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Report on results

Clinical trial of Vidatox ® 30 CH
among patients suffering from advanced tumours

Grupo Empresarial LABIOFAM
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Abstract

A clinical trial of Vidatox 30® CH has been carried out to gauge the effectiveness and safety of administering this homeopathic formulation of the venom of the *Rhopalarus junceus* scorpion. Its volunteer subjects were 114 patients diagnosed with advanced tumours (confirmed histologically) from hospitals and other recognized healthcare centres in various parts of the world, and who attended Grupo Empresarial LABIOFAM's medical service between July 2010 and September 2011. The results of the study included favourable clinical performance by 74.6% of the patients who took the product, reflected in an improved quality of life. The best results were obtained with a dosage regime of 3 times daily. No adverse events were reported.

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I. GENERAL

1.1 Study title
Study of the use of Vidatox ® 30 CH among patients with advanced tumours.

1.2 Participating organizations
Grupo de Investigación y Desarrollo LABIOFAM.

1.3 Carried out by
Laboratorio Vimang
Calle 100 y Ojo del Agua. Municipio Arroyo Naranjo, Havana, Cuba.

1.4 Chief researcher
Dr Mariela M. Guevara García. Grade II specialist in pharmacology.
Assistant researcher,
Grupo de Investigación y Desarrollo LABIOFAM.

1.5 Sponsor
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II. INTRODUCTION

A drug's arrival on the market is preceded by a lengthy period of basic research and preclinical and clinical testing, followed by public-health registration based on an assessment of its efficacy and safety results by the regulating body. But the data derived from these tests needs to be supplemented by evidence gleaned from use of the preparation under the conditions of routine medical practice.

Thus pharmacological monitoring of the drug being marketed plays a key role in detecting, assessing, identifying and preventing adverse effects or any other problem associated with its use.[1] Certain studies have shown that some 4% of new chemical and biological remedies marketed have to be withdrawn because of side effects that were not discovered during the clinical trials. Studies in the United States and elsewhere have reported over 100,000 deaths annually attributable to the adverse effects of medicines.

The reported incidence of such effects varies among studies from 1% to 30%, reflecting differing methods for detecting and assessing these, the various bases for prescribing drugs and the inclusion or exclusion of minor effects. Such experiences have highlighted the need for post-sales monitoring, based on a stage involving a large number of diverse actors and providing daily a source of additional evidence regarding the safety and pharmacological profile of the medication.

This explains why regulatory bodies and public health authorities in various countries adopt their own sets of standards, decrees and other legal instruments as regards post-marketing studies of medicines, aimed at determining whether they are being used for the purposes for which they were approved, or in the context of routine clinical practice, as well as clarifying their beneficial and adverse effects.

In Cuba, the Ministry of Public Health's regulatory body is the Regulatory Bureau for the Protection of Health (BRPS). The latter's institutions include the Centre for State Control of the Quality of Medicines (CECMED), which is tasked with deciding on the registration, within a given timeframe, of any product assessed; it also coordinates the monitoring and post-marketing activities of Cuba's pharmaceutical industry and of centres operated by the country's scientific community.

Homeopathy is a treatment method firmly rooted in the field of medical and human sciences known as holistic medicine. It evokes a reaction by the sick organism, triggering the patient's healing mechanisms. It is held, in theory, that recovery of the balance lost during illness is achieved by stimulating the immune system, through the 'law of similarity'.

One field of application of homeopathic preparations is in the complementary treatment of neoplasm, given the absence to date of totally effective therapies. The application of scorpion venom in anti-tumour treatment originated in research by Debin & col. in 1991, which demonstrated for the first time that the venom of the *Leiurus quinquestriatus* scorpion possessed anti-tumour activity and inhibited glioma migration. The same activity was subsequently demonstrated for the *Buthus martensii* Karsch (BmK) species, although in murine models. Similarly, the venom of the *Euscorpius italicus* Herbst scorpion has been referenced in the Willmar Schwabe homeopathic pharmacopoeia.

In Cuba, the venom of the *Rhopalurus junceus* scorpion, an endemic species, has been used for medical purposes since the early 20th century. Researchers at Grupo Empresarial LABIOFAM have shown that both the venom of this species and molecular mass fractions of less than 5 kDa are significantly toxic to epithelial tumour cells.

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VIDATOX® 30 CH is a homeopathic biotherapeutic whose active principle is *Rhopalarus junceus* venom in a 30th centesimal potency. It is a product with non-toxic potential by oral administration. Its use does not preclude or restrict other conventional cancer treatments; on the contrary, its concurrent application can have a synergistic or magnifying effect on anti-tumour activity in conventional oncological therapy.

A study involving 174 patients of both sexes undergoing oncospecific treatment has demonstrated the effectiveness of VIDATOX® 30 CH in enhancing the treatment of cancer in various sites (breast, lung, prostate). The results included a 96% rate of survival beyond 12 months among the patients receiving the substance, while 90% reported improvement in the clinical symptoms which led them to seek medical help, 62% reported a decline in pain to a moderate level that did not necessarily require analgesic treatment, and 27% experienced remission of pain; none reported any adverse reaction to the treatment.

These results provided significant scientific information about the clinical characteristics of the cancer patients treated with this product, for public-health officials and prescribing physicians, and about the factors affecting the clinical performance of these cases.

The information generated, regarding both the safety of the medication and the clinical performance of the patients in the study during the post-marketing stage, is used as material for analysis.

The following questions suggest themselves, given the newness of the use of VIDATOX ® 30 CH, its potential scientific, economic and social implications and the knowledge that would be generated by its post-market monitoring, in assessing the clinical evolution of the patients treated with it, and its safety:
In the conditions of routine clinical practice:

- *What is the quality of life of patients with advanced tumours treated with* VIDATOX ® 30 CH?
- *What is the clinical performance of patients with advanced tumours treated with* VIDATOX ® 30 CH?
- *What are the characteristics of adverse events experienced by patients with advanced tumours treated with* VIDATOX ® 30 CH?

II.2. Theoretical framework

The introduction of penicillin and the discovery of other antibiotics in the early 1940s heralded a surge of activity in the search for new medicines to expand the therapeutic arsenal, and apply these to combating life-threatening infections and other conditions. But history shows that this trend was not without risks, which became apparent with the emergence of drugs that were efficacious but produced very serious adverse effects.

A historically tragic example was the case of Thalidomide in the early 1960s. It was used a sleeping-pill and to suppress vomiting in pregnancy. Its introduction led to serious deformities in the hands and arms (a congenital condition known as phocomelia) of thousands of newborns in Europe and Japan. The response of the public health authorities throughout the industrialized world was to require testing on humans based on the most rigorous criteria, prior to granting registration of any new drug; this was accompanied by the establishment of the Food & Drugs Administration agency (FDA), the world's first drug-regulation agency.

These events created the need to establish increasingly complex, sophisticated, expensive and protracted tests prior to the marketing of any new medicine. Although legislation was a major factor in

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the introduction of clinical trials, according to many authors the first of these was undertaken in 1747 by James Lind, a British naval surgeon, with the aim of finding the best treatment for scurvy. The term 'clinical trial' appeared for the first time in an anonymous article in the British medical publication 'The Lancet', in 1931, coinciding with the setting up of a clinical trials committee by the UK's Medical Research Council.

Following a number changes in its conceptual basis, reflecting basic methods that evolved and were refined over time, the term's definition was fixed at an International Harmonization Conference in Switzerland in 1996, as follows "A clinical trial is an investigation in human subjects which is intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal products, identify any adverse reactions or study the absorption, distribution, metabolism and excretion, with the object of ascertaining the safety and/or efficacy of those products".

This is not the fullest definition, however, being oriented mainly towards medicines; we are more in favour of that published by Joan-Ramón Laporte, who sees such studies as carefully, ethically designed experiments whose participants are assigned to various types of intervention simultaneously and on a randomized basis and are also subject to simultaneous supervision. This definition is not restricted to medicines, while the earlier concept included assessing or clarifying treatment (clinical, pharmacokinetic, pharmacodynamic etc. effects), and in fact the methodology of these studies is also used for evaluating medical research products and technologies which, moreover, can be classified according to various factors, including the stages in a clinical product's development, participating centres, degree of masking, type of design, type of general aim and the purpose or final objective of the trial.

The clinical trial is regarded as the cornerstone of research into causality in general, and of research into drug efficacy in particular; it is an essential step in the development of any new drug.

After registration of the product and the issue of a licence to market it, the clinical trials are launched. These studies illuminate the effectiveness of the drug - its safety profile in prolonged general use; its possible new indications; dosage, interactions, efficacy in new conditions of use. This stage includes pharmacovigilance aimed at identifying and quantifying the risks associated with short- and long-term use among the public at large or within specific sub-groups. A more up-to-date definition is "the discipline concerned with collecting, monitoring, researching and appraising information generated by health-sector professionals and patients on adverse reactions to drugs, biological products, medicinal plants and traditional medicines, with the aim of deriving new data and protecting patients".

The application of a medicine requires that the benefits of its use outweigh its risks. Ideally, a medication should provide benefits without any risks; in practice, most medicines carry some degree of risk, which must be minimized as far as possible. The fact that a new drug has been registered does not mean that everything about it is known. Its safety must be monitored throughout its life; long-term use reveals the full extent of the associated risks (side effects) and benefits (efficacy) across its various indications, highlighting the importance of such monitoring in checking the behaviour of a drug following its approval for medical use.

Drug safety is a matter of the adverse reactions that may be experienced by any patient that takes it. Side effects or adverse reactions are considered to be any adverse experience that occurs after administration of a medicine. An adverse event in this context may include one that does not have a causal relationship with the treatment.

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Unlike an *event*, a *reaction* is characterized by a suspected causal relationship between the drug and the episode, as judged possible by the notifying agency or the health-sector professional concerned.

The assessment required is of the relationship of causality or attributability, involving case-by-case analysis of the causal connection between the administration of the medicine and the occurrence of an adverse event. It is an individual analysis of a given adverse event, which does not seek to study the overall risk potential of the drug or the importance of the risk to the public at large. This approach has led to the design of various algorithms using either qualitative or quantitative scales. In greatest use by the pharmacovigilance systems are those proposed by Karch and Lasagna, and Naranjo. The common elements of these methods include:

- the time relationship between exposure to the drug and the event
- taking account of previous data: the known pharmacological response
- the evolution of the event following suspension or readministration of the drug
- the role of underlying or concomitant disease in the generation of the event.

The Karch and Lasagna algorithm enables suspected adverse reactions to be classified according to their causality as follows:

- Definitive: A clinical event including changes detected by laboratory tests occurring in a valid time sequence in relation to administration of the medicine that cannot be explained by concurrent disease or other drugs or substances. The response to withdrawal of the drug should be clinically valid. The event must be definitive from a pharmacological point of view, using if necessary a conclusive re-exposure procedure.
- Probable: A clinical event including changes detected by laboratory tests occurring in a reasonable time sequence in relation to administration of the medicine that is unlikely to be due to concurrent disease or other drugs or substances. The response to withdrawal of the drug should be (clinically) reasonably likely. Information on the effect of re-exposure is not a required criterion for this classification.
- Possible: A clinical event including changes detected by laboratory tests occurring in a reasonable time sequence in relation to administration of the medicine but which could also be explained by concurrent disease or other drugs or substances. Information on the effects of withdrawing the drug need not be clear or even present.
- Conditional: The clinical response is reported as an adverse reaction requiring more data before an adequate verdict can be reached, or where additional data is under scrutiny.
- Unrelated: A clinical event including changes detected by laboratory tests that occurs in an unlikely time sequence in relation to administration of the drug and is more plausibly explained by a concurrent disease or other drugs or substances.

The magnitude of the effect caused by an adverse event on an individual is synonymous with its severity and can be classified according to the impact on the patient's daily activity, into slight, moderate, severe and fatal.

1) *Fatal*: Causing or contributing to the patient's death.
2) *Serious*: Directly threatening the life of the patient. This type of event requires treatment, suspension of the drug and may involve any of the following: hospitalization or extension of existing hospitalization; need for intensive care; incapacity or invalidity.
3) *Moderate*: The reaction interferes with normal activity, may result in hospitalization or absence from work, without directly threatening the patient's life. Requires treatment. Does not necessarily require suspension of the drug responsible.
4) *Slight:* Marked by easily tolerated signs and symptoms, generally of short duration, does not disrupt the patient's normal life or prolong hospitalization. Does not require treatment or suspension of the medication concerned.

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Assessment of seriousness involves a specific study of each adverse event and of the duration and intensity of the reaction.

The criteria for classifying an event as serious include whether it:
1. threatens the patient's life,
2. causes the patient's death,
3. causes or prolongs hospitalization,
4. causes incapacity or invalidity
5. causes cancer or a congenital anomaly.

All these cases require suspension of the medication concerned.

Given the importance of pathology induced by drugs, or adverse reactions to medications, there is a need to appraise the latter scientifically. At international level, the World Health Organization has established an medicines monitoring centre (in Uppsala, Sweden) as a means of centralizing drug-safety information. Cuba reports systematically to this agency via a pharmaco-epidemiological development unit within the Ministry of Public Health's national drugs authority, whose functions include overseeing pharmaco-epidemiological research at national level.

Pharmaco-epidemiology is a branch of public health that applies epidemiological knowledge, methods and reasoning to the study of the use and effects of medicines among the public; in 1999, a central, national drug-monitoring coordination unit was established to direct this activity in Cuba.

In terms of methodology, various strategies for post-marketing pharmacovigilance are adopted which, although individually not sufficiently complete to deal with the safety issue, complement each other to some extent. Their design is based fundamentally on that of observational studies (case series, case and control studies, cohort studies, meta-analysis), post-marketing clinical studies, monitoring systems based on spontaneous notification of side effects, studies based on records of morbidity or vital statistics and the use of information from existing databases.

The volume of reports of drug side effects in Cuba is high (7,000-10,000 cases annually) from which signals are usually generated.[1] However, this system suffers the disadvantage of cross-notification and combines information from a large number of sources, giving rise to the need for other, more specific methods that enable targeting of a drug at its launch into the marketplace. An intensive post-marketing monitoring effort would enable the risks and beneficial effects of the drug, not covered by the previous clinical control stages, to be quantified.

Medicines are not always correctly used, a situation with a number of possible causes, such as the enormous proliferation of drugs that have appeared in recent years, the slanted information that almost always originates with the drug companies and lack of critical analysis of the information needed for correct drug selection. The drug-use scenarios created by this situation can be serious.

But when predictable and avoidable adverse reactions are produced, preventive and safety measures can be put in place for the management and rational use of the drug concerned, thereby ensuring safe treatment for the patient.

III. AIMS

III.1. General aims

To assess the effectiveness and safety of VIDATOX ® 30 CH as a complementary treatment for patients with advanced tumours.

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III.2. Specific objectives

1. To gauge the quality of life of patients with advanced tumours treated with VIDATOX ® 30 CH.
2. To describe adverse events among patients with advanced tumours treated with VIDATOX ® 30 CH.

III.3. Hypothesis

Complementary treatment with VIDATOX ® 30 CH of patients with advanced tumours improves their quality of life and is free of severe side effects.

IV. ETHICAL ASPECTS

Carrying out this protocol is ethically justifiable on the following grounds:

1. It involves a post-marketing study of a product registered by the regulatory body (Centre for State Control of the Quality of Medicines - CECMED). An extended programme of clinical use is currently underway.
2. The modus operandi of the study was consistent with the general principles set out in the documents adopted by the international community on biomedical research involving human subjects, established in the Helsinki Declaration as amended by the Edinburgh (2000) and Tokyo (2004) revisions, and with the regulations promulgated by CECMED.
3. None of the patients was deprived of any efficacious treatment opportunity: all received oncospecific treatment in accordance with good clinical/oncological practices. They were additionally administered VIDATOX ® 30 CH, a homeopathic medicine which is being employed in the expanded-use programme.
4. The confidentiality of the patients' primary data was maintained; on publication of the results, their names will not be disclosed under any circumstances.

V. GENERAL CONCEPT

VI.1 Design of the study

A study of the use of VIDATOX 30 CH among patients with advanced tumours was performed. It included patients whose advanced tumours had been confirmed histologically, from hospitals and other recognized centres in various countries. It studied patients who attended Vimang Laboratory consultations between July 2010 and September 2011 (for one year). In all cases, the regime adopted was administration of VIDATOX ® 30 CH in association with oncospecific treatment.

VI.2. Universe

Adult patients of both sexes of any nationality, suffering from advanced tumours, who attended consultations given by the Grupo Empresarial LABIOFAM medical service at the Vimang Laboratory, between July 2010 and September 2011.

VI.3. Diagnostic criteria

1. Histological diagnosis of advanced tumour.

VI.4. Inclusion criteria

1. Suffering from advanced tumours confirmed by pathological anatomy techniques.
2. 18 years of age and over.
3. Any nationality.
4. Volunteering for the study in writing (signed).
5. In possession of case histories in sufficient detail for proper assessment.

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VI.5. Exclusion criteria

1. Pregnancy or lactation.

VI.6. Criteria for interrupting the treatment

1. Voluntary withdrawal.
2. Emergence of any exclusion criterion.
3. Serious adverse events.
4. Death of the patient.

VII TEST SUBSTANCE

VII.1. Dose, frequency, administration route, duration of treatment

Five drops of VIDATOX ® 30 CH sublingually 2, 3 or 4 times daily according to the opinion of the attending physician following assessment of the stage of the disease. This treatment was prescribed for an indefinite period on an outpatient basis and concomitant with oncospecific therapy.

VII.2.Presentation, composition and conservation of the medication

Presentation

The presentation of VIDATOX 30 CH includes primary and secondary packaging:

- Individual box holding 30-mL amber glass bottle with screw cap and dropper insert. Each bottle contains 120 doses.
- Multiple box with sections holding six 30-mL amber glass bottles with screw cap and dropper insert. Each bottle contains 120 doses.
- Multiple box holding twelve 30-mL amber glass bottles with screw cap and dropper insert in their individual boxes. Each bottle contains 120 doses

Full composition of VIDATOX ® 30 CH including ancillary substances, by dosing unit

Component	*Quantity in units of measurement or percentage*	*Function*	*Quality standard reference*
Rhopalurus junceus venom 30 CH	0.01 mL	Active principle	Manufacturer's specification
Ethyl alcohol	As required	Excipient	USP 30
Purified water	As required		USP-30

Conservation

The homeopathic medicine VIDATOX ® 30 CH must be stored in dry, ventilated conditions at temperatures preferably between 20 and 30 °C, protected from light.

Other storage requirements:

- Keep away from equipment that generates electromagnetic fields (refrigerators, televisions, radios, computers, microwave ovens, cellphones etc.).
- Do not refrigerate.
- Keep away from perfumes and strong odours.
- Do not transfer to another container.

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VII.3.Justification for the dose employed

The optimal dose for this type of medication is 5 sublingual drops 3 times daily, based on previous experience in the use of homeopathic products.

The earlier studies with the test substance - preclinical, toxicity with animals and clinical case studies - demonstrate a low probability of adverse events associated with its administration. Accordingly, no risks are foreseen in its administration on an indefinite basis.

VII.5 Technique employed for masking and code access

Not applicable (open study).

VII.6. Rules for the use of concomitant treatment

The medications needed according normal medical practice as defined by the specialists were used.

VII.7 Measures taken to encourage compliance with the prescription

Copies of a written procedure (method) to be followed were handed to the patients or their relatives.

VII.8 Rules for checking that the treatment is being followed

Not applicable (outpatient study).

VIII. ADVERSE EVENTS

Overview
Adverse event: any unfavourable medical outcome presented by a patient or clinical research subject following administration of a drug, whether or not having a causal relationship with such treatment. It can thus be any unfavourable or unexpected sign (including an abnormal laboratory finding), symptom or disorder emerging a short time after administration of a product being studied, whether or not related to that product.
Adverse reaction: Any negative reaction to a product, regardless of the dose employed. Implies that a causal relationship between the medicine and the reaction is a reasonable possibility.
Adverse event flash report: Immediate reports arising from any clinical or epidemiological research regardless of its design or purpose, in order to pass on important information regarding serious, very serious or unexpected events to regulatory bodies, researchers or other relevant actors.

VIII.1. Adverse events expected in the study and measures envisaged

Product being researched

No adverse effects were reported from the administration of VIDATOX ® 30 CH in the previous preclinical toxicity studies with animals, or in the clinical case studies.

Although no such effects were expected, each patient and his/her relatives were interviewed by the researchers to detect any that might arise. The monitoring of adverse reactions following

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administration of the test substance is recorded in the patients' case histories.

VIII.2. Procedure to be followed on the occurrence of adverse events

Whenever a hypersensitive reaction to the test substance was suspected, the patient was advised to interrupt the treatment, while the facts were recorded in his/her case history.

VIII.3. Actions aimed at detecting and adequately describing adverse events during treatment with the test substance

- Detailed interviews with patients or their relatives to detect any symptom not included in the history of the current illness.
- Educating the patients or relatives in keeping a diary for recording the symptoms experienced during treatment with the test substance.

Notification of adverse events

In the case of events that are serious (in terms of the consequences for the patient) and unexpected (in terms of prior knowledge), the promoting centre was to be notified immediately.

Address for notifications to the promoting centre:

Dra. Mariela Margarita Guevara García, E-mail: marielaguevara@infomed.sld.cu
Dra. Carmen Inés Morales Paneque, E-mail: carmen.morales@infomed.sld.cu
Laboratorio Vimang. Grupo de Desarrollo Genix - Labiofam.
Tel.: 680 2500, 680 2518 and 6802514.
Grupo Médico LABIOFAM
Tel.: 684 9661.

All aspects of the adverse events were described and explicitly analyzed in the case histories of the patients concerned.

IX. ASSESSMENT OF THE RESPONSE

IX.1 Response variables

Main variable:
Quality of life
Assessment of the patient's quality of life was based on Karnofsky's index of performance status (KPS) and the Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS) (classification of the physical deterioration of cancer patients according to their general state) and the presence of pain (see Appendices 1 and 2).

Secondary variable:
Adverse events
It was planned to collect all the evidence of adverse effects during the study. This was to be classified according to intensity in accordance with the Common Terminology Criteria for Adverse Events (CTCAE v3.0), and to their causal relationship with the test substance.

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Control variables

- Age
- Sex
- Skin colour
- Histopathological diagnosis
- Tumour location
- Presence of metastasis
- Time of treatment with the test substance
- Oncospecific treatment: chemotherapy, radiotherapy
- Daily administration frequency.

Safety variables

The evaluation and classification of the safety parameters were established according to the NCI CTCAE, version 3, with the test substance and according to the seriousness of the adverse event. On the occurrence of adverse events, the causal relationship between these and the causal agent was determined.

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Operationalization of the variables

Variable	*Type*	*Scale*	*Description*	*Indicator*
Age	Quantitative continuous	Simple ages	Years lived	Arithmetic mean Standard deviation
Sex	Quantitative nominal dichotomic	Male Female	Biological sex	Number Percentage
Skin colour	Qualitative nominal polytomic	Black White Mixed	By observation on physical examination	Number Percentage
Histopath-ological diagnosis	Qualitative nominal polytomic	Adenocarcinoma Carcinoma Glioma Lymphoma Leukaemia Sarcoma	From biopsy results	Number Percentage
Tumour location	Qualitative nominal polytomic	Anatomical location	Site of the tumour	Number Percentage
Presence of metastasis	Qualitative nominal polytomic	Yes No	From case history	Number Percentage
Duration of treatment with test substance	Quantitative continuous	Months	From case history	Arithmetic mean Standard deviation
Oncospecific treatment (chemotherapy)	Quantitative nominal dichotomic	Yes No	From case history	Number Percentage
Oncospecific treatment (radiotherapy)	Quantitative nominal dichotomic	Yes No	From case history	Number Percentage
Daily frequency of administration	Qualitative ordinal	Twice 3 times 4 times	As prescribed	Number Percentage
Quality of life performance	Qualitative ordinal	Improved Stable Worse	Improved: Improvement in signs & symptoms since preceding consultation. Stable: No change in signs & symptoms since preceding consultation. Worse: Worsening of signs & symptoms since preceding consultation.	Number Percentage
Adverse events	Quantitative nominal dichotomic	Yes No	As reported by the patient	Number Percentage

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IX.2. Examinations and assessments

The case histories were studied in detail to derive sufficient elements for adequate assessment of each patient. Patients were assessed by comparing the information collected prior to the treatment and that obtained at the final consultation.

Examinations & assessments

Method	Variable	Frequency
Anamnesis & physical examination	Quality of life	At each consultation
KPS	Quality of life	At each consultation
ECOG PS	Quality of life	At each consultation
Anamnesis, physical & complementary examinations	Adverse events	On each administration of the test substance
Anamnesis, physical & complementary examinations	Control	At each consultation

IX.3 Criteria for individual response assessment

Main variable

- **Quality of life**

The patient's progress was classified according to the KPS and ECOG PS at the start of the study and at the final consultation, adopting the following scale:

- **Improved**: Improvement in signs & symptoms since preceding consultation.
- **Stable**: No change in signs & symptoms since preceding consultation.
- **Worse**: Worsening of signs & symptoms since preceding consultation

Assessment of adverse events

All the evidence of adverse events during the study (July 2010 to September 2011) was collected.

The events were to be classified according to the NCI CTCAE (version 3) table of criteria by degree of intensity and cause. See Appendices 3 and 4.

X. STATISTICAL ASPECTS

Type of study: Prospective, longitudinal analytic.

Sample size: All the patients recruited in the period July 2010 to September 2011 were studied.

Implementation of the statistics plan:

The behaviour of the variables identified for the purposes of the study and the associations between these were analyzed, using the relevant statistical techniques.

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The analysis of the demographic data and the baseline characteristics of the patients was performed by descriptive analysis consistent with the type of quantitative or qualitative variable.

Variable	Type of analysis
Sex	Absolute & relative frequency distribution and graph.
Age	Absolute & relative frequency distribution and graph.
Skin colour	Descriptive statistics (mean, standard deviation, kurtosis, skewness). Boxplot graphs.
Histopathological diagnosis	
Tumour location	
Presence of metastasis	Absolute & relative frequency distribution and graph.
Duration of treatment with the test substance	Calculation of confidence intervals.
Oncospecific treatment with chemotherapy	
Oncospecfic treatment with radiotherapy	
Daily administration frequency	
Adverse events	

The analysis of the variables associated with clinical response was of the following types:

Variable	Type of analysis
Trend in quality of life (based on the KPS and ECOG PS)	Estimation of the proportions of response of the groups. Calculation of confidence intervals.
Patient's symptoms	Descriptive analysis appropriate to the type of variable.

Safety assessment

The toxicity analysis required assessment of the adverse events reported by the patients. This was to involve recording such events by patient, noting the start time of each event.

XI. TIMESCALE

Activity	*Planned timetable*	*Actual timetable*
Protocol preparation	June 2010	June 2010
Start of post-marketing study	October 2011	October 2011
Review & classification of case histories	October - December 2011	October 2011
Patient monitoring	July 2010 – July 2012	July 2010–September 2012
Processing & analysis of results	August 2012 (one month)	October 2012 (7 days)
Preparation of final report	September 2012 – November 2012 (3 months)	October 2012 – November 2012 (15 days)

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XII. PRACTICAL CONSIDERATIONS

XII.1 Detailed description of the trial:

- Assessment of adult patients with advanced tumours who attended consultations at the Vimang Laboratory belonging to Genix, part of Grupo Empresarial LABIOFAM, and selection of potential subjects for the study.
- Detailed review of the documentation provided by the patients or their relatives (case history summary by the attending physician and complementary examinations) for inclusion in the study.
- Provision by the patients of their signed consents for inclusion in the study, to the participating researchers.
- Confirmation of patient compliance with the selection criteria, on a 'non-compliance: exclusion' basis. The patients were to be treated in accordance with the established procedures for their disease.
- Physical examinations and assessment of vital signs, preparatory to prescription of the homeopathic treatment.
- Start of treatment with VIDATOX ® 30 CH as a complementary treatment, as indicated by other attending specialists.
- Every adverse event was to be recorded by the patient concerned or his/her relatives.
- The monitoring consultations were to be held every 4 months.
- The information derived from the laboratory tests, physical and imaging examinations was to be collected before each consultation.

XII.2 Basic duties of the various parties:

SPONSOR:
Grupo Empresarial LABIOFAM

- To write up the rationale for the study, design the research protocol and promote the study among the participating researchers and cooperating institutions.
- To appoint the clinical trial monitors.
- To select the chief researcher and the other participating researchers.
- To approve the final version of the trial protocol.
- To supply the substance to be tested to the pharmacies involved in the study.
- To participate in the processing and analysis of the primary data.
- To report any very serious, unexpected adverse events to CECMED.
- To ensure completion of the trial and preparation of the final report.
- To conserve all the information generated during the study, in accordance with ICH/2000.
- To ensure that the treatment provided in the course of the study is carried out as described in the protocol.
- To ensure that the study complies in all respects and at all times with the guidelines for good clinical practice, standard working procedures and regulations of CECMED.

PARTICIPATING INSTITUTION:
Laboratorio Vimang y Grupo Médico:

- To ensure that the study complies in all respects and at all times with the guidelines for good clinical practice specified by ICH /2000.
- To provide the facilities and keep and manage the materials and medicines essential to carrying

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out the study.

- To ensure individualized management (conservation, handling, availability, quality assurance) of the case histories of the patients included in the study.
- To ensure the physical conservation and custody of the study documentation in compliance with ICH / 2000.
- To ensure that all the patients included in the study have provided signed consents to participate.
- To check compliance with the trial protocol at the specified intervals.
- To provide the conditions needed for the performance of audits of the study.
- To preserve the confidentiality of the information about the patients included in the study.

Bio-statistician responsible for the design of the study and the processing of the research data obtained:

- To ensure that the study complies in all respects and at all times with the guidelines for good clinical practice specified by **ICH /2000.**
- To approve the research protocol.
- To participate in the processing and analysis of the primary data.
- To conserve all the information generated during the trial, in accordance with las ICH / 2000.
- To draw up the partial results report.
- To preserve the confidentiality of the information about the patients included in the study.

XII.3 Confidentiality

- The confidentiality of the participating subjects' personal information was guaranteed.
- Disclosure for scientific purposes of the information generated in the study (publication or presentation), whether preliminary, partial or complete, was made only with the permission of Grupo Empresarial's management.
- Interpretation of the data collected during the study did not favour promotion of the product under test; without compromising its scientific validity, its interpretation was based strictly on the actual results.
- The study data will be retained on the consultation files of the Vimang Laboratory (part of Empresa Genix, Grupo Empresarial LABIOFAM) for 15 years.

XIII. RESULTS

Table 1 below shows the distribution of the patients by age and sex. The more populated age groups were 71-75 (22 cases or 19.3% of the total) and 51-55 (16 cases, 11.4%). The majority in the former were men (15 patients, 13.5% of the total), while in the 51-55 group the majority were women (10 patients, 8.8%). The overall distribution by sex was near-equality (50.9% male, 49.1% female).

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Table. 1: Distribution of patients by age and sex

	SEX				Total	
	Female		Male			
Age group	No.	%	No.	%	No.	%
Under 25	1	0.9	0	0.0	1	0.9
26 - 30	2	1.8	3	2.6	5	4.4
31 - 35	3	2.6	6	5.3	9	7.9
36 - 40	0	0.0	2	1.8	2	1.8
41 - 45	7	6.1	2	1.8	9	7.9
46 - 50	7	6.1	4	3.5	11	9.6
51 - 55	10	8.8	6	5.3	16	14.0
56 - 60	4	3.5	9	7.9	13	11.4
61 - 65	5	4.4	1	0.9	6	5.3
66 - 70	2	1.8	6	5.3	8	7.0
71 - 75	7	6.1	15	13.2	22	19.3
76 - 80	7	6.1	2	1.8	9	7.9
Over 80	1	0.9	2	1.8	3	2.6
Total	56	49.1	58	50.9	114	100.0

Source: Case histories

Table 2 and Chart 1 reflect the distribution of patients by histopathological diagnosis. Lung-cancer patients predominated, numbering (26, or 22% of the total), followed by breast-cancer (17 patients, 14.9%), colon and prostate cancer (14, or 12.3%, in both cases).

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Table. 2: distribution of patients by histopathological diagnosis

HISTOPATHOLOGICAL DIAGNOSIS		NO.	%
Lung	Adenocarcinoma	9	7.9
	Carcinoma	17	14.9
Subtotal lung		27	22,9
Breast	Adenocarcinoma	1	0.9
	Carcinoma	16	14.0
Subtotal breast		17	14,9
Prostate	Adenocarcinoma	11	9.6
	Carcinoma	3	2.6
Subtotal prostate		14	12.2
Colon	Adenocarcinoma	9	7.9
	Carcinoma	5	4.4
Subtotal colon		14	12.3
Pancreas	Adenocarcinoma	3	2.6
	Carcinoma	4	3.6
Subtotal pancreas		7	6.2
Ovary	Adenocarcinoma	2	1.8
	Carcinoma	3	2.6
Subtotal ovary		5	4.4
Glioblastoma		5	4.4
Lymphoma		2	1.8
Sarcoma		2	1.8
Rectal adenocarcinoma		2	1.8
Nasopharyngeal carcinoma		2	1.8
Urethelial carcinoma		2	1.8
Renal carcinoma		2	1.8
Carcinoma of the maxillary sinus		1	0.9
Uterine carcinoma		1	0.9
Vaginal carcinoma		1	0.9
Vesicular carcinoma		1	0.9
Vulval carcinoma		1	0.9
Hepatocarcinoma		1	0.9
Duodenal adenocarcinoma		1	0.9
Endometrial adenocarcinoma		1	0.9
Nasal adenocarcinoma		1	0.9
Cervical carcinoma		1	0.9
Gastric carcinoma		1	0.9
Laryngeal carcinoma		1	0.9
Leukaemia		1	0.9
Total		114	100.0

Source: Case histories

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Chart 1: Distribution of patients by histopathological diagnosis

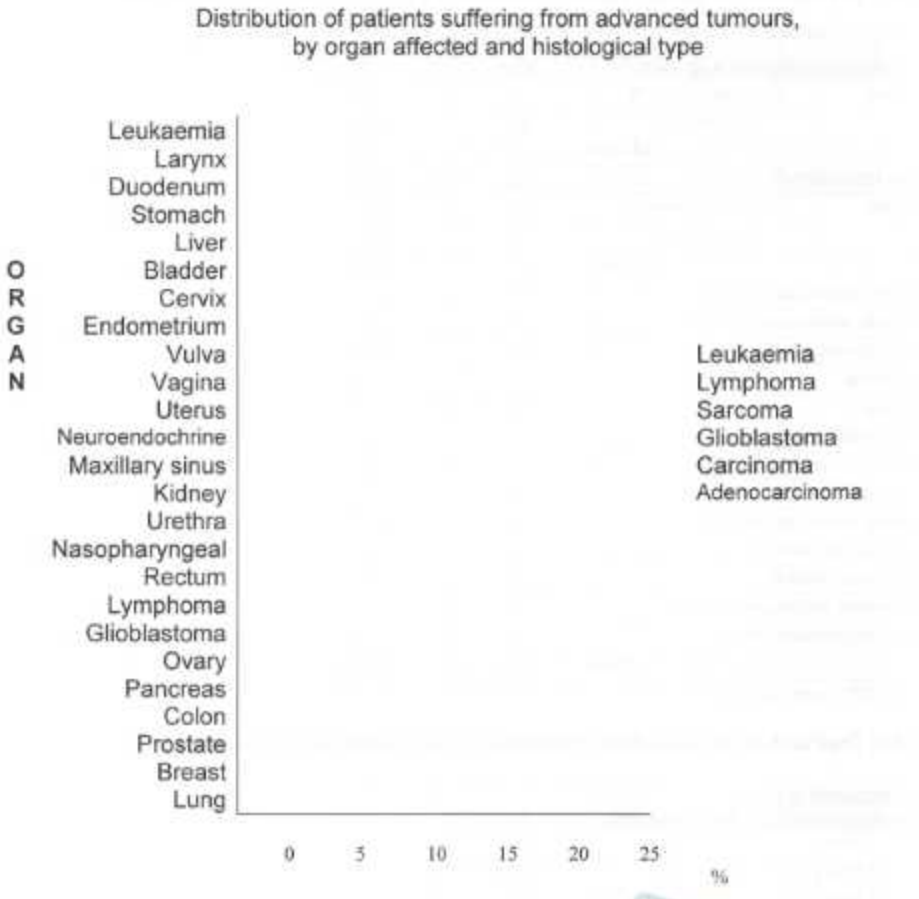

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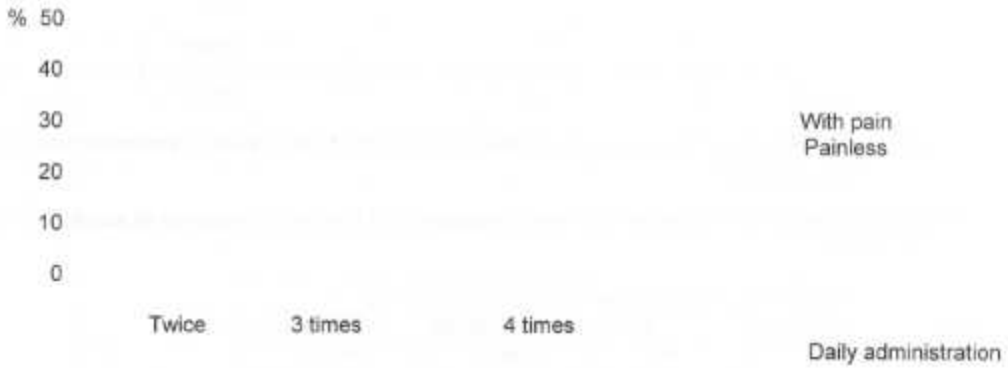
Chart 3. Distribution of patients by presence/absence of pain and frequency of administration of VIDATOX



The above table reflects a predominance of patients without pain among those taking the test substance 2 or 3 times daily.

Table 6: Distribution of patients by frequency of administration of VIDATOX and performance

Performance	VIDATOX ADMINISTRATION FREQUENCY						TOTAL	
	Twice		3 times		4 times			
	No	%	No	%	No	%	No	%
Stable	28	24.6*	14	12.3	6	5.3	48	42.3
Worse	0	0	3	2.6	0	0	3	2.6
Improved	26	22.8	33	28.9	4	3.5	63	55.3
Total	54	47.4	50	43.9	10	8.8	114	100

Source: case histories
Pearson's chi-squared test =10.141 p=0.038

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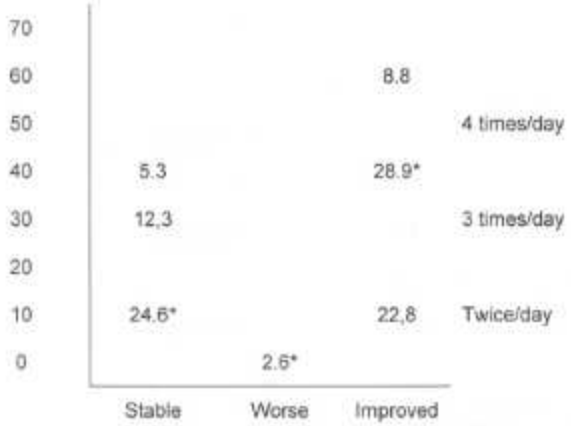
Chart 4: Distribution of patients by frequency of administration of VIDATOX and performance



The above table and graph show the distribution of patients by frequency of administration of the test substance and performance. There was a predominance of patients who experienced improvement among those who took the test substance three times daily. Most of the patients whose condition remained stable took the test substance twice daily.

The result of applying Pearson's chi-squared test of statistical significance indicated that a statistically-significant relation existed between the frequency of taking VIDATOX and patient performance, and that the 3-times daily regime was associated with the most-improved performance.

In order to identify the categories of the variables studied that significantly influenced the association, the corrected typified residuals were determined; a larger-than-expected number of cases of patients whose conditions improved who took VIDATOX three times daily was observed, and also a larger-than-expected number of patients who took the test substance twice daily and improved.

Table 7: Distribution of patients by VIDATOX administration frequency and general performance

General performance	VIDATOX ADMINISTRATION FREQUENCY						TOTAL	
	2		3		4			
	No	%	No	%	No	%	No	%
Favourable	38	33.3	42	36.8*	5	4.4	85	74.6
Unfavourable	16	14.0	8	7.0	5	4.4	29	25.4
Total	54	47.4	50	43.9	10	8.8	114	100

Source: Case histories. Pearson's chi-squared test = 6.029 p = 0.049
** Corrected typified residuals greater than 1.96. More cases of patients with these characteristics than expected were reported.*

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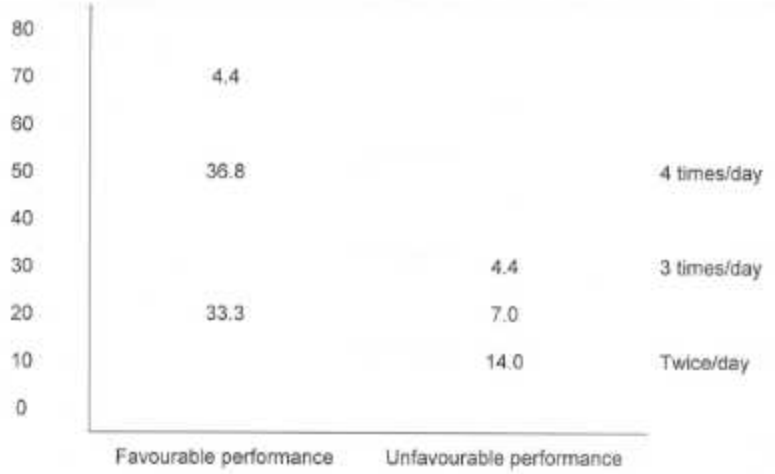

The above table and chart show that the patients whose performance was favourable took VIDATOX three times daily.

A statistically-significant association was obtained from to Pearson's chi-squared test: less than 0.05 ($p = 0.049$).

Determination of the corrected and typified residuals indicated a larger-than-expected number of cases of patients whose performance was favourable and took VIDATOX three times daily.

Table 8: Distribution of patients by Karnofsky's index and frequency of VIDATOX administration

Karnofky's index (KPS)	Frequency of VIDATOX administration (times/day)						Total	
	2		3		4			
	No.	%	No.	%	No.	%	No.	%
30	0	0.0	1	0.9	0	0.0	1	.9
40	0	0.0	1	0.9	0	0.0	1	.9
50	1	0.9	0	0.0	2	1.8*	3	2.6
60	1	0.9	5	4.4*	0	0.0	6	5.3
70	6	5.3	3	2.6	7	6.1*	16	14.0
80	22	19.3*	12	10.5	0	0.0	34	29.8
90	22	19.3	25	21.9	1	0.9	48	42.1
100	2	1.8	3	2.6	0	0.0	5	4.4
TOTAL	54	47.4	50	43.9	10	8.8	114	100.0

** Corrected typified residuals (greater than 1.96): More cases than expected with the characteristics of the cells were reported.*
Source: case histories
Pearson's chi-squared test = 53.974 p=0.000
Non-parametric Wilcoxon signed-rank test:
Z statistic = -7.693 p = 0.000

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The table above shows how the **patient's KPS** is related to the frequency of administration of the test substance. There was a larger-than-expected number of patients with a **KPS score** of over 60 among those who took VIDATOX three times a day.

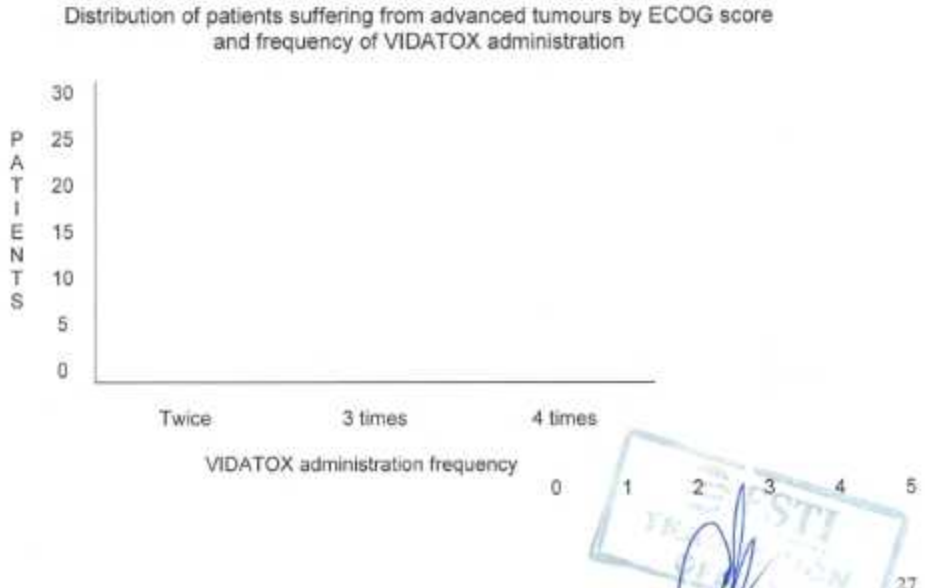
The result of the Wilcoxon signed-rank test indicates that the changes in patient progress as measured by the latter index were statistically significant.

Only two patients experienced adverse performance as measured by the KPS, based on the comparison before and after treatment.

Table 9: Distribution of patients by ECOG score and frequency of VIDATOX administration

ECOG scale	Frequency of VIDATOX administration (times/day)						Total	
	2		3		4			
	No.	%	No.	%	No	%	No.	%
0	3	5.6	7	14.0	0	0	10	8.8
1	29	25.4	29	25.4	2	1.8	60	52.6
2	19	16.7	11	9.6	6	5.3*	36	5.3
3	3	2.6	1	0.9	2	1.8	6	5.3
4	0	0	2	1.8	0	0	2	0
Total	54	47.4	50	43.9	10	8.8	114	100.0

Pearson's chi-squared = 17.320 P = 0.027
*Corrected typified residuals. There was a larger-than-expected number of patients who took VIDATOX four times a day and had an ECOG score of 2.
Non-parametric Wilcoxon signed-rank test: Z statistic = -7.408 p=0.000



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The table above shows that most of the patients with ECOG scores of 2 took the test substance twice or 3 times daily.

The result of the Wilcoxon signed-rank test indicates that the differences in ECOG scores before and after the trial were statistically significant. There was a predominance of patients whose performance received an ECOG score between 0 and 2 (67 cases or 35.18% of the total).

XIV. CONCLUSIONS

- There was an improvement in the quality of life of 74.6% of the patients studied.
- There were no adverse events during the period of administration of the test substance.
- The best results were obtained with a regime of administration of the product twice or three times daily.

XV. RECOMMENDATIONS

- The staging of a dose-response study to corroborate the results obtained in relation to frequency of administration.
- The design of a study of survival among patients taking the product.

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References

I. Viewpoint Part 2 Uppsala Monitoring Centre Uppsala: WHO Collaborating Centre for International Drug Monitoring 2004: 3-66.
II. Pouyanne P, Haramburu f, Imbs I, Beagud B. Admission to hospital caused by adverse drug reactions: cross sectional incidence study. BMJ 2000, (15 April); 320:1036.
III. Marqués C. Estudios postautorización: una necesidad real. ICB Digital. 2004; 25 [quoted 14 Jul 2009]. Available at URL:http://www.icf.uab.es/icbdigital/pdf/articulo/articulo25.pdf.
IV. Bernard C. Estudios postautorización en España: marco legal, problemáticas y posibles soluciones. Med Clin (Barc). 2009; 133:676-81 [quoted 28 oct 2009]. Available at: http://www.icbdigital.org/.
V. Chavarría Quirós I. Farmacovigilancia: Editorial nacional de salud y seguridad social, Caja Costarricense del Seguro Social. Costa Rica 2000: 5-26.
VI. Hernández R-A. Fundamentos de los ensayos clínicos. In: Hernández R-A, (eds) Ensayos Clínico, 3rd ed. Cuba.2000.
VII. ICH Organizator. General considerations for clinical trials. IFPMA. Switzerland, 1996.
VIII. Laporte J-R. J-R, Tognoni G. Estudios de utilización de medicamentos y farmacovigilancia. In JR Laporte, G Tognoni (eds) Principios de epidemiología del medicamento, 2ª ed. Barcelona. Ediciones Científicas y Técnicas, 1993: 1-24.
IX. Hernández R-A. Fundamentos de los ensayos clínicos. In: Hernández R-A, (eds) Ensayos Clínico, 3rd ed. Cuba.2000.
X. Laporte J-R. Extrapolación de los resultados de los ensayos clínicos a la práctica habitual. In JR Laporte, (eds) Principios básicos de investigación clínica, 2nd ed. Barcelona. Ediciones Científicas y Técnicas, 2000: 61-78.
XI. The importance of pharmacovigilance. WHO 2002.
XII. Strom Brian L, Pharmacoepidemiology, 3rd Edition, Wiley 2000.
XIII. WHO. Vigilancia de la seguridad de los medicamentos. Guía para la instalación y puesta en funcionamiento de un Centro de Farmacovigilancia. The Uppsala Monitoring Centre, Sweden 2001; 23.
XIV. Buenas Prácticas de Farmacovigilancia del Sistema Cubano de Farmacovigilancia. Ministry of Public Health, Havana. 2007: 9-15.
XV. Yera Alós I. Vigilancia poscomercialización de la efectividad y seguridad del Heberprot-P en Cuba. Datos preliminares .In Fernández-Montequín J, Berlanga A J, López Saura P, López Mola E, Herrera M L, Yera Alós I (eds) Infiltración del Heberprot-P. Havana. Ediciones Elfos Scientiae.2009:100-106.
XVI. Unidad Coordinadora Nacional de Farmacovigilancia.2009
XVII. Armijo J, González Ruiz M. Estudios de seguridad de medicamentos: Métodos para detectar las reacciones adversas y valoración de la relación causa-efecto. In: El ensayo clínico en España.2002; 161:190.
XVIII. Valsecia M. Farmacovigilancia y mecanismos de reacciones adversas a medicamentos. Available at: http://med.unne.edu.ar. Date of access June 2009.

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