

MINIMUM CRITERIA TO BE CONSIDERED FOR THE PRESENTATION OF THE ACTIVE PHARMACOVIGILANCE PLAN

ACTIVE PHARMACOVIGILANCE			
REGISTER OF THE POSTMARKETING STUDY			
NCT number:	NCT02910167	Date of protocol submission:	10 January 2017
1. ORGANIZATION / REQUIRING INSTITUTION			
Name of the Organization / Institution:	Boehringer Ingelheim Perú S.A.C	Type of Organization / Institution:	Pharmaceutical Industry
Legal address:	Av. Canaval y Moreyra 480 Urb. Limatambo (piso 20)		
District:	San Isidro	Province:	LIMA
Region:	Lima		
Tax Number:		e-mail:	
Phone:			
2. INFORMATION ABOUT THE PHARMACEUTICAL PRODUCT			
Tradename of the pharmaceutical product	Buscapina Compositum N	Generic name	Hioscina N – Butilbromuro / Paracetamol
Type of product	Chemical synthesis	ATC	A03DB04
Number of sanitary register	E8613	Date of sanitary register	Expiration date: 7/7/2020
Safety problems identified	Hepatobiliary disorders: Increased hepatic transaminases (ASAT/ALAT).		
Observational study proposed (analytic or descriptive)	Descriptive cohort study		
3. GENERAL INFORMATION OF THE PHASE IV STUDY			
Study Title (average 20 words)			
Observational prospective cohort study to evaluate the incidence of adverse events (AE), risk factors, and drug utilization patterns related to treatment with BUSCAPINA COMPOSITUM N from March to December 2016 in patients from Metropolitan Lima.			
Study rationale or problem identified:			
<p>Buscapina Compositum N is an oral analgesic indicated for adults and children over 12 years old, for the relief of spasmodic pain in stomach and intestinal illness, colic-type pain and functional disorders of biliary and urinary tracts and of the female genital organs. Each tablet of Buscapina Compositum N has a combination of 10 mg of hyoscine n-butylbromide and 500 mg of Paracetamol. The dose of Buscapina Compositum N is one to two tablets by mouth every 8 hours, swallowed whole with sufficient water. The following is a description of each of the components of Buscapina Compositum N, as well as the studies of efficacy and safety that have evaluated these components.</p> <p>Paracetamol</p> <p>Paracetamol is a derivative of acetanilide with antipyretic and analgesic properties, and weak anti-inflammatory properties. The mechanism of action of paracetamol is still debated. The mechanism proposed was the inhibition of prostaglandin synthesis by blocking cyclooxygenase (COX) enzymes COX-1, COX-2 and a variant of COX-1 centrally expressed, COX-3. But to explain the differences with other analgesics, other mechanisms were postulated for paracetamol: central activation of descending serotonergic pathways, inhibition of the nitric oxide synthase enzyme, involvement of the metabolite N-arachidonoylphenolamine (AM404) which activates the vanilloid</p>			

subtype 1 receptor (TRPV1), influence on subtype 1 cannabinoid receptors (CB1) and inhibition of the uptake of the endocannabinoid anandamide. Endogenous opioids could also contribute to the antinociceptive effects of paracetamol at a spinal level (1, 2, 3). It presents a lower number of toxic effects in the GI tract compared to NSAIDs, as constipation, vomiting (initially), nausea and, uncommonly, dry mouth. It can produce, but very rarely, thrombocytopenia and leukopenia. Other haematological reactions including agranulocytosis or pancytopenia have been reported. It rarely causes bronchoconstriction in asthmatic patients who are sensitive to aspirin. Paracetamol produces only a moderate inhibition of COX-1, as reflected in its weak anti-clotting activity and its good gastrointestinal safety. At normal therapeutic doses, metabolism is principally hepatic to sulfate and glucuronic conjugates, while a small amount is metabolized in the liver by CYP2E1. It has a half-life of elimination in adults of approximately 2 hours, while 3 to 7 hours in pediatric populations, and is excreted principally in urine (4, 5).

Efficacy

Paracetamol, also known as acetaminophen, has been commonly used as an antipyretic as well as analgesic for mild to moderate pain relief for approximately 50 years and has relatively few side effects (4). Li Wan published a meta-analysis in 1997 that evaluated the efficacy and tolerance of paracetamol against a placebo, finding 15 randomized control trials. In total, 1144 patients were included, and the difference in grouped means of pain intensity was 9.4% (6.9% to 11.9%) with a fixed effects model and 9.4% (6.6% to 12.2%) with a randomized model, indicating that paracetamol is an effective analgesic based upon this measured effect (6).

In 2013, Moore and Derry published a review analyzing the Efficacy of OTC analgesics; the main sources for this review are Cochrane reviews or overviews of the efficacy of analgesics. Regarding acetaminophen the authors analyze doses ranging from 500 mg in fixed combinations to 1000 mg as a single substance. The single substance use (18 studies with a mixed sample of 2171 patients) show an NNT of 3.3 (3.0-3.7) using a dental pain extraction model. In comparison, the authors report a NNT of 4.7 (3.4-7.6) for Acetylsalicylic Acid 1000 mg as a single substance (7). This means that in the mentioned doses fewer people have to be treated with Acetaminophen to obtain one positive result in post dental surgery pain management.

Another review, published by Cochrane (Toms et al.) in 2008 analyzes the use of oral paracetamol for postoperative pain in adults; this review included randomized, double blind, placebo controlled clinical trials. A mixed sample of 3277 patients belonging to 51 studies was analyzed. The reviewed outcomes included patient reporting pain at baseline with hourly evaluation over four to six hours, patient global evaluation of treatment, rescue medication utilization, withdrawals and adverse events (AE). About half of the patients reported improvement of at least 50% over four to six hours (v. 20% in placebo group). The reported NNT for the group of patients using a dose of 500 mg of paracetamol was 3.5 (2.7-4.8) and there was no dose response relationship (NNT did not change much with higher doses). AE were mostly of mild intensity and the occurrence rate was similar to the placebo one. This results show that for an important number of patients, paracetamol is an effective and safe way to treat pain (8).

The role of paracetamol prevails in the treatment of mild acute pain and the management of fever, especially in the

pediatric population. For greater pain intensity, paracetamol has been used in combination with other non-steroidal anti-inflammatory, or opioids. A review conducted in 1999 by Ward and Alexander-Williams (2) found diverse meta-analyses in which the combination of paracetamol with opioids presents greater efficacy for the relief of post-operative pain (3, 6).

Safety

AE reports for paracetamol are relatively rare. Paracetamol presents a rate of AE that is much lower than other pharmaceuticals, such as acetylsalicylic acid, whose gastrointestinal effects (gastrointestinal ulcer and bleeding associated with ulcers) are frequent (9). The various studies that have subsequently been done with paracetamol, both in humans and in animals, have established this as an analgesic drug with low ulcerogenic capacity (10). The principal AE of paracetamol are hepatic and renal toxicity that are produced infrequently, either by suicide or by accidental poisoning at high doses (11). A single dose of paracetamol of approximately 6g (12) or more in adults or 140 mg/kg in children (13) may cause hepatocellular necrosis.

The lethal dose for paracetamol is about 10 g (hepatotoxicity) (14, 15). The symptoms in the first 24-48 hours do not reflect the gravity of the hepatic damage. Nausea, vomiting, and abdominal pain can occur initially, but clinical signs of hepatic damage take 2-4 days to appear. In serious cases, acute renal insufficiency and coagulopathies can present (16).

In the pediatric population, acute ingestion of more than 140mg/kg is associated with hepatotoxicity and death when not treated in time. Children under six years of age are relatively less susceptible to toxicity, and tend to have a lesser incidence of clinical and biomedical hepatotoxicity in levels of paracetamol similar to older children and adults (17).

Hyoscine n-butylbromide

This is a quaternary antimuscarinic amine derivative of scopolamine. It is used to treat cramps in the gastrointestinal, urinary, and uterine tract, as well as biliary ducts and to facilitate the radiologic visualization of the gastrointestinal tract. It is principally metabolized in the liver, with an elimination half-life of between 5 and 11 hours, and is 42-61% excreted in urine, and 28-37% excreted in stool. (18)

Safety

Due to its low level of absorption, HBB is well-tolerated, presenting few AE. Studies by Schäfer (19) and Mueller-Lissner (20) compared, in total, 30mg/day of HBB (n=597) with placebo (n=592). There was no significant difference in the presence of AE between the two groups, including those effects most commonly associated with anticholinergics, such as nausea, constipation, dry mouth, and blurred vision among others. These events occurred in less than 1.5% of the participants (21).

In the same way, Herxheimer and Haefeli conducted a study with healthy volunteers who received high doses of

HBB (200, 350 and 600mg) without finding the induction of anticholinergic effects (cardiac frequency changes, vision changes, or salivary excretion). Additionally, the patients exposed to the highest doses did not present central nervous system effects, demonstrating that HBB is safe (18).

Combination of hyoscine n-butylbromide and Paracetamol

Multiple studies have evaluated the efficacy and safety of the combination of HBB and paracetamol, especially in the management of colic-like abdominal pain. Schafer and Ewe conducted a randomized double blind study in 1990 that involved 712 patients with irritable bowel syndrome. During a treatment period of 4 weeks they compared: hyoscine n-butylbromide (30 mg/day) plus paracetamol (1500 mg/day), hyoscine n-butylbromide (30 mg/day), paracetamol (1500 mg/day) or placebo (3 tablets/day). Patients maintained a record and classification of their symptoms (visual analogue scale). At the end of the four weeks 81% of the patients in the group with HBB + Paracetamol presented marked or somewhat improvement in symptoms. Statistically significant improvement was seen in 76% of the HBB group, 72% in the paracetamol group, and 64% in the placebo group. The daily rating of pain in analogue scale showed statistically significant improvement in the intensity of abdominal pain in the group with HBB + paracetamol in comparison with the placebo group and the paracetamol group. AE were present in 5% of the participants, without differences between the treatment groups, and did not require treatment (19).

Similar results were reported by Mueller-Lissner et al. when comparing the efficacy and the tolerance of 10 mg of HBB, 500mg of paracetamol and their fixed combination in doses three times a day against placebo in patients with recurrent colic-type abdominal pain. They found that the three treatments were more effective than the placebo related to symptom relief, without differences among these three (20).

In November 2014, the Peruvian General Direction of Medicines, Supplies and Drugs (DIGEMID) began requiring an active pharmacovigilance program in category C products. Additionally, in June 2015 DIGEMID requested that all holders of products containing paracetamol in quantities over 325 mg submit an Active Pharmacovigilance Plan. In order to meet this requirement, Boehringer Ingelheim will conduct active pharmacovigilance by implementing an observational prospective cohort study on Buscapina Compositum N to identify, describe, and assess the incidence of AE and drug utilization patterns of BUSCAPINA COMPOSITUM N when used in routine, clinical practice, according to the label indications in Lima.

Objective(s)

The objectives of this Non-interventional Study (NIS) are to:

- 1.) Identify and describe the AE and adverse drug reactions (ADR) presented in patients that are undergoing treatment with BUSCAPINA COMPOSITUM N in Metropolitan Lima.
- 2.) Descriptively analyze transaminase levels found by the doctor during the clinical evaluation of patients with symptoms related to potential liver damage.
- 3.) Determine the drug utilization pattern of BUSCAPINA COMPOSITUM N in patients in Metropolitan Lima.
- 4.) Determine related variables for the occurrence of increase of transaminases in patients under treatment with BUSCAPINA COMPOSITUM N in Metropolitan Lima, Peru.

Hypothesis:

Our hypothesis is that the frequency of AE is no greater than 1.0%

Research Questions:

What AE occur in routine clinical practice in patients that are in treatment with BUSCAPINA COMPOSITUM N (when it is used according to the label indications)?

What is the incidence of AE and ADR in patients that are in treatment with BUSCAPINA COMPOSITUM N when it is used in routine clinical practice according to label indications?

How many patients present with AE symptoms related to a potential liver injury?

What are the drug utilization patterns in patients who receive BUSCAPINA COMPOSITUM N in pharmacies, clinics and private doctor’s office in Metropolitan Lima Peru?

What are the predisposing factors for the occurrence of adverse events and adverse drug reactions in patients who receive BUSCAPINA COMPOSITUM N in Metropolitan Lima Peru?

Protocol population:

We will include patients 18 years of age and older who attend pharmacies, clinics, or private doctor’s office in Lima - Peru and who have received at least one dose of BUSCAPINA COMPOSITUM N according to the label indications (Patients with any type of gastrointestinal, hepato-biliary, urinary or genital spasmodic syndromes).

<p>Simple size(number of subjects to be enrolled)</p>	<p>Since most studies have reported a frequency of AE higher than 1%, to calculate the sample size we used this percentage as reference. We should therefore enroll 300 people in order to detect up to 2 AE, considering an anticipated incidence of 0.01 and a power of 80%. Additionally we will enroll 60 more patients to offset a possible loss to follow up of patients of 20%. In total, therefore, we will enroll 360 persons.</p>	<p>Rationale for the sample size (procedure, formula and software used)</p>	<p>To calculate the sample size, we have used the following formula for cohort studies with no background incidence of AE:</p> <div data-bbox="1045 1270 1437 1417" style="border: 1px solid black; padding: 10px; margin: 10px 0;"> $\beta = \sum_{i=0}^{A-1} \frac{N^i (R0)^i e^{-N(R0)}}{i!}$ </div> <p>The anticipated incidence rate of AEs is $R0$, the number of occurrences of a particular AE is A, the number of patients is N, and β the probability that we will not find A events in the sample of N patients. If $R0$ is small, we may assume that the occurrence of an AE follow the Poisson distribution. The formula shown above is useful in determining the values of β, $R0$, A and N. Given that we have the values for β, $R0$ and A, once introduced in the formula we obtain the result of N (the sample size).</p>
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			The sample size was calculated using the PASS program version 11 (www.ncss.com/software/pass).
Number of patients according to sex (initial number)	We will enroll both genders in the sample in order to reach the desired sample size	Age range for subjects to be enrolled	Patients 18 years and older.
Inclusion criteria (sex, diagnostic criteria, comorbidities etc.)			
<ol style="list-style-type: none"> 1) Patients 18 years of age and older who have received at least one dose of BUSCAPINA COMPOSITUM N according to label indications and who attend to one of the pharmacies, clinics, or private doctor's office selected for the study. 2) Patients who agree to adhere to the protocol procedures of this study. 3) Women who are not pregnant or breast feeding 4) Persons who sign the informed consent 			
Exclusion criteria			
<ol style="list-style-type: none"> 1) Patients with allergy to BUSCAPINA COMPOSITUM N or any of the compounds in the formula. 2) Patients with mechanical stenosis of the gastrointestinal tract. 3) Patients with myasthenia gravis. 4) Patients with megacolon. 5) Patients breastfeeding at the time of enrollment or who have become pregnant during treatment with BUSCAPINA COMPOSITUM N. 6) Patients with clinical evidence of immunosuppression. 7) Patients with urinary retention subvesical obstruction (such as prostatic adenoma). 8) Patients with right-angle glaucoma. 9) Patients with tachycardia and tachyarrhythmia. 10) Patients with severe hepatic impairment. 11) Patients with psychiatric disorders. 12) Patients with alcohol dependence or drugs. 13) Patients who discontinue the protocol are not eligible for re-enrollment. 14) Researchers, company personnel or their relatives. 			
Study period	Approximately 12 months	Medical specialty (ex oncology)	Emergency, General Medicine, Internal Medicine, Gastroenterology and any other department identified where BUSCAPINA COMPOSITUM N is prescribed
Condition under study (Classification ICD-10)	Other and unspecified abdominal pain R10.4 Calculus of bile duct without cholangitis or cholecystitis K80.5 Unspecified renal colic N23 Dysmenorrhoea, unspecified N94.6		
City (ies) in which the study will be conducted	Lima		
Study procedure and data collection (surveys, interviews, home visits, etc)			

PROTOCOL DESIGN

This is a 12-month active pharmacovigilance, prospective, cohort multicenter study to determine the incidence of AE associated to increase of transaminases in patients who have received at least one dose of BUSCAPINA COMPOSITUM N according to label indications.

We will select approximately 15 patient recruitment centers (Clinics, private doctor's office and pharmacies). We will prioritize the clinics, pharmacies and private doctor's office with the highest volume of BUSCAPINA COMPOSITUM N sales.

Enrollment of Patients and Informed Consent

All of the patients who attend a pharmacy to buy BUSCAPINA COMPOSITUM N or patients who have been treated in Emergency, General Medicine, Internal Medicine, Gastroenterology or any other department, or private practice where BUSCAPINA COMPOSITUM N is prescribed will be approached by a trained health person of the Project (a nurse technician, a nurse, or a licensed midwife). The health personnel will conduct an informed consent. The consent will include all of the information that patients need to know about the study such as protocol objectives, the risks and benefits of participating in the study, and the contact information of the principal investigator and co-investigator whom the participant shall call if they have any question or any AE. It will also include the contact number of the IRB.

After reading the informed consent and once the patients' questions are resolved, the site personnel will ask them if they want to participate. If a patient agrees to enter into the study, the investigator or designee and the patient will sign an informed consent. The investigator or designee will give a copy of the informed consent to the participant. Inclusion and exclusion criteria shall be met before patient enrollment.

Baseline survey

Once a patient has agreed to participate, we will proceed with applying a face to face survey, administered by the surveyor, in order to collect demographic data, and information related to the BUSCAPINA COMPOSITUM N prescription. This data will include: name, birthdate, gender, race, telephone contact, diagnosis, indication for initiation of treatment with BUSCAPINA COMPOSITUM N, date of initiation of treatment, dose regimen prescribed, treatment duration (at least one dose), treatment end date, administration route, symptoms prior to initiating treatment (it is important to identify possible pre-existing liver injuries), laboratory test results, medical history, itself and familial history of liver disease and biliary tract disease, concomitant therapy, alcohol and drug consumption history, and name and phone of prescribing doctor.

For this survey, we will use Open Data Kit Collect (www.opendatakit.org), a mobile application based in Android that serves to digitize data collection through formats that automatically include georeferencing data. This application has been widely used in epidemiology in the field in various parts of the world for real-time monitoring in outbreaks, for example, of influenza (22) and Ebola (23).

Patient Follow Up

All patients who enter the study will be given a follow up card. In this card we will ask participants to register daily whatever symptoms or bothers that he/she may experience. Additionally, we will register their consumption of other

concomitant pharmaceuticals or vaccines. The patient alert card will also have the contact information of investigators, should the participant wish to contact him. Participant responses will be collected in the Smartphone with Open Data Kit collect.

Given that the half-life of the components of BUSCAPINA COMPOSITUM N is from 2-11 hours, we will perform follow up to patients until a maximum of 3 days after their final dose of the drug. During follow up with patients, we will describe in CRF and Non-Interventional Study AE form the AE that occur, the date of the start of the AE, its intensity, the date of its resolution, the treatments that were a result of the AE, how the adverse event was resolved, the causal evaluation of the AE medical history information and any relevant laboratory information, concomitant medications and the contact information of the attending doctor.

Drug Utilization Patterns

In order to evaluate drug utilization patterns, both in the baseline survey as well as in the follow-up we will ask How have you been instructed to take BUSCAPINA COMPOSITUM N? When did you start to take BUSCAPINA COMPOSITUM N? When did you finish taking BUSCAPINA COMPOSITUM N? How many doses per day did you receive of BUSCAPINA COMPOSITUM N? Where do you store BUSCAPINA COMPOSITUM N?

If the participant takes another medication, What is the indication? What is the formulation of that medication (capsule, suspension, injectable)? What is the route of administration? What is the start date and stop date of the medication, the concentration, dose and frequency?

Registry of Adverse Events

Definition of Adverse Event

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Whatever adverse change clinically significant in the frequency or intensity of a preexisting condition associated temporally with the use of the pharmaceutical will also be considered an AE. We will not consider the changes that result in normal growth and development as AE, which do not vary in the frequency of severity in respect to expected levels (Example: beginning of menstruation or menopause). All AE will be collected from the moment that the participant signs the informed consent document until a maximum of 3 days following the last time that the patient used the medication. Such events will be registered in the Non-Interventional Study AE form of the study and will be reported to Boehringer Ingelheim Peru S.A.C. within 24 hours/ 1 work day of the occurrence of the AE.

Adverse Drug Reaction (ADR)

An ADR is defined as a response to a medicinal product, which is noxious and unintended. Response in this

context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Definition of an overdose

An overdose will be defined as the administration of more than 6 tablets of BUSCAPINA COMPOSITUM N per day.

Report of an Overdose

We will collect information about any cases of overdose, related or not to the occurrence of an AE.

Report of Pregnancy/ Breast Feeding Events

In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken Buscapina Compositum N, the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject to the Sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

The report will be forward to Boehringer Ingelheim Peru S.A.C. within 24-hours/1-work day of the confirmed event.

Serious Adverse Events

We will collect information about all AEs, including serious AE that occur for any participant from the moment that the informed consent is signed until 3 days after the participant stops receiving BUSCAPINA COMPOSITUM N, whether or not the event is associated with the product under investigation. We will complete follow up with all of the participants that present with serious AE to determine the outcomes of the events. The serious AE will be registered in the NIS AE form of the study and will be reported to Boehringer Ingelheim Perú S.A.C. who will report to DIGEMID within 24 hours/ 1 workday from the time of the event's occurrence. A summary of reporting is in the table below.

Expedited Reporting of AEs and Drug Exposure During Pregnancy

The following must be reported by the investigator on the NIS AE form from signing the informed consent onwards until the end of the study:

Type of Report	Timeline
All SAEs associated with Buscapina Compositum N	immediately within 24 hours
All AEs with fatal outcome in patients exposed to Buscapina Compositum N	immediately within 24 hours
All non-serious AEs associated with the Buscapina Compositum N	7 calendar days
All pregnancy monitoring forms	7 calendar days

EVALUATION OF ADVERSE EVENTS

For participants that present with AE we will offer a free evaluation by one of the study's physicians within 3 days of the occurrence of the report. The medical evaluation will be the habitual medical evaluation that the patient could

require according to the reported symptoms and detected signs. The evaluation will be given in the same place that the patient was attended to. During such evaluation, the physician will evaluate if the medication is definitively related, probably related, possibly related, probably not related or definitively not related to the event. In the NIS AE form the investigator should define the causality as related or not related. If the patient is taken without study supervision to a clinic or emergency, the study physician/supervisor must be informed immediately in order to attend the patient and be able to evaluate the situation. This evaluation will be shared with the attending physician and will be reported to Boehringer Ingelheim Perú S.A.C. within 24 hours/ 1 workday from the time of the event's occurrence. Causal assessments by Investigator will be based on the Karch Lassagna model (24). As Boehringer Ingelheim assessment in NIS is yes or no, in the table below it is summarized how the causality will be matched.

Karch Lassagna Assessment	BI Assessment
Certain Probable /Likely Possible Conditional, unclassified	Yes, positive relationship
Not assessable, unclassified	Not reported
Unlikely Not related	No, not related

The study physician will register the following information:

1. Maximum Intensity

- a. Light/Minimal: The signs or symptoms are perceived but easily tolerated
- b. Moderate: Sufficient discomfort that interferes with daily activities
- c. Severe: Incapacitating, impeding work or daily activities

2. Seriousness

2.1 A serious AE is any event that occurs with whatever doses and that implies at least one of the following situations:

- Causing death
- Risking the life of the participant or putting the participant at risk for imminent death due to the event that occurred
- Causes a state of permanent or significant disability
- Causes or prolongs an existing hospitalization
- Is a birth anomaly or birth defect
- Is a type of cancer
- Is an accidental or intentional overdose
- Other important medical events that possible do not cause death, nor put at risk the life of the participant, or do not involve hospitalization can be considered a serious AE if the event puts at risk the participant and requires a possible medical or surgical intervention in order to avoid one of the four previously mentioned results.

3. Duration

We will register the dates of the beginning and the end of the AE. If it is less than one day, we will indicate the lapse in time and the appropriate unit of measurement.

4. Action Taken

Did the AE result in the discontinuation of BUSCAPINA COMPOSITUM N?

5. Relation to BUSCAPINA COMPOSITUM N

Did BUSCAPINA COMPOSITUM N cause the AE? A qualified physician will determine the probability that BUSCAPINA COMPOSITUM N was the cause of the AE. For the determination of the causality of the AE we will use the Karch Lassagna algorithm modified by the Spanish Pharmacovigilance System.

The following criteria will serve as a reference to evaluate the probability of the relation between BUSCAPINA COMPOSITUM N and the AE:

5.1 Presentation

Is there some evidence that the participant was actually exposed to BUSCAPINA COMPOSITUM N? (Medical Record, etc.)

5.2 Time Lapse

Did the AE occur in a reasonable amount of time after the use of BUSCAPINA COMPOSITUM N? The start of the AE is compatible with an effect induced by BUSCAPINA COMPOSITUM N?

5.3 Alternative Causes

Is the AE reasonable explained by another etiology such as an underlying illness, other medications or other factors of the host, or environmental factors?

5.4 Interruption

Did the participant interrupt the course of BUSCAPINA COMPOSITUM N administration? Did the AE improve or disappear? If the answer is positive to both questions it is considered a positive interruption.

5.5 Re-exposure

Was the participant re-exposed to BUSCAPINA COMPOSITUM N? Did the AE reappear or get worse? If the answer to both questions is affirmative, it is considered a positive re-exposure. If the answer is negative, it is considered a negative re-exposure.

5.6 Consistency with the profile of BUSCAPINA COMPOSITUM N

Is the clinical and pathological presentation of the AE consistent with previous knowledge of BUSCAPINA COMPOSITUM N?

The study's physician will communicate the evaluation of the relationship using the best clinical criteria, taking into account the previously noted criteria.

Definitively related

Evidence exists of the exposure to BUSCAPINA COMPOSITUM N. The temporal sequence of the start of the AE in relation to the administration of BUSCAPINA COMPOSITUM N is reasonable. It is very probable that the AE has its explanation in BUSCAPINA COMPOSITUM N use as opposed to another cause. The interruption is positive. The re-exposure (if plausible) is positive. The AE follows a consistent pattern with what is previously known about BUSCAPINA COMPOSITUM N.

Probably related

There is evidence of the exposure to BUSCAPINA COMPOSITUM N. The temporal sequence of the start of the AE in relation to the administration of BUSCAPINA COMPOSITUM N is reasonable. It is very probably that the AE has its explanation in BUSCAPINA COMPOSITUM N rather than in another cause. The interruption (if occurs) is positive.

Possibly related

There is evidence of the exposure to BUSCAPINA COMPOSITUM N. The temporal sequence of the start of the AE in relation to the administration of BUSCAPINA COMPOSITUM N is reasonable. The AE could have been caused by another cause that is as equally probable. The interruption (if occurs) is positive.

Probably not related

There is evidence of the exposure to BUSCAPINA COMPOSITUM N. There is another cause that is more probable for the AE. The interruption (if occurs) is negative or ambiguous.

Definitely not related

The participant did not receive BUSCAPINA COMPOSITUM N, or the temporal sequence of the start of the AE in relation to the administration of BUSCAPINA COMPOSITUM N is not reasonable, or other obvious causes exist for the adverse event.

Ethics Committee

We will obtain ethical approval from the ethical committee of the Non-Governmental Organisation (NGO) Via Libre. This committee holds a national registration as committee RCEI-32 and its approval is found active on the webpage of the Instituto Nacional de Salud (the Peruvian National Institute of Health) (<http://www.ins.gob.pe/portal/jerarquia/2/937/busqueda-de-comites-institucionales-de-etica-en-investigacion-registrados/jer.937>)

Protocol activities table:

	2015	2016										
	Dic	Mar	Abr	May	Jun	Jul	Ago	Set	Oct	Nov	Dic	
	1	2	3	4	5	6	7	8	9	10	11	
IRB approval	X											
Patient enrollment		X	x	x	x	x	x	x	x			
Patient follow-up		X	x	x	x	x	x	x	x			
Data analysis											X	
Final study report writing												X

Data analysis and interpretation of results

1. Name of the result:

-Description of AE

-Incidence of AE
-Frequencies of use types
-Predisposing factors for AE occurrence

2. Statistical method used:

1. For the first objective of the study a descriptive statistical analysis of frequencies will be conducted for the adverse events that are discovered.
2. For the second objective of the study, If data is available the incidence rate will be calculated including in the numerator the number of cases of people who develop an adverse event, and in the denominator the sum of the different amounts of person time that each participant in the study contributes.
3. For the third objective, we will complete a descriptive statistical analysis related to the drug utilization patterns in all patients. and compare patterns between those with and without AE.
4. For the fourth objective, we will conduct a logistic regression analysis to identify risk factors (such as past medical history, concomitant illnesses, drug utilization factors of the medication, and concomitant treatments) in patients that present with AE and adverse drug reactions related to treatment with BUSCAPINA COMPOSITUM N.

Descriptive analysis:

For the univariate analysis of quantitative variables such as age, dose, and time of product intake, and transaminases values (if become available) we will use central tendency and dispersion measures. For the analysis of categorical variables such as gender, race, indications for which BUSCAPINA COMPOSITUM N is prescribed, physician causality assessment, physician seriousness assessment, among others, we will use frequencies and percentages. For the bivariate analysis of categorical variables we will use chi-squared or Fisher exact test. For the analysis of quantitative variables, we will use the student T test or Mann-Whitney U test. Analysis will be conducted using STATA software version 13.

3. Study period

We will conduct the study in approximately 12 months; this period will include the IRB application, patient recruitment and follow-up, data analysis and final study report writing. The time between first patient first visit and last patient last visit will be 8 months.

4. Limitations of the study

Our study has some limitations. First, since we are conducting the study only at pharmacies, clinics (and not Hospitals) and private doctor's office, our study cannot be generalized to the whole population who use BUSCAPINA COMPOSITUM N in Lima. Second, we are conducting a cohort study without a control group, thus we will not be able to compare the incidence of AE with a group of patients not exposed to BUSCAPINA COMPOSITUM N. To address this issue we will perform a comparison with the incidence of AE found in other studies described in the introduction section of this protocol. Additionally, the weekly phone calls to participants to assess if they have developed an AE will affect the frequency of reporting of AE (compared to the frequency that

could have been found with spontaneous reporting of AE)

Sponsor :			
Boehringer Ingelheim Perú S.A.C.			
Financial source			
Boehringer Ingelheim Perú S.A.C.			
Executing institution :			
Sin Brechas S.A.C.			
Date for study start	March 2016	Estimated date for end of study	December2016

4. INVESTIGATIONAL SITES, PRINCIPAL INVESTIGATOR, ETHICS COMMITTEE

Investigational sites where the study will be conducted (*)	Principal investigator	institutional review board that approves the study for the site			Term	Observations
	Name and Surname	Name of the institutional review board	approval date	Expiration date		
Pharmacy chains: Boticas InkaFarma, Mifarma, Arcángel, Boticas y Salud, Nortfarma. Seguro Social de Salud, among others. Clinics: Clínica Internacional, Clínica Médica Cayetano Heredia, among others. private doctor's offices Independent pharmacies such as América Salud, Corporación Boticas Perú, Grupo Lives, Ceci Farma, Farmacia universal, Inversiones Farmacom, Drugstores: Droguería Las Américas, among others.	[REDACTED]	Vía Libre				
	Co-Investigadores					
	[REDACTED]					

5. INFORMATION OF CONTACT PERSONS FOR THE STUDY

NAME and Surname	Email	phone	Type of queries to answer		
			Queries from public in general	administrative queries	scientific queries
[REDACTED]	[REDACTED]	[REDACTED]	X		X
[REDACTED]	[REDACTED]	[REDACTED]	X	X	

APPROVAL STATUS (DIGEMID)

Under evaluation() approved: () Observed:()

REASON FOR OBSERVATION:

Active Pharmacovigilance. Consists in obtaining information of the safety profile of the medicinal products in a systematic way in general regarding a certain medicinal product (or group of medicinal products), or a certain disease during an specific timeframe. It allows to determine the frequency of ADR, identification of predisposing factors, drug utilization factors etc.

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