Haemonine®

Post marketing study for long-term treatment of

Haemophilia B patients

Synopsis:

A non-randomised, open, observational study to evaluate the efficacy, safety and tolerability of Haemonine® in patients with Haemophilia B

Clinical Phase:	**Not applicable**, NON-INTERVENTIONAL
Study Objectives:	efficacy, safety and tolerability of Haemonine® in patients with haemophilia B
Study Design:	prospective observational; open, not randomised;
Study Population:	Diagnostically confirmed haemophilia B Residual factor IX activity of less than 2% Factor IX inhibitor concentration <0.6 BU Exceptions must be motivated.
No. of Patients:	**50**.
No. of Centre(s):	Approximately 10
Study Drugs:	Prescription Haemonine®
Dosage and Mode of Administration:	According to prescribing information, at the discretion of prescriber
Duration of Treatment(s):	At least 50 exposure days
Criteria for Evaluation **- of Efficacy:**	• Factor IX consumption of investigational product. • Treatment period and batch numbers of administered product. • Prophylaxis or treatment on-demand. • Expected therapeutic effect reached. • Overall assessment on efficacy and ease of use
- of Safety:	• Incidence and nature of adverse events • AEs related to thrombogenicity • AEs related to immunogenicity • Laboratory assessments including serological monitoring • Factor IX inhibitors • Overall assessment on tolerability
Biometrical Concept:	Only descriptive statistical methods are applied. All quantitative and derived data are to be described by using the common descriptive parameters (sample size, numbers missing, mean, standard deviation, median, extrema). Qualitative data are to be described by absolute and relative frequencies. The <u>evaluation of efficacy</u> is based on the factor IX consumption represented as IU per kilogram bodyweight per month, year, and event, respectively. Respective data are listed according to forms provided by the Paul-Ehrlich-Institute and statistically analyzed. The <u>evaluation of tolerability</u> is based on a descriptive analysis of AE data, the overall assessment of tolerability, the assessment of possible seroconversions and changes of laboratory parameters. All evaluations are to be stratified according to the country involved, age group and the reason for treatment (prophylaxis or treatment on demand). Patients are not distinguished according to the intention-to-treat or per protocol approaches known for randomized clinical trials. Data are analyzed by means of the SAS system (version 9 for Windows XP).

Index

Signature page

Observation plan Version 1.0 from 2. September 2013

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[redacted]

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Date, Signature

Introduction

Haemonine® is a chromatographically purified Factor IX preparation extracted from human plasma. It has a specific activity of approximately 130 IU per milligram of total protein.
Haemonine® is indicated for the prophylaxis and treatment of bleeding in patients with Haemophilia B (congenital Factor IX deficiency)

1. Objective

With Haemonine® Biotest succeeded in producing a Factor IX concentrate with a high safety level. Two virus inactivating / virus removing processes cover different pathogens by using different active principles: Solvent / detergent treatment with a mixture of TNBP and Polysorbate 80 captures the lipid membrane enclosed viruses, the nano filtration with 70 kDa filters captures the non-enclosed viruses. Besides these two processes, the safety concept for the manufacture of Haemonine® includes the comprehensive testing of single donations and plasma pools (including NAT for HBV, HCV and HIV-1).

The post marketing study (PMS) aims to enhance knowledge on the **safety profile** of the preparation in the long-term treatment of Haemophilia B patients. Based on the developmental data, there is no particular safety concern for Haemonine®. However, thrombogenicity as well as immunogenicity are critical for all factor IX products. Therefore, particular attention is paid to adverse events related to thrombogenicity and immunogenicity. It is expected that the existing safety profile is confirmed by the collection of data derived from this study.
With regard to the fact that Haemophilia B is a congenital disease, this study is also aimed to collect data in the paediatric population during routine administration of Haemonine® for prophylaxis and on demand. In a comparative analysis, data on treatment regimens, efficacy, safety and tolerability may be compared between children and adults.

As all observational studies conducted by Biotest, planning, inclusion of participating physicians, evaluation and reporting is with the Corporate Drug Safety department, under management by the Scientific Coordinator function reporting into the EEA Qualified Person for Pharmacovigilance.

2. Study Design

The planned post-marketing study is open**,** multi-centred and non-interventional and will be conducted in Austria, Italy, Greece and Germany. Further countries may be included after granting of marketing authorisation.
It is expected to involve approximately 10 centres initially with a recruiting rate of 2 patients per country per year, thereof 30% children.
Final evaluation is planned with 50 patients treated.

Within this study the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation.

The assignment of the patient to a particular therapeutic strategy is not decided in advance but is at the discretion of the physician and falls within the current practice and the prescription of the medicine and is clearly separated from the decision to include the patient in the study.

The collecting of the research parameters is carried out within the framework of routine treatment of patients with congenital Haemophilia B.

Additional parameters which fall outside the routine are not included.

The observation period for patients should be covering a minimum of 50 exposure days. The examination intervals are in accordance with the requirements of the respective treatment centres. Apart from the initial examination a minimum of at least one further examination per year should be documented.

There is a descriptive evaluation at the end of the observation period.

4. Materials

The Factor IX concentrate Haemonine® used complies with all the manufacturer's specifications. It is acquired through normal distribution channels in the commercial packaging. All information can be found in the enclosed package leaflet.

5. Selection of patients

The PMS is intended for patients with diagnostically confirmed Haemophilia B. The Factor IX residual activity should be less than 2 %, the patient's inhibitor titre less than 0.6 Bethesda units. Exceptions to these criteria must be motivated.

Children
The concept is well suited to collect efficacy and safety data on Haemonine® administration in the paediatric population. However, it is obvious that the access to this patient population is restricted.
The following cases should not be included in the PMS:

- Patients for whom the substitution with Factor IX concentrates is contra-indicated.
- Patients where it is known that intolerance reactions have frequently occurred after receiving plasma preparations, especially coagulation concentrates.
- Patients with concurrent infections with fever and shivering.
- Patients of less than 6 years of age.

The patient should be asked about concomitant illnesses before inclusion in the PMS.

6. Execution of the post marketing study

6.1 Treatment and dosage

The treatment is carried out in accordance with the guidelines of the relative treatment centre. If possible, only the Factor IX concentrate Haemonine® to be tested is used during the observation period, since with intermittent changes in preparations the data correlation may become unclear. The dosage, the administration frequency and the duration of the substitution therapy depends on the severity of the factor IX deficiency, on the location and extent of the bleeding and on the patient's clinical condition. The following formula can be used for calculating the required Factor IX quantities:

> One unit Factor IX (IU) per kilogram body weight raises the Factor IX plasma level by
> 1–2 % of normal activity.
> Required units = body weight (kg) x desired factor IX rise (%) (IU/dl) x 0.80

Every Factor IX substitution is recorded in the substitution calendar (patient diary) together with the Factor IX quantity (IU) and the batch number of the preparation.

6.2 Concomitant medication

Patients should not receive any therapies with other blood or plasma derivatives during the observation period. Any other concomitant treatment is to be documented in the Case Report Form (CRF).

6.3 Outcome and concomitant variables

The outcome variables in the long-term observation of patients given Haemonine® are efficacy, tolerability and safety.

6.3.1 The following anamnestic data will be assessed at admission (visit 1):

- Demographic data: age, sex, ethnic origin
- Body measurements: body height, body weight
- History of hemophilia including the date of the initial diagnosis, factor IX baseline activity, previous treatment of hemophilia with either the investigational product or with other factor IX preparations
- Family history including the questions whether father or mother was currently suffering from immunodeficiencies and whether they had been suffering from infections after previous transfusion
- Consumption habits concerning alcohol, tobacco, and drugs
- Concomitant diseases and concomitant medication

6.3.2 The following laboratory parameters can be documented within the framework of routine therapeutic care:

- Factor IX antibodies (Bethesda test)
- Hepatitis-B virus marker (HBsAg, Anti-HBs and Anti-HBc using commercial tests such as ELISA or RIA)
- Hepatitis-C virus marker (Anti-HCV by means of ELISA)
- Hepatitis-A virus marker (IgG, IgM)
- HIV-1-/HIV-2 virus marker (Anti-HIV by means of ELISA; Western Blot where anti-HIV findings are positive)
- Liver disease marker (Transaminases AST, ALT and Gamma-GT by means of colorimetry at 37°C; bilirubin, AP and LDH)
- Haematocrit
- Thrombocyte counts
- CD4 and CD8.

6.3.3 Parameters for efficacy

At each haemophilia monitoring visit the following assessments are to be documented on patients diary forms:

- Treatment period and batch numbers of investigational product administered.
- The administration was due to prophylaxis or treatment on-demand.
- The quantity of administered investigational product in I.U.
- Expected therapeutic effect reached has to be indicated as ‘yes’ or ‘no’.

6.3.4 Parameters of safety

At each visit, enquiry is made on:

Occurence and nature of adverse events
AEs related to thrombogenicity
AEs related to immunogenicity
    Factor IX inhibitors
    Allergic/anaphylactic reactions
    Decrease of efficacy
Overall tolerability

At each collection of blood samples, laboratory assessments including serological monitoring
is performed.

6.3.5 General aspects

At the start of each treatment and at each collection of blood samples, the patients are asked about their subjective findings (illness symptoms) and concomitant medication respectively. Body weight and height are controlled. This data must be documented.

If a positive antibody diagnosis (inhibitor formation) or noticeable virological finding is made (e.g. suggestion of infection) during the PMS, Biotest must be informed immediately (see address in section 7. below).

6.3.6 Final evaluation

At the termination of the study, a final evaluation is made and the following parameters documented:

- Premature termination of the study (yes or no), including reason, if applicable
- Overall efficacy
- Overall tolerability
- Overall ease of use of the preparation

7. Adverse events / side effects

Every adverse event is documented in the respective form of the case record file as well as side effects which are related to the administration of Haemonine®.
In case of adverse events caused by thrombogenicity or immunogenicity, detailed questionaries should be filled in and send together with the AE-reporting form.

All serious adverse events (see SAE sheets) must be reported by the treatment centre promptly within 24 hours to:

Biotest AG
Corporate Drug Safety
Landsteinerstraße 5
63303 Dreieich
Telephone: +49 (0)6103/801-756
Telefax: +49 (0)6103/801-854
E-mail: drugsafety@biotest.de

Exception: Reporting routine treatment of bleeding is not required. Only bleeding where the cause is assumed to be lack of efficacy or inhibitor formation is regarded as an adverse event.

8. Termination criteria

The PMS can be terminated at any time on agreement with the patient. The administrator will be informed in writing of the reason.

Further treatment with the preparation should be stopped if there are recurring side effects after administration of Haemonine®, which make it necessary to discontinue the injection/infusion or to take concomitant medication. Biotest's Drug Safety Department must be informed immediately.

9. Documentation of findings

Documentation is carried out on the attached data capture sheets. Should any data not be available, the attending doctor should notate the respective point as:

n. d. ⇒ not done

- Coding will be done as follows: Each center will receive a Country code, center code (D for Germany, Post indent number of the city and initials from the leading investigator from the centre)
- Each patient will receive a number starting with 01 for the whole documentation
- For e.g. the code will look like: D-63303BT-01

10. Archiving period of test report

The archiving period for all data obtained from the post marketing study (capture sheets, laboratory data, etc) is 15 years from completion or termination.

The documentation is archived at Biotest.

Each completed pseudonymized sheet is forwarded to:

Biotest AG
[redacted]
Landsteinerstraße 5
63303 Dreieich

Telephone: [redacted]
E-mail: drugsafty@biotest.de

11. Miscellaneous

11.1 General duty to notify

Notice of the post marketing study in accordance with § 67 paragraph 6 (AMG) has been given by Biotest AG to the National Association of Statutory Health Insurance Physicians, the Board of Medical Funds as well as the relative federal authority. Recording of the names and addresses of participants is prescribed.

11.2 Evaluation and publication

An interim report after 2 years and a final evaluation after treatment of 50 patients will be presented by the pharmaceutical company. A draft for a possible joint publication may then be produced. All the parties have the right of publication but publication can only be made jointly and by mutual agreement. Biotest has the right to examine a draft publication and to request necessary, motivated changes.
In addition, the outcomes of the PMS will be addressed in each Periodic Safety update Report on Haemonine.

The biometric evaluation is carried out in collaboration with Metronomia (München).

Only descriptive statistical methods are applied. All quantitative and derived data are described by using the common descriptive parameters (sample size, numbers missing, mean, standard deviation, median, extrema). Qualitative data are to be described by absolute and relative frequencies.

The evaluation of efficacy is based on the factor IX consumption represented as I.U. per kilogram bodyweight per month, year, and event, respectively. Respective data are listed according to forms provided by the Paul-Ehrlich-Institute and statistically analyzed.

The evaluation of tolerability is based on a descriptive analysis of AE data, the overall assessment of tolerability, the assessment of possible seroconversions and changes of laboratory parameters.
All evaluations are stratified according to the country involved and the reason for treatment (prophylaxis or treatment on demand). Patients are not distinguished according to the intention-to-treat or per- protocol approaches known for randomized clinical trials.

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