and version date of the protocol:

Protocol LDP0114, Final Version 2.0 (Amendment 1) dated September 14, 2017

Table of Contents

TABLES

FIGURES

ABBREVIATIONS AND TERMS DEFINITIONS

ADR	Adverse drug reaction
AE	Adverse events
ALT	Alanine transaminase
ARVI	Acute respiratory viral infection
AST	Aspartate transaminase
BA	Bronchial asthma
BMI	Body mass index
BP	Blood pressure
CI	Confidence Interval
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CPK	Creatine phosphokinase
CRF	Case report form
CVS	Cardiovascular system
ECG	Electrocardiogram/electrocardiography
ED	Early discontinuation (early discontinuation visit)
ESR	Erythrocyte sedimentation rate
ET	End of treatment
ETV	Early Termination Visit
FEV1	Forced expiratory volume per 1 second
FS	Food Supplement
FVC	Forced vital capacity
GGT	Gamma-glutamyl transferase
GI tract	Gastro-intestinal tract
HDPE	High density polyethylene
HR	Heart rate
ICD	International Classification of Diseases
IEC	Independent Ethics Committee (local)
IP	Investigational product
IWRS	Interactive Web Response System
LDPE	Low density polyethylene
MoH RF	Ministry of Healthcare of the Russian Federation
NSAID	Non-steroid anti-inflammatory drugs
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Polypropylene
RBC	Red blood cells
RR	Respiration rate
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SOP	Standard Operation Procedures
TC	Telephone contact
WBC	White Blood Cells
WHO	World Health Organization

1 INTRODUCTION

1.1 Acute respiratory infections of upper airways

According to International Classification of Diseases, 10th revision (ICD-10) acute respiratory infections of upper airways belong to class X, Diseases of the Respiratory System. In routine practice, the most common diagnosis corresponding to that complex of symptoms is acute respiratory viral infection (ARVI). ARVIs are clinically and morphologically similar acute inflammatory respiratory diseases caused by pneumotropic viruses. The epidemiology of ARVI is characterized by broad global incidence and includes influenza, para-influenza, respiratory syncytial infection, rhinoviral and adenoviral infections, and other catarrhal inflammations of upper respiratory tract.[1]

Clinical signs of ARVI include typical symptoms, including nasal congestion, rhinorrhea, sneezing, throat ache and cough. Cough is one of the most common reasons for seeking outpatient medical aid. With estimated annual incidence of respiratory infections of 27.3 – 51.2 mln cases, approximately ½ of patients of that numerous population seek medical aid for their cough symptoms.[2]

In clinical practice cough is often classified depending on the underlying cause. Therefore high diagnostic value is attributed to information about the time of cough onset, its productivity, and related symptoms.

The commonest causes of acute non-productive cough include ARVI, acute bacterial sinusitis, complications of chronic bronchitis, allergic rhinitis, pertussis.

Cough associated with colds is generally caused by mechanic irritation of respiratory areas with secretions from upper airways (postnasal drip, sneezing). Cough may be of significant duration because of developing bronchial hyperreactivity. Moreover, acute cough may be a symptom of a more serious disease – pneumonia, cardiac failure, pulmonary artery thromboembolia (present in almost half of all cases, and being the sole respiratory symptom in individual patients), aspiration.[3]

1.2 Medical Therapy of Acute Non-Productive Cough in Acute Respiratory Infections of Upper Airways.

After the nature of cough is determined, etiotropic or pathogenetic treatment of the underlying disease should be initiated. Concurrently symptomatic treatment of cough may be administered, with either antitussive agents, i.e. those preventing, managing and inhibiting cough; or expectorants (protussive) agents, providing more effective cough.

Antitussive agents are recommended in cases when cough does not lead to clear airways. Possible measures include specific antitussive therapy, etiotropic or pathogenetic in nature (smoking cessation, removal of causes of postnasal drip). Non-specific antitussive therapy is rather symptomatic and is of limited use because of high probability of determining the cause of cough and initiation of targeted treatment.[3]

1.3 Development of Levopront ®

Levopront® is a drug of Dompe farmaceutici S.p.A., Italy, authorized in European Union, and established within the past two decades as a reliable and safe cough agent. The active ingredient (Levodropropizine) is a levorotary isomer of the dropropizine racemic mixture, and it is registered as a non-narcotic anti-cough agent of predominantly peripheral action. Levodropropizine suppresses coughing by inhibiting the stimulation of peripheral sensorial nerves and modulations of the neuropeptides involved in the coughing reflex. At the same time, it does not modify the spirometry parameters, the rheology of the bronchial secretion and the ciliary activity of the bronchial epithelium. Levodropropizine does not bind to beta-adrenergic,

muscarine, and opioid receptors, it does not have the affinity to H1-histamine and alpha-adrenergic receptors. The drug has less pronounced effect on the central nervous system, it has no effects on cardiovascular system and respiratory functional parameters, nor does it promote the development of drug dependence. The sedative effect of the drug is mild.

This Phase 3 clinical trial is designed to assess the non-inferiority of the efficacy and safety of Levopront® (Levodropropizine) 30 mg/5 ml syrup in patients with non-productive cough associated with acute upper respiratory tract infection.

2 CLINICAL STUDY OBJECTIVES

2.1 Primary objective

To assess the efficacy of Levopront® in comparison with Libexin® based on daytime cough resolution rate by Day 8.

The daytime cough symptoms resolution corresponds to 0 or 1 points on the "Six-point daytime and nighttime cough assessment scale".

2.2 Secondary objectives

Secondary objectives of the study include treatment effect assessment in terms of the following efficacy and safety parameters:

- To assess the efficacy of Levopront® in comparison with Libexin® based on nighttime cough resolution rate by Day 8.
- Daytime and nighttime cough symptoms resolution according to "Six-point daytime and nighttime cough assessment scale" by Day 4.
- Change in severity and frequency of daytime and nighttime cough according to "Six-point daytime and nighttime cough assessment scale" on Day 4 and Day 8 from baseline on Day 1.
- Cough intensity change according to the visual-analogue scale on Day 4 and Day 8 from baseline on Day 1.
- Change of FEV1 on Day 8 from baseline values on Day 1.
- Rate of Adverse events (AE) and Serious Adverse Events (SAE) of the various severity according to subjective complaints, laboratory test results, physical examination, vital signs and spirometry.

3 STUDY DESIGN

3.1 Overall Study Design and Schedule

This is a multicenter open-label randomized comparative Phase 3 clinical trial in parallel groups. The study will be conducted at 8 Russian sites. The total expected number of enrolled patients is 184 (92 per each group). Taking into account the possibility of 20% screen-failure rate, up to 230 patients will be screened in the study.

3.1.1 Study Design

The study will consist of 3 periods: screening and randomization, study therapy, follow-up.

3.1.1.1 Screening and Randomization.

At Visit 1, Day 1 after signing the Informed Consent Form, the patients will be screened for assessment of inclusion/exclusion criteria. Demography, medical history, and information on concomitant medications will be collected; physical examination, vital signs, weight and height measurements will be performed; blood and urine samples for laboratory tests will be collected; the cough severity and frequency rate will be assessed using the "Six-point daytime and nighttime cough assessment scale"; cough intensity will be assessed using the visual-analogue scale; ECG and spirometry will be performed (pre- and post-bronchodilator) along with the chest x-ray or fluorography. Women of childbearing potential will take the pregnancy test before conducting the chest x-ray or fluorography.

According to the study schedule (considering acute condition of patients), screening and randomization will be performed in one day. Patients meeting all inclusion/exclusion criteria will be randomized into two groups (at a 1:1 ratio)

- Levopront® syrup 30 mg/5 ml — 10 ml t.i.d. for 7 days
- Libexin® 100 mg tablets — 1 tablet t.i.d. for 7 days

3.1.1.2 Study Treatment Period

The study drugs will be taken 3 times a day (with the interval of not less than 6 hours, between meals) during 7 days. The first study drug administration will be performed at the clinical site on the day of randomization; the last study drug administration will be performed in the evening before Day 8.

During the study treatment period, patients will keep a diary on a daily basis and fill in the cough severity and frequency data, body temperature, study drug dosing, concomitant medications and adverse events. Cough severity and frequency assessment should be performed in the morning after waking up using the "Six-point daytime and nighttime cough assessment scale" provided in the Diary and in the evening before retiring to bed. Patients will visit the clinical site on Days 4 and 8 for assessment of efficacy and safety parameters. Patients should bring the completed Diary and the unused study drug at each visit. During the visits, physical examination will be performed, vital signs will be assessed, cough severity and frequency assessment will be performed using the "Six-point daytime and nighttime cough assessment scale", and also cough intensity assessment will be made using the visual-analogue scale. On Day 8, blood and urine samples for laboratory tests will be collected, spirometry (without-bronchodilator) will be conducted, and then the study treatment period will be completed. If necessary, patients will continue treatment according to the local standards of medical care.

3.1.1.3 Follow-up Period

On Day 10, patients will be contacted by the Investigator via the telephone to follow-up for possible adverse events. After that, the patient's participation in the study will be over.

3.1.1.4 Study Diagram and Study Procedure Schedule

The summary of the study design and the study schedule are reported in Figure 1 and table 1, respectively

Figure 1. Study Diagram.

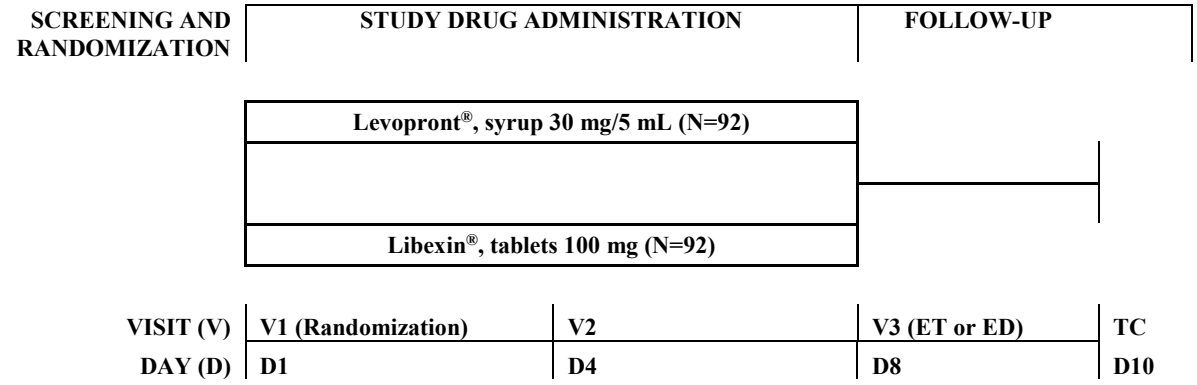

Table 1 Study Procedure Schedule, Protocol LDP0114

	Screening and randomization	Study treatment		Follow-up
Visit (V)	**V1**	**V2**	**V3 ET or ED**	**TC**
Day (D)	**D1**	**D4**	**D8**	**D10**
Visit window		**± 1 day**	**± 1 day**	**± 1 day**
Informed consent	☒			
Patient's registration	☒			
Demography data	☒			
Medical history	☒			
Physical examination	☒	☒	☒	
Vital signs	☒	☒	☒	
Body height and weight[5]	☒			
Cough severity and frequency assessment with the "Six-point daytime and nighttime cough assessment scale"	☒	☒	☒	
Cough intensity assessment with the visual-analogue scale.	☒	☒	☒	
Laboratory testing:				
- hematology	☒		☒	
- biochemistry	☒		☒	
- urinalysis	☒		☒	
- pregnancy test[1]	☒		☒	
ECG	☒			
Spirometry[2]	☒		☒	
Chest X-ray or fluorography[3]	☒			
Inclusion/exclusion criteria	☒			
Randomization[4]	☒			
Study drug and Patient's dairy distribution to patient[4]	☒	☒		
Return and accountability of the study drug, Patient's dairy review		☒	☒	
Concomitant medications assessment	☒	☒	☒	
AE assessment	☒	☒	☒	☒

Abbreviations: ET — end of treatment, ED — early discontinuation, ECG — electrocardiography, AE — adverse events, TC – telephone contact

Footnotes:

[1] Pregnancy test will be performed at the clinical site using the test-strip (only for the women of childbearing potential including the women in menopause of less than two years) before chest x-ray of fluorography.

[2] At visit Day 1 pre- and post-bronchodilator spirometry will be performed. At visit Day 8 only pre-bronchodilator spirometry will be performed.

[3] Results of the chest x-ray or fluorography performed before signing the Informed Consent Form as a part of routine patient's examination for main disease (ARVI) can be used for the protocol purposes (if written conclusion report is available).

[4] Patient's randomization and distribution of the study drug to the patient (along with the Patient's dairy) on Day 1 will be performed only after assessment of all inclusion/exclusion criteria. The first dose of the study drug will be taken at the clinical site.

[5] The growth measure should be performed only during screening visit. For calculated values of lung function growth measured only at screening and weight measured during screening and Visit 3 (Day 8) should be used.

3.2 Justification of Study Design

This is an open-label randomized comparative clinical trial of the efficacy and safety of Levopront®, syrup 30 mg/5 mL and Libexin®, tablets 100 mg in patients with dry non-productive cough associated with acute respiratory infection of upper airways.

Patients from reference group will receive Libexin ®. The choice of Libexin® is based on the similarity of its mechanism of action (it is a peripheral antitussive drug) and on the fact that it belongs to the same group in the International anatomical therapeutic chemical classification. Open design was chosen because of differences in the pharmaceutical forms of the investigational drugs and technical problems with blinding process of investigational products.

Study population includes patients with dry non-productive cough associated with non-complicated acute respiratory infection of upper airways. At Visit 1, Day 1 patients meeting inclusion/exclusion criteria will be enrolled into the study. During that period patients will receive either Levopront®, syrup 30 mg/5 mL or Libexin®, 100 mg tablets along with standardized concomitant treatment allowed by this protocol for 7 days, if necessary. Patients will keep a diary where they will record their condition using a "Six-point daytime and nighttime cough assessment scale". Assessment of the cough intensity with the visual-analogue scale will be done on each visit of the patients at the clinical site.

Patients with severe and chronic diseases of the respiratory system, burdened with smoking anamnesis, as well as patients who have indicated administration of the antibacterial therapy will not be included in the study.

Study drug dosing regimen and treatment duration of 7 days were chosen according to the European label. The treatment duration is necessary and sufficient to establish control over efficacy of antitussive therapy (frequency of resolution of cough symptoms) in acute respiratory infections of the upper respiratory tract. The intermediate evaluation of the efficacy will be held on Day 4.

The proportion of patients who responded to treatment, i.e. daytime cough symptoms resolution by Day 8 Visit was chosen as the primary efficacy endpoint. Resolution of daytime cough symptoms corresponds to score 0 or 1 at the Six-point daytime and nighttime cough assessment scale. The choice of primary and secondary study endpoints was based on WHO recommendations[15], national guidelines “Pulmonology. National Guidelines”, concise edition/ed. By A.G. Chuchalin. - M. : GEOTAR-Media, 201410, Guidelines for clinical trials ed. by A.N. Mironov[7].

Besides the study will assess secondary efficacy endpoints according to spirometry, Diary and visual-analog scale. At the end of treatment, all patients will undergo a three-day follow-up period to assess the safety parameters.

The sample size is calculated for the primary efficacy endpoint - the proportion of patients with response to therapy (daily cough symptoms to visit Day 8), and the non-inferiority hypothesis to the efficacy[19,22].

The aim of this amended protocol is to provide justification of the increasing of the patients number in this study based on the results of the analysis, planned by the original protocol (Final version 1.0), that showed lack of power due to lower efficacy rate in both treatment groups than had been projected initially.

For this reason this analysis are considered interim analysis and an interim report will be issued to show these results. The full final report will be issued at the end of the study with the inclusion of the results of all patients.

The sample size estimation in the protocol amendment is based on the results of the study interim analysis that showed approximately 70% efficacy in both groups vs. 80% efficacy that had been projected initially. Thus the interim analysis at $\alpha = 0.05$ (one-sided) showed lack of power for the hypothesis testing (< 80%).

In order to achieve power 80%, with corrected $\alpha = 0.025$ (one-sided), expected efficacy rate of 70% in both groups, non-inferiority margin $\delta = 20\%$, and ED rate not exceeding 10%, 184 patients should be enrolled in the study at 1:1 ration (92 patients per treatment group).

This approach complies with the general considerations for sample size re-estimation study designs (adaptive design used in both efficacy and BE studies). The alpha correction will provide the additional control over the type I error[20,21].

3.3 Study Duration and Dates

The duration of participation of each patient in the study will be approximately 10 days and will include: screening and randomization (1 day), study treatment (7 days, including the day of randomization), follow-up (3 days).

The first part of the study started on 09 November 2016 (First Visit First Patient) and it has been completed on 27 April 2017 (Last Visit Last Patient). For the second part of the study the start of patient enrollment is expected in November, 2017 and the completion of the study visits in February 2018.

3.3.1 Preclinical Trials

Investigational studies of general toxicity (acute, subacute, chronic) of finished pharmaceutical form of Levopront® have shown that the drug at acute and chronic experimental conditions (3 months) does not exhibit toxic effects in warm-blooded laboratory animals (rodent and non-rodent species – rabbits), including at the stage of development. It is of note that planning and conduct of the study strictly met Russian MoH requirements and international standards in the field of preclinical study of safety of new pharmacological drugs – GLP (Good Laboratory Practice).

Results of toxicometry, data of observations of test animals in postintoxication period of acute poisoning, and necropsy data suggest that Levopront (Levodropropizine syrup) belongs to class VI of relatively innocuous drugs (H. Hodge et al. Clinical Toxicology of Commercial Products. Acute Poisoning. Ed. IV, Baltimore, 1975, 427 p.; K.K. Sidorov, 1973).

Condition of animals after acute intoxication suggests its good tolerability at doses exceeding human therapeutic doses (approximately 0.5 mL/kg) by several ten-fold.

Subacute (30 days) daily intragastric administration of Levopront in sexually immature animals (rats, rabbits) and chronic (90 days) daily intragastric administration of Levopront in mature animals (rats, rabbits) had not harmful effects on the key adaptive systems (nervous, cardiovascular, hematopoietic, excretory, respiratory), metabolism, general condition and development, key hemostatic body parameters.

A lack of irritating effects on GI tissues should also be noted. It applies both to rodent and non-rodent species, suggesting of universal nature of innocuous properties of the drug.

The drug has shown to be free of allergenic potential.

According to Classification of hazardous drugs for clinical use (SI > 5) Levopront® belongs to class III of low toxic (low hazardous) drugs.

Results of Levopront ® toxicity tests in sexually immature animals supported its safety in pediatric population.

Key pharmacokinetic parameters were defined, and analysis of pharmacokinetic response after oral administration of Levorpont® to dogs was performed. No evidence of drug accumulation in the body and possible cumulative effects were observed.

Results of investigation of safety of Levopront (Dompe farmaceutici S.p.A., Italy) support low toxicity of the drug both in adult and pediatric populations.

3.3.2 Clinical Trials

Efficacy:

The administration of levodropropizine has been associated in all studies with a statistically significant decrease in cough starting from the first day of treatment, a finding that confirms that results may not be attributed to the natural course of the disease.

Moreover, the observed statistically and clinically significant reduction in the number of cough-related night awakenings following levodropropizine treatment should translate into a better quality of life, both in children and in adults, particularly in neoplastic patients.

The magnitude of the drug's antitussive effect has been shown to be superimposable among the different underlying disease groups. This represents an advantage for the drug since use is not to be limited to specific etiologic diseases with non-productive cough, but can be extended to any lower and upper respiratory tract diseases, to cough associated with asthma, neoplasia, whooping cough (pertussis), cardiac cough, and can also be used in the prevention of cough during and after surgical interventions or fiberbronchoscopy.

Types of diseases covered in the conducted trials can be considered representative of those present in the population that will receive cough-suppressing agents in clinical practice.

Controlled studies, both placebo- and active-control, have shown levodropropizine to be more active than placebo and equally effective than tested reference drugs (i.e. dextromethorphan, clobutinol, dropropizine; dihydrocodeine, cloperastine and morclofone) in reducing the frequency of cough as measured by the number of coughing spells in the post-treatment period in adult patients. Levodropropizine was also shown to be clinically as effective as dihydrocodeine in reducing the cough associated with thoracic neoplasia (particularly persistent, invalidating cough, resistant even to radiotherapy).

In children, efficacy has been demonstrated both in a dose-finding study and in comparative and/or open-label clinical studies on a total of 608 subjects receiving levodropropizine.

Finally, the results of a meta-analysis, carried out on an ITT sample rigorously selected across trials, and through appropriate patient stratifications, have confirmed the lack of influence of cough etiology or patients age on the efficacy of the medication.

The level of clinical efficacy and substantial benefit from levodropropizine treatment has been recognized by the reference medical community and this is reflected in the article "Cough Suppressant and Pharmacologic Protussive Therapy: ACCP Evidence-Based Clinical Practice Guidelines" published in Chest (Bolser, 2006), where the drug is recommended as the treatment of choice, amongst the peripheral cough suppressants, for the short-term symptomatic relief of cough in patients with chronic or acute bronchitis.

Safety:

The safety of levodropropizine has been studied in clinical pharmacology and clinical studies comprising 107 healthy volunteers and 2868 patients, 788 of whom were under 14 years of age.

Out of the 2868 subjects exposed to 1-22 days of levodropropizine in clinical studies, suspected ADRs have been reported in as few as 60 patients (2.1%) without any excess risk for paediatric patients.

Amongst the reported ADRs, CNS effects, such as cephalalgia, somnolence, fatiguability/asthenia accounted for 25 events (0.9%); gastrointestinal events, such as nausea, diarrhoea, abdominal cramps, pyrosis/dyspepsia, gastralgia and vomiting for 31 events (1.1%). In 1 case dyspnea was reported, but the relationship to levodropropizine administration was not assessed.

Allergic reactions were evident in 7 cases. Cardiovascular organ system was involved in 3 cases with palpitations and in 1 case with precordial pain; in none of these cases was a relationship to study drug considered.

Tolerability data from clinical studies confirm results from animal experiments with regard to the lack of CNS effects of levodropropizine. Indeed, no changes in the EEG pattern or significant modifications of the psychomotor performance have been observed. Comparative clinical studies have shown that the frequency of somnolence reported with the reference drugs (dihydrocodeine, dextromethorphan, clobutinol, dropropizine) was more than double that reported with levodropropizine, and at times statistically significant

Neither age nor concomitant therapies did modify the safety profile, even when benzodiazepines were concomitantly administered (Bejor et al., 1988; Arrigo et al., 1988; Bejor et al., 1990; Fiocchi et al., 1989; 1991).

As levodropropizine does not interfere with the respiratory center and with the clearance capacity of the lung, drug administration can be considered safe also in patients with severe respiratory insufficiency (Bossi et al., 1988).

Results from special population studies, such as mild to moderate renal impaired and hepatic impaired patients, do not contraindicate the use of levodropropizine in such patients. Post marketing studies and spontaneous reporting confirmed the frequency and type of AEs observed in clinical trials.

3.3.3 Risk/Benefit Analysis

This study is aimed at collecting data on efficacy and safety of Levopront ® in patients with acute non-productive cough associated with acute respiratory infection of upper airways. It is suggested that study subjects receiving Levopront® for 7 days could be achieved a high frequency resolution of cough due to stimulation of peripheral ends of sensitive nerves and modulation of neuropeptides involved into the cough reflex.

According to results of previous preclinical trials, Levopront® was free of allergenic, immunotoxic, cancerogenic, mutagenic potential, did not affect respiratory, cardiovascular, urinary system, blood hematology and biochemistry parameters.

Preclinical studies have shown that the drug , both in terms of acute administration, and prolonged use for 3 months did not have a toxic effect on the body of warm-blooded laboratory animals (rodents and non-rodents - rabbits) , including on growing organisms.

In bioequivalence studies of two pharmaceutical forms of levodropropizine, the drug demonstrated good tolerability and safety at single doses.

Efficacy and safety of levodropropizine was also evidenced in multiple Phase II and III trials, including studies in pediatric populations.

3.3.4 Significant Potential Risks

Levopront® is a drug of Dompe Farmaceutici S.p.A., Italy, authorized in European Union and in extra European countries (Brazil, Mexico, Chile Columbia, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Indonesia, Nicaragua, Panama, Philippines, Thailand, Venezuela, Turkey, South Korea), and established within the past two decades as a reliable and safe cough agent. Potential risks (known side effects) of Levopront® include:

Eye disorders: Mydriasis, bilateral blindness.

Immune system disorders: Allergic and anaphylactoid reactions, eyelid edema, angioneurotic edema, urticaria.

Psychiatric disorders: Nervousness, drowsiness, personality change, or personality disorder.

Nervous system disorders: Syncope, dizziness, vertigo, tremor, paraesthesia, tonic-clonic seizures and attacks of petit mal, hypoglycemic coma.

Cardiac disorders: Palpitations, tachycardia, atrial bigeminy.

Vascular disorders: Hypotension.

Respiratory, thoracic and mediastinal disorders: Dyspnea, cough, edema of the respiratory tract.

Gastrointestinal disorders: Gastric pain, abdominal pain, nausea, vomiting, diarrhea.

Hepatobiliary disorders: Cholestatic hepatitis.

Skin and subcutaneous tissue disorders: Urticaria, erythema, rash, pruritus, angioedema, skin reactions, aphthous stomatitis and glossitis. Epidermolysis.

Musculoskeletal and connective tissue disorders: Weakness of the lower limbs.

General disorders and conditions regarding the side of administration: General malaise, generalized edema, asthenia.

Preclinical study results have shown that the drug after acute and chronic dosing for 3 months has no toxic effects in warm-blooded laboratory animals (rodent and non-rodent species – rabbits), including developing organisms.

Potential risks of Libexin® include: hypersensitivity reactions: bronchospasm, skin rash, angioedema; GI tract disorders: dry mouth and throat, transient numbness and loss of sensitivity of the oral mucosa, stomach ache, predisposition to constipations, nausea; nervous system disorders: light sedative effect, fatigue (sedative effect and fatigue are observed at doses exceeding therapeutic, and all symptoms spontaneously resolve within several hours after drug discontinuation).

The study will include only the patients who agree to use adequate contraception measures for the whole study period.

Particular attention in the study will be paid to adverse events on the part of essential organs according to subjective complaints, physical examination, vital signs, laboratory test results, and ECG.

4 SELECTION OF STUDY POPULATION

4.1 Study population

Patients from 18 to 65 years old with dry non-productive cough associated with acute respiratory infection of upper airways. Up to 230 patients will pass screening procedures to randomize 184 patients into one of two study groups at a ratio of 1:1

- Levopront® syrup 30 mg/5 ml — 10 ml t.i.d. for 7 days
- Libexin® 100 mg tablets — 1 tablet t.i.d. for 7 days

4.2 Inclusion Criteria

Subjects should meet the following inclusion criteria to be included into this clinical trial:

1. Signed Informed Consent Form
2. Male or female aged from 18 to 65 (inclusive)
3. Dry non-productive cough as a symptom of acute upper respiratory infection (IDC codes J00-J06)
4. Daytime cough symptom score ≥ 3 points according to the "Six-point daytime and nighttime cough assessment scale"
5. Pre-bronchodilator FEV1 ≥ 70% of the predicted values, post-bronchodilator FEV1 increase of ≤ 12% or ≤ 200 ml compared to the baseline, FEV1/FVC (Tiffeneau index) ≥ 0.7
6. Patient's consent to follow the protocol procedures, including the completion of the patient's diary
7. Patient's consent to use the adequate contraception methods throughout the study period. The adequate birth control methods are as follows:
    - Oral or transdermal contraceptives
    - Condoms or diaphragms (barrier method) with spermicide
    - Intrauterine contraceptive devices

4.3 Exclusion criteria

Subjects with any of the following conditions will be excluded from the study:

1. Hypersensitivity or individual contraindications to Levodropropizine, Prenoxdiazine or additives of the study drug
2. Hereditary fructose intolerance, glucose-lactose malabsorption, lactase deficiency, sucrose-isomaltose deficiency
3. Tuberculosis, bronchial asthma, malignant tumors of lungs or bronchi, COPD, severe respiratory failure (cyanosis, need for respiratory support) or other lung pathology at screening or in history
4. Inhalation anesthesia within 3 months before screening
5. Smoking history of more than 10 pack-years
6. Previous use of cough medicines, ACE inhibitors or amiodarone within 30 days before screening

7. Contraindications or inability to perform spirometry
8. Necessity (in the Investigator's opinion) of prescribing mucolytic agents, expectorants, antibiotics or other medications prohibited by the protocol during the study
9. Excessive mucous excretion which (in the Investigator's opinion) could be a contraindication to prescribing anti-cough medicines; decreased mucociliary function (Kartagener's syndrome, ciliary dyskinesia)
10. Malignant tumors in the past 5 years (except for the basal cell carcinoma)
11. Serious cardiovascular disease at the moment or within 12 months prior to screening, including: Chronic heart failure class III or IV (according to the classification of the New York Heart Association), severe arrhythmias requiring treatment with antiarrhythmic drugs class Ia, Ib, Ic or III, unstable angina, myocardial infarction, heart surgery and coronary arteries, serious valvular heart disease, transient ischemic attack or stroke, uncontrolled hypertension with systolic blood pressure > 180 mmHg and diastolic blood pressure > 110 mmHg, pulmonary embolism or deep vein thrombosis
12. Gastric or duodenal ulcers, gastroesophageal reflux disease within a period of 12 months before screening
13. Systemic autoimmune disorders and connective tissue diseases that require (currently or previously) administration of systemic glucocorticosteroids, cytostatic medications or penicillamine
14. Signs of intensive non-controlled concurrent disease, including disorders of the nervous system, endocrine system, kidneys, liver or gastrointestinal tract, which (in the Investigator's opinion) could prevent the patient's participation in the study
15. History of alcohol or drug abuse at screening or in the past, which results in the inability of the patient to participate in the study at the Investigator's discretion
16. Taking part in another clinical trial or use of study drug within 30 days before screening
17. Pregnant or breast-feeding women or women planning pregnancy during the clinical trial; women of childbearing potential (including not sterilized operatively and in postmenopausal period of less than 2 years), not using appropriate methods of contraception
18. Inability to read or write; unwillingness to understand and follow the procedures of the study protocol; violation of the drug administration regimen or procedure execution that, at the discretion of the Investigator, can impact he results of the study or safety of the patient and interfere his further participation in the study; any other concomitant medical or serious mental conditions that make the patient unsuitable for participation in the clinical study, limit the validity of receiving an informed consent or may affect the patient's ability to participate in the study.

4.4 Patient Withdrawal After Randomization

The randomization procedure will be performed before laboratory test results are available. In case of significant abnormalities that in the Investigator's opinion interfere with the patient's participation in the study, the patient should be withdrawn from the study.

5 STUDY DRUG

5.1 Study Drug Description

Study Drug:	**Levopront®**
Active substance:	Levodropropizine
Pharmacological Group:	Antitussive drug with peripheral action
Pharmaceutical form and composition:	syrup 30 mg/5 mL Active substance: Levodropropizine Excipients: Saccharose, Methyl-p-hydroxybenzoate, Propyl-p-hydroxybenzoate,Monohydrate citric acid, Sodium hydroxide, Cherry flavour, Purified water
Presentation:	Package 220 ml brown glass bottle containing 200 ml of solution and closed with an HDPE child-proof cap, complete with an LDPE seal and a PP measuring cap.
Daily dose	180 mg or 30 mL
Dosing regimen:	Orally 10 mL (60 mg) t.i.d. at intervals of at least 6 hours, between meals
Storage conditions:	Keep in a place, out of reach of children Keep at a temperature below 25° C
Manufacturer:	Dompe farmaceutici S.p.A. (Italy)

Comparator product::	**Libexin®**
Active substance:	Prenoxdiazine
Pharmacological Group:	Antitussive drug with peripheral action
Pharmaceutical form and composition:	100 mg tablets Active substance: prenoxdiazine hydrochloride - 100 mg. Other ingredients: glycerol (glycerin), magnesium stearate, talc, povidone, corn starch, lactose monohydrate.
Presentation:	20 tablets in a blister, one blister per 1 carton
Daily dose	300 mg
Dosing regimen:	orally 1 tablet (100 mg) 3 times a day, no chewing
Storage conditions:	Keep at a temperature below 25° C Keep in a place, out of reach of children
Manufacturer:	Chinoin Pharmaceutical and Chemical Works Private CJSC (Hungary)

NB: Libexin® Prescribing Information are reported in Appendix 1

5.2 Administration of the Study Drug and Randomization

At Visit 1, Day 1 all patients complying with selection criteria will be randomized into one of the two study groups at 1:1 ratio using an Interactive Web-Response System (IWRS):

- The group receiving the study drug Levopront ®, syrup 30 mg/5 mL - 92 patients

- The group, receiving reference drug Libexin®, tablets 100 mg - 92 patients.

Randomization and the first intake of study drug at the center is carried out after all the procedures for screening and confirmation of the presence of all the inclusion criteria and the absence of criteria for exclusion.

Further, patients will take investigational products three times a day at intervals of not less than 6 hours, between meals.
The investigational product Levopront® syrup is dispensed by a measuring cup.

Reference drug Libexin®, tablets are swallowed without chewing, with appropriate amount of drinking water at room temperature (200-250 mL).

Overall duration of treatment with the study drug within the study treatment will take 7 days ± 1 day.

5.3 Treatment Compliance

The first dose of the study drug should be taken by patient at the study site under Investigator's control (Visit 1, Day 1). Compliance with guidelines on self-administration of study drugs will be checked by Investigator at Visit 2 and 3 based on account of returned study drug with the diary filled in by the patient. It should be strictly monitored that patient takes 30 mL of the study drug or 3 tablets of reference drug daily.

NB: Patients must take the last dose of the study drug in the evening before Visit 3 (i.e. in the evening of Day 7(±1)) because the **patients should submitted to the examinations requested by the protocol for Day 8 (±1) without having taken the study drug**.

Compliance with the test drug treatment Levopront® will be assessed by the Investigator at Visits 2 and 3. All study sites will be provided with certificated scales. The bottles with syrup will be weighted at the study sites before and after dispensing. The Investigator will measure the difference between initial and final weight. The density of Levopront® is known (indicated in IP documentation), after that calculation of compliance for the syrup will be calculated according to the following formula:

$$\text{Compliance (ml)} = \frac{\text{(m disp. – m return.)}}{\rho\ \text{(g/ml)} * \text{V calc.(ml)}} \times 100\%$$

where m disp. = the m (g) of dispensed syrup, m (g) return. = the number of returned syrup, ρ (g/ml) - density, V (ml) calc. = calculated ml of syrup that the patient had to take from the time of previous visit.

Calculation of compliance for the reference drug will be calculated according to the following formula:

$$\text{Compliance} = (\text{N disp.} - \text{N return.})/\text{N calc.} \times 100\%$$

where N disp. = the number of dispensed tablets, N return. = the number of returned tablets, N calc. = calculated number of tablets that the patient had to take from the time of previous visit.

Patient compliance for each drug should be similar and be within the interval of 80% to 120%. In case of need patient should be additionally instructed to take the drug.

5.4 Packaging and labeling of the study drug

The study drug will be provided by Sponsor. The study drug will be packed and labeled according to the current legislation and applicable requirements, in particular, Federal Law of the Russian Federation of April 12, 2010 No 61 FZ On Drug Circulation, current edition.[17]

Labeling of the study drugs is shown in Figure 2, 3.

Figure 2. Draft Label of the Study Drug, Trial LDP014

For clinical trial only

Clinical trial N° LDP0114

Patient n° ☐☐-☐☐

Visit No _____ KIT XXX*

Levopront (Levodropropizine), syrup 30 mg/5 mL - 200 ml for oral use

Dosage: Take 10 mL three times per day. between food intakes

Keep in a dry, dark place at a temperature below 25° C

Manufacturer Dompe Farmaceutici S.p.A. (Italy);

Study sponsor Dompé farmaceutici S.p.A.

Local contact: IPHARMA LLC Russia, tel. + 7 (495) 276-1143

Date dispensed _____

Batch: XXXXXX Expiry date: XXXXXXX

Keep out of reach of children

Figure 3. Draft Label of Reference Drug, Trial LDP0114

For clinical trial only

Clinical trial N° LDP0114

Patient n° ☐☐-☐☐

Visit No _____ KIT XXX*

Dosage: Take 1 tablet 3 times per day

Date dispensed _____

5.5 Storage and Account of the Study Drug

Investigator will be responsible for ensuring adequate acceptance, storage, distribution and return of the study drug, as well as keeping records of its account and registration in IWRS.

Limited access and suitable temperature regimen should be ensured. Temperature control should be performed using thermometers, registering minimum and maximum temperature in the

reporting period. Information of temperature monitoring should be regularly included into the temperature monitoring log every day at least two times a day.

Patients will be instructed to return to the study site bottles with the study drug or blisters with reference drug at Visit 2 (Day 4) to assess patient compliance. If the study drugs are lost by the patient a corresponding record should be made in the source documentation and in the study drug log. At the end of the trial after final calculation the study drugs should be returned to Sponsor or to its representative.

5.6 Concomitant Therapy

Patients may receive symptomatic treatment of the main disease.

For allowed symptomatic treatment are permitted antipyretics - NSAIDs: Paracetamol (maximum single dose of 2 g, the maximum daily dose of 4 g); ibuprofen (200 mg 3-4 times a day), acetylsalicylic acid (a single dose of 0.5-1 g, maximum single dose of 1 g, the intervals between doses of the drug for at least 4 hours, the maximum daily dose of 3 g). To improve nasal breathing may be used vasoconstrictor nasal drops and sprays. In case of appearing of any symptoms of laryngotracheitis it is permitted to use local antiseptics.

The decision on the appointment of concomitant therapy in each case takes the Investigator.

All basic and concomitant drugs, including food supplements (FS) should be recorded in the source documents and in Case Report Form (CRF). It includes all drugs and food supplements except the study therapy taken by patients within three months before screening and at any time during the clinical trial. Name (predominantly name of the active substance), dosage, frequency of dosing, route of administration, indications for use (including underlying disease, concomitant conditions, adverse events or prevention), dates of start and completion of the study drug intake should be reflected in the source documentation and in CRF. If study therapy intake was ongoing at the time of study completion, an appropriate remark should be made in the CRF.

5.7 Prohibited Concomitant Therapy

During the study treatment with other investigational products and drugs listed below is not permitted:

- Expectorant drugs (Farfara, violet, licorice, marjoram, inula, hormopsis, polygala, althea, herpinhydrate, lycorine, ether oil preparations)
- Mucolytics: enzymes (trypsin, chemotrypsin, ribonuclease), sulfur-containing compounds (acetylcysteine, carbocysteine), vasicine alkaloid derivatives (bromhexine, ambroxol)
- Antitussive agents of central and peripheral action, expect the study IMPs provided for by the study
- Antibiotics
- Combined "anti-commoncold" drugs
- Antihistamines
- Drugs that have a sedative effect and reinforcing the depressive effect on the central nervous system, as well as other cough suppressants, except for the study drugs.
- Antiviral drugs (except Arbidol®)

5.8 Patient Nutrition and Activity Limitations

Patients should maintain usual diet and limit physical exercise, refrain from alcohol and smoking for the whole period of the study.

For the whole duration of the study, subjects must agree to use adequate contraception measures. Adequate birth control measures include:

- oral or transdermal contraceptives,
- condom or diaphragm (barrier method) with spermicide or
- intrauterine device.

6 DESCRIPTION OF PROCEDURES

All study procedures will be performed according to the requirements and recommendations of the Good Clinical Practice guidelines of International Conference for Harmonization (ICH GCP) and Eurasian Economic Union (EAEU), principals outlined in the Declaration of Helsinki, as well as according to the current legislation and applicable regulations of Russian Federation. The Investigator must consent to accept monitoring, audits and inspections at the clinical site and provide direct access to the study materials to the Sponsor and its representatives, Independent Ethics Committee and regulatory authorities.

6.1 Informed Consent

Informed consent will be obtained at screening before any study-related procedures are made.

6.2 Patient Registration

Each patient signing Patient Information Leaflet and Informed Consent Form will be assigned an individual registration number consisting of four digits: ☐☐-☐☐ - the first two digits denote the site number, the last two digits – the number of patient at the site (01, 02, 03 etc.). Guidelines for patient registration in the IWRS will be provided to the Investigator before the study.

6.3 Demographic Data and Medical History

To asses patient compliance to inclusion/non-inclusion criteria, patient demographic data (sex, date of birth/age, race) and full medical history, including significant acute and chronic disorders and conditions (e.g. menopause), surgical interventions and allergic reactions should be collected. Besides, patient should be asked about hospitalizations and/or surgical interventions scheduled within the study period (if applicable). All new diagnoses and conditions detected at screening (including results of laboratory and instrumental studies) should be attributed to the patient's medical history.

History of smoking is assessed by the pack/year index according to the following formula:

$$\text{Pack/year index} = \frac{\text{No. of cigarettes per day x Smoking experience (years)}}{20}$$

6.4 Physical Examination

Physical examination includes assessment of general appearance, condition of skin, mucous membranes, neck (including thyroid gland), eyes, ears, nasopharynx, lungs, heart, abdomen, lymph nodes and neurological status.

Changes versus baseline characteristics, determined to be AEs should be appropriately reported in the source documentation and in CRF.

6.5 Vital signs, height, weight

The examination includes measurement of body temperature in the armpit, sitting blood pressure, pulse, respiratory rate. Changes of vital signs versus baseline values, regarded as AEs, should be appropriately reported in the source documentation and in CRF.

Weight and height of patients are measured with shoes off. Body mass index (BMI) is calculated according to the following formula: $\boldsymbol{BMI = mass/height^2}$ (kg/m^2), where mass is measured in kilograms, and height in meters.

6.6 Electrocardiography

12-lead electrocardiography (ECG) is performed in supine position. Investigator should review the ECG record, assess deviations (if any), sign and date the report.

6.7 Spirometry

Lung function assessment will be performed using regularly calibrated spirometric equipment according to the Federal clinical guidelines on spirometry by Russian Respiratory Community, 2013. [13]

To assess lung function and whether it meets study inclusion criteria, at Visit 1, Day 1 spirometry is performed pre- and post-bronchodilator, and registered spirometry parameters shall include:

- Pre-bronchodilator FEV1 ≥ 70% of the predicted values,
- Post-bronchodilator FEV1 increase of ≤ 12% or ≤ 200 ml compared to the baseline,
- FEV1/FVC (Tiffeneau index) ≥ 0.7

At visit on Day 8, spirometry is performed without bronchodilator, spirometry values will include FEV1.

The growth measure should be performed only during screening visit. For calculated values of lung function growth measured only at screening and weight measured during screening and Visit 3 (Day 8), should be used.

Tests should meet quality criteria for technical suitability and repeatability. To obtain reproducible results, at least three technically satisfying tests corresponding to acceptance criteria should be obtained; the best (maximum) result should be reported in the CRF.

Investigator should review the report of spirometry, assess test results, sign and date the report. Change of spirometry values versus baseline determined to be AEs should be appropriately reported in the source documentation and in CRF.

6.8 Six-point of daytime and nighttime cough assessment scale

Assessment of the severity and frequency of daytime and nighttime cough will be conducted with the "Six-point daytime and nighttime cough assessment scale" on visits to the center. Also, the patient will independently evaluate the severity and frequency of daytime cough (evening before retiring to bed) and nocturnal cough (in the morning after waking up) and enter the data in the patient diary.

"Six-point scale assessment of daytime and nighttime cough" is presented in Appendix 2. The patient will choose the most appropriate answer to the question and the corresponding points for the daytime and nighttime cough.

The investigator will record the results of the evaluation of severity and frequency of daytime and nighttime cough in the primary documentation and CRF.

6.9 Visual Analog Scale

The cough intensity will be assessed with Visual Analog Scale (Appendix 3).Visual analog scale is a 100 mm line where patient needs to mark cough intensity, where the extreme left point corresponds to no cough, and the extreme right point corresponds to severe cough of high intensity, significantly impairing daily activities. Investigator will measure the number of millimeters reported by patient with a ruler and report results in the source documentation and in CRF.

6.10 Patient Diary

During the period of study therapy, patients are on a daily basis to keep a diary in which to record the severity and frequency of daytime and nighttime cough, the investigational product intake, concomitant treatment, and adverse events occurred.

Also, patients will be advised to the measurement of body temperature twice a day: in the morning after waking and at night before retiring to bed.

6.11 Tests Performed at Local Laboratory

Local laboratory will be used for laboratory tests. Collection, preparation and storage of biological samples will meet requirements of the study site local laboratory.

At baseline, all local laboratories will provide the required certificates and laboratory reference values. Local laboratory is responsible for sending laboratory reports to the Investigator, and for reporting abnormal laboratory values to the Investigator. Investigator should review the laboratory report, all abnormal values should be assessed, signed and dated. Deviations of laboratory values from baseline, reported as AEs should be appropriately reported in the source documentation and in CRF.

Patient randomization is performed before laboratory test results are available. In case of significant abnormality which, at the Investigator's opinion, could interfere with patient's participation in the study or impact interpretation of efficacy or safety parameters, the patient should be withdrawn from the study.

6.11.1 Laboratory Parameters

Laboratory tests will be performed at predefined visits (D1 and D8) according to the Study Procedure Schedule (Table 1). Table 2 shows laboratory parameters which will be assessed in this clinical trial.

Table 2. Laboratory Blood Test Parameters

Blood Hematology	**Blood Biochemistry**		
Hemoglobin Hematocrit RBC WBC Neutrophils Lymphocytes Monocytes Eosinophils Bazophils Platelets ESR	Total Protein Albumin	Total cholesterol Total bilirubin Conjugated bilirubin ALT AST	Serum creatinine GFR

Abbreviations: ESR – erythrocyte sedimentation rate, ALT – alanine transpherase, AST – aspartate transaminase, RBC - red blood cells, WBC - white blood cells, GFR - Glomerular filtration rate

Table 3 shows laboratory parameters of urine to be assessed in this clinical trial.

Table 3. Urine Laboratory Parameters

Clinical Urine Test	**Special Tests**
General properties: color, clarity, specific gravity, pH, protein, glucose, bilirubin, urobilinogen, ketone bodies, nitrites,	Pregnancy test (only for women of childbearing potential, including women at menopause of less than two years)

Clinical Urine Test	Special Tests
hemoglobin Sediment microscopy: epithelium, erythrocytes, leukocytes, casts, bacteria, salts	

6.11.2 Collection, Preparation, Storage and Delivery of Biological Samples

Collection, preparation, storage and delivery of biological samples will be performed according to normative regulations and local laboratory guidelines. The overall volume of blood collected from each patient during the study will be approximately 20 mL.

6.12 Assessment of Adverse Events (AE)

6.12.1 Definitions of AEs

Adverse Event (AE) – is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, complaint or disorder. In this study AEs will be reported from the moment of signing Informed Consent Form (prior to administration of the first dose of the study drug) to Day 30 after the last visit of the patient or last procedure per protocol.

Adverse Drug Reaction (ADR) – any adverse event for which there is a reasonable possibility that the drug caused the adverse event. “Reasonable possibility" means there is evidence to suggest a causal relationship between the drug (at any dose) and the adverse event.

Serious Adverse Event (SAE) and/or Serious Adverse Drug Reaction (SADR) – Any adverse medical event which, irrespective of the dose of the study drug:

- results in death;
- is life-threatening;
- requires hospitalization (initial or prolonged);
- results in significant, persistent or permanent impairment or disability; or
- is a congenital anomaly or birth defect
- is an important medical event that may be not immediately life threatening or result in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition above.

Significant medical events that do not pose an immediate threat to life, do not result in death or hospitalization, but put patients at risk or require interventions aimed at the prevention of the above outcomes can also be included in SAE/SADR. Examples of such events may include bronchospasm of allergic genesis, convulsions, malignant neoplasms.

NOTE: Hospitalization for social reasons, visits to day patient facility, hospitalization or operation preplanned prior to patient enrollment into the study for treatment of underlying condition, are not to be considered SAEs.

Unexpected ADR – ADR of nature and severity not corresponding to the known information about the product (e.g. to the Investigator’s Brochure for unauthorized investigational product or to the prescribing information for authorized product). The group also includes ADRs specified in the investigator’s brochure as characteristic for the class of products

or expected as related to the pharmacological properties of the study product, but which had not been observed earlier.

Serious and Unexpected Suspected Adverse Reaction: Any suspected adverse reaction that is both serious and unexpected (SUSAR).

6.12.2 Pregnancy

Women of childbearing potential are not excluded from the study as long as adequate birth control methods are being utilized. Women of childbearing potential are defined as all women physiologically capable of becoming pregnant.

For the whole duration of the study, subjects must agree to use adequate contraception measures. Adequate birth control measures include:

- oral or transdermal contraceptives,
- condom or diaphragm (barrier method) with spermicide or
- intrauterine device.

Pregnancy is not a SAE, but refers to events that require an urgent reporting to the Sponsor. In case of pregnancy during the study, either occurring in a female patient or in a male patient's partner, the pregnancy status should immediately be reported to the Sponsor. Female patient will be withdrawn from the study and will be monitored throughout pregnancy and up to 30 days after its outcome. Health conditions of any newborn who was conceived during the study will also be followed up to 30 days after birth (including pregnancy of patient's partner). Relevant information will be recorded in source documents, CRF and Pregnancy Report Form. Pregnancy reports should be completed and e-mailed/faxed following the procedure described in Paragraph 6.12.7.

6.12.3 Reporting AEs and SAEs

At every visit, patients should report any AEs, responding to open, non-probing questions (e.g. How have you been doing since the last visit?). For each AE/SAE reported by a patient, the Investigator should collect and document in source documents and CRF all the needed information, including diagnosis and symptoms, date of onset and date of resolution, outcome, severity, criteria of seriousness, circumstances, that may denote possible relatedness to the study drug and concomitant therapy, underlying diseases or concomitant conditions, study procedures or other causes, actions related to the study drug, pharmaceutical treatment, medical interventions, results of laboratory and instrumental tests for AE, other circumstances, which may add to comprehensive description of the event

Within the period of self-administration of the study drug, patients will enter information about possible adverse events in a diary.

Increase in severity of the ongoing adverse event shall be considered a new AE. The date of further worsening in severity will be the start date of the new AE, and the previous day shall be the end date of the original AE.

The date of onset of SAE is the date of onset of the seriousness criterion. The preceding condition, if applicable, should be reported as a non-serious AE.

If an AE is serious, Investigator should also promptly submit a SAE report (specifying the seriousness criteria), within 24 hours from first knowledge to the IPHARMA Medical Monitor. New information about SAE which becomes known later, should be reported to the Sponsor in the same way and in the same time. Besides, the Sponsor should be provided with certified

copies of source documents for that SAE (hospital discharge summary, autopsy report, death certificate etc.). Data in source document and SAE form shall be duly anonymized.

AEs should be followed up and reported from the date of signing informed consent to the last visit or study related procedure (teleconference at follow-up). Any AE or SAE which is spontaneously reported by a patient within 30 days after the last study visit, will be reported and assessed in the same way as AEs occurring during the study. AEs should be reported until resolution or stabilization of patient's condition.

In line with ICH E2A provisions on Post-Study events, although such information is not routinely sought or collected by the Sponsor, serious adverse events that occurred after the patient had completed a clinical study (including any protocol-required post-treatment follow-up) will possibly be reported by the Investigator to the Sponsor. Such "post-study cases" should be regarded for expedited reporting purposes as though they were study reports. Therefore, a causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required.

Monitor is responsible for verifying compliance of CRF and SAE reports to the source documentation.

6.12.4 Assessment of AE Severity

For each AE, the Investigator will assess the severity grade. For that purpose the following severity grading scale is used:

1. Mild	Grade 1 - does not interfere with patient's usual function (awareness of symptoms or signs, but easily tolerated [acceptable]).
2. Moderate	Grade 2 - interferes to some extent with patient's usual function (enough discomfort to interfere with usual activity [disturbing]).
3. Severe	Grade 3 - interferes significantly with patient's usual function (incapacity to work or to do usual activities [unacceptable])

For each episode, the highest severity grade attained should be reported.

It should be noted that severe AEs not always comply with criteria of seriousness, while SAE is not always severe. The urgency of reporting of SAE does not depend on the severity of the event.

6.12.5 AE Relatedness to the Study Drug

For each AE the Investigator should assess its possible causal relationship to the study drug according to the Modified WHO scale/ICH E2B, shown in Table 4.

Table 4. Causal Relationship to the Study Drug

AE Category	Definition
1. None (Intercurrent Event)	An event that is not and cannot be related to the Investigational Product, e.g. patient is a passenger in a road traffic accident.
2. Unlikely (remote)	Relationship is not likely e.g. a clinical event including laboratory test abnormality with temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals or underlying disease provide more plausible explanations
3. Possible	Relationship may exist, but could have been produced by the patient's condition or treatment or other cause
4. Probable	Relationship is likely, the AE abates upon discontinuation of Investigational Product and cannot be due to the patient's condition
5. Highly Probable	Strong relationship, the event abates upon discontinuation of Investigational Product and, if applicable, re-appears upon repeat exposure

6.12.6 Assessment of Expectedness

Expectedness will be determined based on the contents of the Investigators' Brochure/SmPC as applicable for the suspected drug. Please also refer to Section 3.4.4 "Significant Potential Risks".

Expected	An adverse reaction, the nature or severity of which is consistent with the applicable product information (e.g. Investigators' Brochure)
Unexpected	An adverse reaction, the nature or severity of which is not consistent with information in the relevant source document (e.g. Investigators' Brochure)

6.12.7 Providing Reports about SAE/Pregnancy

All SAE irrespective of severity and relatedness to the study drug, as well as pregnancy cases should be reported to IPHARMA Medical Monitor and the Dompé Pharmacovigilance, by fax or e-mail, within 24 hours from the moment of first knowledge by the Investigator. Information about SAE should be sent in the form of SAE report. Information about pregnancy should be sent in the form of pregnancy report. In case of need Investigator may contact with Medical Monitor for consultation or explanations.

Reporting about SAE/pregnancy

IPHARMA LLC Medical department:

Medical Monitor: Dmitry Davydov

Tel+7 (495) 276-1143

Fax: +7 (495) 276-1147

Mob.: +7 (915) 397-3447

e-mail: SAE@ipharma.ru

Dompé Pharmacovigilance:

Laura Boga, Safety Manager

Direct line: +39 02 58383462; Mobile: +39 335 219580

Fax: +39 02 36026913

E-mail: farmacovigilanza@dompe.com

IPHARMA Medical Monitor will be then responsible for verifying consistence of information reported and data included in SAE/Pregnancy Report Form, obtaining and reporting any additional information received from the Investigators, and forwarding fully completed SAE/Pregnancy Report Forms to the Dompé Pharmacovigilance, by e-mail immediately and anyway within 24 hours of knowledge of event. **SAE reports with fatal outcome shall be transmitted to the Dompé Pharmacovigilance as soon as possible, and within a maximum of 12 hours from the time IPHARMA has knowledge of the death.**

Investigator should instruct each patient to report SAE or pregnancy during study and 30 days after the last visit to the study site or last study procedure. Investigator should provide in the SAE/pregnancy report form all information about the event. Each SAE report form should include at least the following information: patient details, event title, seriousness criterion, relatedness to the study drug, and outcome at the time of report.

For primary report the Investigator makes the following remark to the SAE report – "Primary report". If additional information about SAE (for example, new information about patient condition or results of laboratory tests) occurs Investigator should fill in a new form of SAE report with "Additional report" mark. Original of SAE report form should be kept in Investigator File.

The Investigator (or an authorized staff member) will be responsible for reporting any SAEs/SUSARs to the Local Ethics Committee and local institutions in accordance with local regulations and requirements.

The Sponsor shall be responsible to prepare and approve Periodic safety reports and SUSAR report and to forward them the IPHARMA for submission. IPHARMA will be responsible Periodic safety reporting to the Regulatory Authorities in the Russian Territory and Investigators, and expedited reporting of SUSARs to the local Regulatory Authorities, in accordance with local regulations and requirements. The Sponsor will be responsible for regulatory reporting outside the Russian Territory, as applicable.

6.12.8 Overdose

Cases of overdose (accidental or intentional) which may or may not result in serious adverse reactions are to be reported by Investigator to IPHARMA and Sponsor Pharmacovigilance, following the same procedure for SAE, within 24 hours from the Investigator's knowledge of its occurrence. This includes reports related to drug intake with suicidal intentions and consequent drug overdose.

An overdose of LEVOPRONT is defined as the administration of more than 30 ml (180 mg) on any given treatment day (with allowances of 120% compliance). An overdose of LIBEXIN is defined as the administration of more than 900 mg on any given treatment day, according prescribing information for LIBEXIN.

The Investigator shall provide in the SAE form information about symptoms, corrective treatment and outcome of overdose.

6.12.9 Emergency Procedures

Investigator is responsible for obtaining information about all emergency medical conditions of patients in the study. The Patient information leaflet and Informed consent form contains contact details of Investigator. Patients will be recommended to contact the Investigator in case of any emergencies during the study.

6.12.10 Assessment of AE with concomitant therapy

To assess relatedness of AE to concomitant therapy please refer to prescribing information for the drugs (State Register of Medicinal Drugs http://grls.rosminzdrav.ru/GRLS.aspx).

6.12.11 Clinically Significant Laboratory Abnormalities

Any clinically significant abnormalities of laboratory parameters or results of the instrumental methods of examination noted at screening shall be registered in the patient's medical history. After screening, new or worsened clinically significant abnormalities shall be reported as adverse events in source documents and CRF.

6.13 Early Withdrawal of Patients from the Study or Discontinuation of Study Treatment

The patient has the right to refuse to take part in the study at any stage without giving reasons.

The patient should be withdrawn from the clinical study if:

- Investigator considers it important from the medical point of view
- Patient withdraws his consent
- Patient does not comply with the study drug dosing regimen or study related procedures
- AE or SAE which may impact safety or well-being of patient
- Infection of lower respiratory tract
- Patient is included into the study with violation of inclusion/exclusion criteria

In the following cases immediate discontinuation of the study drug is required:

- Patient starts administration of another study drug
- Pregnancy in a study subject
- Significant protocol deviations that may impact patient's safety and integrity of the study data
- Use of prohibited drugs

If possible, the Investigator should discuss the need to withdraw the patient with the Medical Monitor or inform about patient withdrawal from the study within 48 hours. The reason for patient withdrawal should be specified in the source documents and in CRF. If a patient discontinues from the study for more than one reason, only the main reason should be specified. If a patient withdraws consent because of AE or SAE, the AE or SAE should be specified as the reason for patient withdrawal.

Besides, the Sponsor may terminate the study at any time. The Investigator has the right to terminate the study at any time for medical or regulatory reasons. Study may only be terminated after mutual consultations between the Investigator and the Sponsor.

If the study is terminated early, all patients should undergo procedures of early termination and all study materials should be returned to the Sponsor or his/her representative.

Follow up of AEs, SAEs and pregnancy ongoing at the time of study termination should be continued per protocol if not agreed otherwise between the Investigator and the Sponsor.

6.14 Validity of assessments

Efficacy and safety assessments in patients with dry non-productive cough associated with acute respiratory infection of upper airways are standard and well-characterized. Patients will receive stable symptomatic treatment for the whole study period. Open, randomized, clinical study in parallel groups will enable receiving maximum objective data about efficacy and safety of the study drug.

7 STUDY PROCEDURES

7.1 Screening and Randomization

7.1.1 Visit 1, Day 1

- Procedure of obtaining Informed Consent
- Patient registration
- Collection of demographic data, medical history and concomitant therapy
- Assessment of the severity and frequency of daytime and nighttime cough according to "Six-point daytime and nighttime cough assessment scale"
- Assessment of the cough intensity with the visual-analogue scale
- Physical examination
- Vital signs
- Height, weight
- ECG (12 leads)
- Collection of blood samples for blood hematology and biochemistry
- Collection of urine sample for clinical urine analysis and pregnancy test (women of childbearing potential, including women at menopause of less than two years)
- Spirometry (pre- and post-bronchodilator use)
- Chest X-ray or fluorography
- Inclusion/exclusion criteria
- Assessment of adverse events
- Patient enrolment (After examination, obtaining ECG results, spirometry, fluorography (or X-ray) or confirming compliance to all inclusion/exclusion criteria patients will be randomized)

Patients not meeting all inclusion/exclusion criteria will not be included into the study. Patients not included into the study for manageable reasons, may once pass re-screening on agreement with the Sponsor or his/her representative.

Randomization

- Prescription and dispensing of the study drug (administration of the first dose of the study drug at the site)
- Assessment of adverse events
- Dispensing patient diaries

Patient randomization is performed before laboratory test results are available. In case of significant abnormality which, at the Investigator's, opinion could interfere with patient's participation in the study or impact interpretation of efficacy or safety parameters, the patient should be withdrawn from the study.

7.2 Study Therapy

7.2.1 Visit 2, Day 4

(Visit Window Day ±1)

- Assessment of adverse events and concomitant therapy
- Physical examination
- Vital signs
- Account of the study drug, compliance assessment
- Review of patient diaries
- Assessment of the severity and frequency of daytime and nighttime cough according to "Six-point daytime and nighttime cough assessment scale"
- Assessment of the cough intensity with the visual-analogue scale
- Dispensing of the study drug and patient diaries

7.2.2 Visit 3, Day 8

(Visit Window Day ±1)

- Assessment of adverse events and concomitant therapy
- Return and account of the study drug, compliance assessment
- Review of patient diaries
- Assessment of the severity and frequency of daytime and nighttime cough according to "Six-point daytime and nighttime cough assessment scale"
- Assessment of the cough intensity with the visual-analogue scale
- Spirometry
- Physical examination
- Vital signs
- Collection of blood samples for blood hematology and biochemistry
- Collection of urine sample for clinical urine analysis and pregnancy test (women of childbearing potential, including women at menopause of less than two years)

NB: Patients must take the last dose of IP in the evening before Visit 3 (i.e. last dose should be taken in the evening on Day 7(±1)). **On the day of Visit 3 (Day 8 ±1) patients must not take the study drug because they will be submitted to the last examinations requested by the protocol. Patients must be instructed accordingly.**

7.3 Follow up

7.3.1 Telephone Contact, Day 10

(Visit window ± 1 day)

- Assessment of adverse events

7.4 Unscheduled Visits

At the Investigator's discretion patients may be invited to an unscheduled visit at any time during clinical trial for safety reasons, should repeated examination or procedure be required. At unscheduled visits the Investigator may perform the required procedures, including laboratory and instrumental studies. Unscheduled visits should be documented in the source documentation and CRF. Unscheduled visits should not modify the preplanned visit schedule per protocol.

7.5 Early Termination Visit

In case of early withdrawal from the study after Visit 1 (Randomization) and before Visit 3 (Day 8) the patient should be invited to the study site for early termination visit (ETV). Investigator should make all reasonable efforts to perform all the required assessments at the ETV. Early termination visit should occur not later than on Day 3 after the last dose of the study drug.

ETV should include all procedures of Visit 3, (Day 8). If ETV cannot be performed in full volume, the Investigator should agree his/her actions with the Medical Monitor.

At ETV the patient should return to the site all used and unused packages of the study drug. The patient will be given recommendations for further treatment within standard ARVI treatment options.

If possible, the Investigator should discuss patient withdrawal with Medical Monitor in advance. Otherwise, the Investigator should contact the Medical Monitor within 24 hours after the early termination visit.

8 QUALITY ASSURANCE

This clinical trial will be performed according to Standard Operating Procedures (SOPs) of Sponsor and/or its representative, according to the Good Clinical Practice Guidelines of International Conference on Harmonization (ICH GCP) and Eurasian Economic Union (EAEU), principles outlined in the Declaration of Helsinki, and applicable regulations of Russian Federation. The compliance will be assured by auditing the clinical sites, study data and study relevant documents.

9 STATISTICAL METHODS

9.1 General Provisions

This is comparative clinical study of efficacy and safety of Levopront®, syrup 30 mg/5 mL and Libexin®, 100 mg tablets in patients with drug non-productive cough associated with acute respiratory infection of upper airways.

Statistical analysis described below will be performed according to the statistical analysis plan (SAP) created and finalized before database lock. SAP will be included into the clinical study report for the present protocol.

9.2 Sample Size Determination

The sample size is calculated for the primary efficacy endpoint - the proportion of patients with response to therapy (daily cough symptoms permission to visit Day 8) and non-inferiority hypothesis.

According to available data in the literature (Schroeder K., Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings) in clinical studies antitussives difference between the active treatment group and the placebo group was about 44%. In the placebo-controlled study (Smith SM, Schroeder K., Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in community settings) the difference between the active treatment groups and the placebo group was 25% and 35%. According to the meta-analysis of clinical trials of levodropropizine in two placebo-controlled studies the difference between the efficacy of the study drug and placebo was 45% in the pediatric population of patients (study Fiocchi) and 39% in the adult population of patients (study Allegra, where efficacy of levodropropizine was about 80% [17,18]).

According to ICH guideline, the selected non-inferiority margin (non-inferiority margin) should not exceed the minimum difference between the performance indicators of the active drug and placebo[19]. Based on the above data, non-inferiority margin δ = 20% was chosen for the study.

The sample size estimation in the protocol amendment is based on the results of the study interim analysis that showed approximately 70% efficacy in both groups vs. 80% efficacy that had been projected initially. Thus the interim analysis at α = 0.05 (one-sided) showed lack of power for the hypothesis testing (< 80%).

The sample size was calculated using the formula for non-inferiority for comparison of two independent proportions:

$$n = (Z_{\alpha/2}+Z_{\beta})^2 \times [p_1 \times (100\% - p_1) + p_2 \times (100\% - p_2)] / (p_1 - p_2 - \delta)^2$$

where n – sample size for each group, p_1 - success rate in the control group, p_2 – success rate in the treatment group, δ – non-inferiority margin, $Z_{\alpha/2}$ is 1.96 for one-sided α = 0.025 and Z_{β} is 0.84 for 80% power.In order to achieve power 80%, with corrected α = 0.025 (one-sided)[20,21], expected efficacy rate of 70% in both groups, non-inferiority margin δ = 20%, and ED rate not exceeding 10%, 184 patients should be enrolled in the study at 1:1 ration (92 patients per treatment group).

Assuming the screen-failure rate of about 20%, up to 230 patients will be screened in the study.

9.3 Randomization

Randomization will be performed at Visit 1 with Interactive Web Response System (IWRS). Patients will be randomly distributed into one of two study groups at 1:1 ratio (92 patients per group). No stratification will be performed.

9.4 Analyzed Populations

9.4.1 Per Protocol Population

Per-protocol population includes all randomized patients completing treatment with the study drug, having primary efficacy analysis assessment done and considered to be compliant. Patients without serious deviations from protocol during the study will be considered compliant. The key protocol deviations will be discussed in more detail in the SAP and will be determined before the date of database lock.. PP population is the primary population for the primary endpoint (Non-inferiority) analysis[22].

9.4.2 Intent-to-Treat Population

The population of patients is based on the initial treatment assignment and not on the treatment eventually received (ITT)..

9.4.3 Safety Population

All patients who received at least one dose of the study drug will be included into the safety population.

9.5 Patient Allocation, Demographic and Baseline Characteristics

Patient distribution, demographic and baseline characteristics will be provided using descriptive statistics. The number and per cent of patients taking concomitant drugs will be provided in the frequency tables for ATC class, international non-proprietary name (INN). Besides, the number of patients with concomitant disorders and underlying conditions will be provided.

9.6 Study Drug Administration

Information about dosing, including daily doses, duration of exposure and total doses, will be provided descriptively for treatment groups.

9.7 Efficacy Analysis

9.7.1 Primary Efficacy Endpoint

Primary endpoint: The main efficacy analysis population includes all randomized patients completing treatment with the study drug (PP population)

Study statistical testing hypothesis will be expressed as:

H_0: Lower bound of the 97.5% one-sided CI $(p_1-p_2) \leq -20\%$ → Non-inferiority rejected

H_1: Lower bound of the 97.5% one-sided CI $(p_1-p_2) > -20\%$ → Non-inferiority accepted

The primary objective is to demonstrate the "non-inferiority" of Levopront® comparing to Libexin® with regards to the primary endpoint. For this purpose, the one-sided 97.5% CI will be calculated for the two proportions difference — the rate of patients who responded to treatment by Day 8 in the study treatment group and in the control group with a non-inferiority margin of $\delta = 20\%$. The null hypothesis (H_0) that in the study treatment group the rate of treatment responders is less than in the control group, will be declined if the lower bound of the 97.5%

one-sided CI for the two proportions difference is located to the right of the -0.20, with the final conclusion of non-inferiority of Levopront® versus Libexin®.

9.7.2 Secondary Efficacy Endpoints

For the secondary efficacy endpoints analysis, the descriptive statistic methods will be used along with calculating the 95% CI and independence testing. To compare the dynamic changes of the parameters obtained for the study groups, independent samples T-test will be used.

9.8 Safety Analysis

All patients who receive at least one dose of the study drug will be included into the safety population.

The number and percentage of the patients with AE and SAE for every treatment group (along with the total numbers) will be summarized in tables by system organ class and preferred term, relationship to the study drug and severity; the laboratory results will be summarized in tables with change from baseline. The vital signs, laboratory and spirometry results will be summarized by means of descriptive statistics.

9.9 Procedures of Account of Missing, Non-Analyzable and Doubtful Data

Missing data will not be substituted. For analysis of efficacy end points the last observation carried forward method (LOCF) will be used. For sensitivity assessment will be used sensitivity analyses: first the patients with missing data as failure will be analysed and second the patients without substitution of missing data

9.10 Procedures of Reporting of Deviations from Primary Statistical Plan

In case of deviations from the planned statistical analysis all changes versus methods described in the protocol should be identified. Similarly, if there is a need for some additional modifications after analysis, these should be reflected in the study report.

10 ADMINISTRATIVE PROCEDURES

10.1 Legal Aspects

Names of all patients should be kept strictly confidential. Patient identification is performed by assigned number and date of birth. Patients should be informed that any information stored at the study site, with the Sponsor or his/her representatives, will be kept in strict compliance with confidentiality requirements according to regulatory norms.

10.2 Investigator's Responsibilities

The Investigator shall perform the clinical trial according to the terms specified in this Protocol, Guidelines on Good Clinical Practice of the International Conference on Harmonization (ICH GCP) and Eurasian Economic Union (EAEU), Helsinki Declaration principles, and applicable regulations of the Russian Federation.

The Investigator shall give his/her consent for monitoring, audits and inspections of the study site at any time, and provide direct access to the study materials for the Sponsor and his/her representatives, Independent Ethics Committee and authorized bodies at their request.

The Investigator shall keep originals of all signed Informed Consent Forms and full list of study patients specifying their full name, personal number, date of birth, address and telephone number to enable their identification. These documents should not be copied for transfer to Sponsor or his/her representatives.

The Investigator shall ensure security of study materials, including source documentation, copies of CRF and Investigator File for at least 15 years after study completion or to the time specified by the Sponsor.

10.3 Monitoring Procedures

The Investigator shall provide direct access to source documentation, CRF and Investigator File to Sponsor and his/her representatives, IEC and authorized bodies. Source documentation includes primary documents, data and records, including medical history, outpatient records, laboratory records, notes, diaries, questionnaires, drug dispensing logs, automatic records, verified and certified copies or extracts, photonegatives, microfilms or magnet carriers, X-ray images, any records related to patient, including records kept in the pharmacy, in laboratories and instrumental diagnostic departments used in clinical study.

Monitoring will be performed by Sponsor or his/her representative according to Standard operation procedures and Study monitoring plan.

10.4 Data Entry in CRF

The Investigator should transfer clinical data from source documents to the CRFs. CRF completion training for the Investigator will be conducted at the Investigators Meeting and at/or during the Site Initiation Visit. If the Investigator delegates the CRF completion responsibility to other site employees, their names, positions, initials and signatures should be listed in the Delegation of Responsibilities Form and provided to the Sponsor or its representative.

All changes in CRFs should be made with audit trail; that means that data before and after correction should be seen, along with the reason of correction, date and initials of a person who made correction. Completed CRFs should be signed by the Investigator.

The Investigator must transfer the data obtained during clinical trial from the source documentation into CRF. The Investigator will review the rules of data entry into CRF during investigator meeting and/or during initiation visit. If the Investigator authorizes filling CRF to

another member of personnel of the study site, the name, position, signature and initials of such persons should be included into the list of distribution of study site personnel responsibilities, which is to be provided to the Sponsor or his/her representative.

If corrections are made in the CRF, physical traces of corrections should be left, i.e. data before and after corrections should be kept visible, the reason for correction (if applicable) should be available, the date and initials of the person making amendments should be documented. Completed CRFs must be electronically signed by the Investigator.

10.5 Storage of Documentation

Source documentation, copies of CRF and Investigator File must be stored at the study site or in a specially reserved archiving area with limited access for at least 15 years after completion of the study or for another term specified by the Sponsor. The Sponsor must be informed in case of documentation transfer to other persons or to another institution. Study related materials will be kept by the Sponsor and his/her representatives according to the normative regulations.

10.6 Ethical Aspects

10.6.1 Independent Ethics Committee

Prior to clinical study initiation, written approvals of Independent ethics committees (IEC) will be obtained according to the Guidelines on Good Clinical Practice of the International Conference on Harmonization (ICH GCP) and Eurasian Economic Union (EAEU), Helsinki Declaration principles, and applicable regulations of the Russian Federation. The following documents should be submitted to IEC: study protocol with amendments, patient information leaflet and Informed Consent Form, written materials to be provided to patients, investigator brochure, safety information of the study drug, information about payments and compensations to patients, academic CV of Investigator, and other documents as required.

A list of IEC members and declaration of conformity of its organization and operations to Good Clinical Practice principles and normative guidelines should be provided to the Sponsor.

10.6.2 Ethical Conduct of the Clinical Study

Procedures described in the clinical study protocol, related to its conduct, assessment and documentation of results, were developed to guarantee that Sponsor or Investigator comply with the Guidelines on Good Clinical Practice of the International Conference on Harmonization (ICH GCP) and Eurasian Economic Union (EAEU) and applicable regulations of the Russian Federation. This clinical trial will be performed according to the current legislation and applicable guidelines. It includes potential audits and inspections of representatives of the Sponsor and/or authorized bodies. The Investigator must give consent to monitoring, audits and inspections at the study center and provide direct access to study materials to Sponsor and his/her representatives, Independent Ethics Committee and authorized bodies.

10.6.3 Informed Consent

Prior to clinical study initiation written approvals by Independent Ethics Committee (IEC) should be obtained for Patient Information Leaflet and Informed Consent Form as well as any other written information which can be provided to patients. Written approval by IEC and approved documents will be kept in the Investigator File.

The process of obtaining informed consent should occur according to the Guidelines on Good Clinical Practice of the International Conference on Harmonization (ICH GCP) and Eurasian Economic Union (EAEU), Helsinki Declaration principles, and applicable regulations of the Russian Federation. Informed Consent Form must be personally signed and dated by the

patient before study initiation or any of the study procedures performed. The procedure for obtaining informed consent must be described in detail in the source documentation, including the fact of patient consent for participation in the clinical study and the date of signing and the version of the Informed Consent Form.

10.6.4 Financing and insurance

Financing conditions are described in a separate document drawn up between the organizer and the research center for the study.

Participation in the study does not require any financial expenses. The conduct of the clinical study is completely sponsored by Dompé farmaceutici s.p.a. (Italy). All clinical study procedures, including the administration of the investigational drug, clinical visits, laboratory tests and assessments, will be free.

In the course of the study patients will receive the drugs for treatment of dry cough that will be assigned during the study and thermometer for free.

Participation in this study does not suggest payments to patients.

Patient's life and health as a participant of a clinical study is insured according to the legislation of the Russian Federation (article 44 of the Federal Law on Drugs Circulation No 61-FZ of April 12, 2010 and other regulatory requirements in force). Mandatory insurance of the clinical study participants will be provided by «INGOSSTRAKH» Insurance Company. The address of the insurance company, insurance terms, information about payments and compensations is provided in the insurance policy.

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12 APPENDICES

Appendix 1

Libexin® Prescribing Information

П N015126/01-291008

LIBEXIN® PRESCRIBING INFORMATION

Marketing Authorization Number:
Trade Name: Libexin®
International Non-Proprietary Name: prenoxdiazine
Pharmaceutical form: tablets.
Composition
Active ingredient: prenoxdiazine hydrochloride – 100 mg
Excipients: glycerol (glycerine), magnesium stearate, talc, povidone, maize starch, lactose monohydrate.

Appearance: round, flat, white to off-white tablets beveled at both sides. LIBEXIN engraved on one side and a scoreline dividing the tablet into quarters – on the other side of the tablet

Pharmacotherapeutic group: antitussive drug of peripheral action.
ATC code: R05DB18

Pharmacological Properties
Pharmacodynamics
Prenoxdiazine is an antitussive drug of peripheral action. The drug inhibits peripheral links of cough reflex for the following effects:

- Local anesthetic effect decreasing irritability of peripheral sensitive (cough) airway receptors;
- Bronchodilatory activity, blocking stretch receptors involved in cough reflex;
- Slight inhibition of respiratory center activity (without respiratory distress).

The antitussive effect of the drug is approximately similar to that of codeine. Prenoxdiazine does not cause addiction or drug dependence. Anti-inflammatory action of prenoxdiazine occurs in chronic bronchitis.

Prenoxdiazine does not affect the central nervous system function except possible indirect anxiolytic action.

Pharmacokinetics
Prenoxdiazine is quickly and largely absorbed from the gastrointestinal tract.

Maximum plasma concentration of prenoxdiazine is achieved 30 minutes after drug intake, its therapeutic concentration is maintained for 6-8 hours.

55-59% of the drug is bound to plasma proteins.

Half-life is 2.6 hours.

Most part of the dose is metabolized in liver, just about 1/3 of the dose is excreted unchanged, the rest of the drug is excreted in the form of metabolites (4 metabolites of prenoxdiazine are known).

In the first 12 hours of metabolism of prenoxdiazine, biliary excretion of prenoxdiazine and its metabolites plays the most important role. 93% of the drug is excreted within 24 hours after intake. 72 hours after oral intake 50-74% of the dose is excreted with feces and 26-50% with urine.

Therapeutic Indications

Non-productive cough of any nature (respiratory catarrh, influenza, acute and chronic bronchitis, pneumonia, emphysema, night cough in patients with cardiac failure, patient preparation for bronchoscopy or bronchography).

Contraindications

Hypersensitivity to the drug
Conditions associated with excessive bronchial secretion.
Condition after inhalation anaesthesia.
Galactose intolerability, lactase deficiency or glucose-galactose malabsorption.
With caution: children.

Pregnancy and lactation

Libexin® use by pregnant and nursing women is only possible if potential benefit for the mother outweighs potential risk for fetus and baby.

Posology and Method of Administration

The mean adult dose is 100 mg three or four times daily (1 tablet 3-4 times a day). In more complicated cases the dose may be increased to 200 mg three-four times or 300 mg three times daily (2 tablets 3-4 times daily or 3 tablets 3 times daily)

Mean dose for children depending on age and body weight: 25-50 mg three or four times daily (¼– ½ tablets 3-4 times daily).

Maximum single dose for children is 50 mg (½ tablet) for adults – 300 mg (3 tablets). Maximum daily dose for children is 300 mg (2 tablets), for adults – 900 mg (9 tablets).

As preparation for bronchoscopy the dose of 0.9 – 3.8 mg/kg body weight is combined with 0.5 – 1 mg atropine 1 hour before the procedure.

Tablets need to be swallowed without chewing (to avoid anesthesia of oral mucosa).

Side Effects

Allergic Reactions

Rare: - skin rash;

- Angioedema

Gastrointestinal tract disorders

Rare: - dry mouth or throat;

- Anesthesia (temporary numbness and loss of sensitivity) of oral mucosa;

Less than in 10% cases:

- Gastric pain;
- Disposition to constipations;
- Nausea

Nervous system disorders (at high doses)

- Mild sedative effect;
- Fatigue.

Sedative effect and fatigue occur at doses exceeding therapeutic, all symptoms spontaneously resolve within a few hours after drug discontinuation.

Overdosage

No data about overdosage in humans are available. Sedative effect and fatigue may develop if taken at doses exceeding therapeutic.

Drug Interactions

It is not recommended to combine the drug with mucolytic or expectorant agents, as it may inhibit expectoration, fluidified by the latter.

There are no preclinical or clinical data available on interaction with other drugs.

Special Warnings

The drug may cause gastrointestinal problems in patients with lactose intolerability, as tablets contain lactose (0.38 mg lactose in each tablet).

Effects on Ability to Drive and Perform Operations Associated with Increased Hazard:

Product intake at high doses may affect the speed of reaction, that is why when the drug is taken at high doses, the possibility of driving or performing operations associated with increased hazard should be assessed individually.

Presentation

Tablets 100 mg
20 tablets in a blister of polyvinylchloride film and Alu foil.
1 blister and a package insert in a carton pack.

Storage Conditions

Keep at a temperature below 25 °C.
Keep out of reach of children.

Shelf Life

5 years.
Do not use after the expiry date specified on the package.

Rx Status:

Over the counter drug

Manufacturer

CHINOIN Pharmaceutical and Chemical Works, JSC
1045 Budapest, To U 1-5, Hungary.

Consumer claims are to be sent to the following address:

115035 Moscow, ul. Sadovnicheskaya, 82, bld. 2
Tel. (495) 721-14-00, fax (495) 721-14-11.

Acting Director of the Institute of Preclinical and Clinical Drug Expertise (signature) A.N. Vasiliev

(stamp)
FEDERAL STATE INSTITUTION * MOSCOW
Scientific Center of Expertise of Medicinal Drugs
Ministry of Healthcare of the Russian Federation
Institute of Preclinical and Clinical Drug Expertise

For Copies and Instructions
Company Representative (signature) A.B. Raskurazhev
(stamp)
Representation of joint stock company * Permission of State Register under the Ministry of Justice of the Russian Federation No 11772 * Moscow
Sanofi-aventis groupe (France)

(stamp)
RUSSIAN MINISTRY OF HEALTHCARE
П N015126/01 – 19.07.13
APPROVED

MINISTRY OF HEALTHCARE OF THE RUSSIAN FEDERATION

PRESCRIBING INFORMATION
For a medicinal drug

Libexin®

Name of the medicinal drug

Tablets

Pharmaceutical form, dosage

CHINOIN Pharmaceutical and Chemical Works, JSC, Hungary

Manufacturer name, country

Amendment No 1

Date of amendment: 19/07/13

Previous Version	Current Version
Side effects *Allergic Reactions* Rare: - skin rash; - Angioedema *Gastrointestinal tract disorders* - Rare: - dry mouth or throat; - Anesthesia (temporary numbness and loss of sensitivity) of oral mucosa; - Less than in 10% cases: - Gastric pain; - Disposition to constipations; - Nausea *Nervous system disorders* (at high doses) - Mild sedative effect;	**Side effects** *Allergic Reactions* Rare: - skin rash; - Angioedema Frequency unknown: bronchospasm *Gastrointestinal tract disorders* - Rare: - dry mouth or throat; - Anesthesia (temporary numbness and loss of sensitivity) of oral mucosa; - Less than in 10% cases: - Gastric pain; - Disposition to constipations; - Nausea *Nervous system disorders* (at high doses) Mild sedative effect

Appendix 2
Six-point daytime and nighttime cough assessment scale

Score	Daytime cough	Score	Nighttime cough
0	No cough	0	No cough
1	Single cough impulses	1	Cough does not interfere with sleep
2	Rare cough at daytime	2	Cough interrupting sleep not more than 2 times in a night
3	Frequent cough not interfering with daily activities	3	Cough interrupting sleep over 2 times in a night
4	Frequent cough impairing daily activities	4	Frequent sleep interruption caused by cough
5	Severe cough, impossible to maintain daily activities	5	Cough precluding sleep

Appendix 3

Visual analog scale

Please mark on the scale below your cough intensity.

Cough Intensity

no cough — Heavy, Severe cough

NB: Please use only VAS provided by IPHARMA and avoid to perform any copy of the form.

In case, for any reason, you need to perform a reproduction of the form, after any reproduction verify the length of the VAS: the line must be 100 mm