1. NAME OF THE MEDICINAL PRODUCT

Haemocomplettan® P 1g
Haemocomplettan® P 2g

Powder for solution for injection / infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Haemocomplettan is presented as a powder for solution for injection or infusion for intravenous administration containing 1g or 2g human fibrinogen per vial.

The product contains approx. 20 mg/ml human fibrinogen after reconstitution with 50 or 100 ml water for injections.

The content of clottable fibrinogen is determined according to Ph. Eur. monograph for human fibrinogen.

Excipients with known effect: Sodium up to 164 mg (7.1 mmol) per 1g fibrinogen.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for injection/infusion.
White powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Haemocomplettan P 1g/2g, Fibrinogen Concentrate (Human) is indicated for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.
Haemocomplettan P 1g/2g is not indicated for dysfibrinogenemia.

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders.

Posology
The dosage and duration of the substitution therapy depend on the severity of the disorder, location and extent of bleeding and the patient's clinical condition.

The (functional) fibrinogen level should be determined in order to calculate individual dosage and the amount and frequency of administration should be determined on an individual patient basis by regular measurement of plasma fibrinogen level and continuous monitoring of the clinical condition of the patient and other replacement therapies used.

Normal plasma fibrinogen level is in the range of 1.5 – 4.5 g/l. The critical plasma fibrinogen level below which haemorrhages may occur is approximately 0.5 – 1.0 g/l. In case of major surgical intervention, precise monitoring of replacement therapy by coagulation assays is essential.

1. Prophylaxis in patients with congenital hypo- or afibrinogenaemia and known bleeding tendency.
To prevent excessive bleeding during surgical procedures, prophylactic treatment is recommended to raise fibrinogen levels to 1 g/l and maintain fibrinogen at this level until haemostasis is secure and above 0.5 g/l until wound healing is complete.

Initial Dose
If the patient's fibrinogen level is not known, the recommended dose is 70 mg per kg of body weight (bw) administered intravenously.

Subsequent Dose

The target level (1 g/l) for minor events (e.g. epistaxis, intramuscular bleeding or menorrhagia) should be maintained for at least three days. The target level (1.5 g/l) for major events (e.g. head trauma or intracranial haemorrhage) should be maintained for seven days.

$$\text{Dose of fibrinogen (mg/kg b.w.)} = \frac{\text{[Target level (g/L) - measured level (g/L)]}}{\text{0.017 (g/L per mg/kg b.w.)}}$$

Furthermore, the amount to be administered and the frequency of application of Haemocomplettan P 1g/2g should always be oriented to the degree of bleeding and the clinical efficacy in the individual case.

In case of major surgical intervention, precise monitoring of replacement therapy by coagulation assays is essential.

Treatment of bleeding

Adults

Generally 1-2 g is administered initially with subsequent infusions as required.
In case of severe haemorrhage i.e. obstetric use / abruption placenta, large amounts (4-8 g) of fibrinogen may be required.

Children
Limited data from clinical studies regarding the dosage of Haemocomplettan P1 g/2g in children are available.
The dosage should be determined according to the body weight and clinical need but is usually 20-30 mg/kg.

Method of Administration
Intravenous infusion or injection.
Haemocomplettan should be reconstituted according to section 6.6. The reconstituted solution should be warmed to room or body temperature before administration, then injected or infused slowly at a rate which the patient finds comfortable. The injection or infusion rate should not exceed approx. 5 ml per minute.

4.3 Contraindications

Known hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

There is a risk of thrombosis when patients with congenital deficiency are treated with human fibrinogen concentrate, particularly with high dose or repeated dosing. Patients given human fibrinogen concentrate should be observed closely for signs or symptoms of thrombosis.

In patients with a history of coronary heart disease or myocardial infarction, in patients with liver disease, in peri- or post-operative patients, in neonates, or in patients at risk of thromboembolic events or disseminated intravascular coagulation, the potential benefit of treatment with human fibrinogen concentrate should be weighed against the risk of thromboembolic complications. Caution and close monitoring should also be performed.

If allergic or anaphylactic-type reactions occur, the injection/infusion should be stopped immediately. In case of anaphylactic shock, standard medical treatment for shock should be implemented.

In the case of replacement therapy with coagulation factors in other congenital deficiencies, antibody reactions have been observed, but there is currently no data available with regard to fibrinogen.

Important information about specific excipients of Haemocomplettan
Haemocomplettan contains up to 164 mg (7.1 mmol) sodium per 1g fibrinogen. This correlates with 11.5 mg (0.5 mmol) sodium per kg body weight of the patient if the recommended initial dose of 70 mg/kg body weight is applied. To be taken into consideration by patients on a controlled sodium diet.

Virus safety
Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.
The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) and for the non-enveloped hepatitis A virus (HAV).
The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19.
Parvovirus B19 infections may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

Appropriate vaccination (hepatitis A and hepatitis B) should be considered for patients in regular/repeated receipt of products from human blood or plasma.

It is strongly recommended that every time that Haemocomplettan is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal reproduction studies have not been conducted with Haemocomplettan (see section 5.3). Since the active substance is of human blood plasma origin, it is catabolized in the same manner as the patient's own protein. These physiological constituents of the human blood are not expected to induce adverse effects on reproduction or on the foetus.

The safety of Haemocomplettan for use in human pregnancy has not been established in controlled clinical trials.

Clinical experience with human fibrinogen concentrate in the treatment of obstetric complications suggests that no harmful effects on the course of the pregnancy or health of the foetus or the neonate are to be expected.

Lactation
It is unknown whether Haemocomplettan is excreted in human milk. The safety of Haemocomplettan for use during lactation has not been established in controlled clinical trials.

A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Haemocomplettan therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
There are no data on fertility available.

4.7 Effects on ability to drive and use machines

Haemocomplettan has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Tabulated list of adverse drug reactions (ADRs)
This table combines the adverse reactions identified from clinical trials and post marketing experience. Frequencies presented in the table below have been based on pooled analyses across two company-sponsored clinical trials performed in aortic surgery with or without other surgical procedures [BI3023_2002 (N=61) and BI3023_3002 (N=152)] and have been evaluated according to the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). For spontaneous post marketing ADRs, the reporting frequency is categorized as unknown. In view of the fact that these trials were conducted in only the narrow population of aortic surgery adverse drug reaction rates observed in these trials may not reflect the rates observed in clinical practice and are unknown for clinical settings outside the studied indication.

MedDRA System Organ Class	**Undesirable effects**	**Frequency (In aortic surgery with or without other surgical procedures)**
General Disorders and Administration Site Condition	Pyrexia	Very common
Immune System Disorder	Anaphylactic reactions (including anaphylactic shock)	Uncommon
	Allergic reactions (including generalized urticaria, rash, dyspnoea, angioedema, tachycardia, nausea, vomiting, chills, pyrexia, chest pain, cough, blood pressure decreased)	Unknown

Vascular Disorder	Thromboembolic events*	Common**

** Isolated cases have been fatal.*
*** Based on results of two clinical trials (aortic surgery with or without other surgical procedures), the pooled incidence rate of thromboembolic events was lower in fibrinogen treated subjects (N=8, 7.4 %) compared with placebo group (N=11, 10.4 %).*

For safety with respect to transmissible agents, see section 4.4.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/
and emailed to the Registration Holder's Patient Safety Unit at:
drugsafety@neopharmgroup.com

4.9 Overdose

In order to avoid overdosage, regular monitoring of the plasma level of fibrinogen during therapy is indicated (see 4.2).
In case of overdosage, the risk of development of thromboembolic complications is enhanced.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group*:* antihaemorrhagics**,** human fibrinogen,
ATC code: B02B B01

Human fibrinogen (coagulation factor I), in the presence of thrombin, activated coagulation factor XIII (F XIIIa) and calcium ions, is converted into a stable and elastic three-dimensional haemostatic fibrin clot.

The administration of human fibrinogen concentrate causes an increase in plasma fibrinogen level and can temporarily correct the coagulation defect of patients with fibrinogen deficiency.

The pivotal Phase II study evaluated the single-dose pharmacokinetics (see 5.2 Pharmacokinetic properties) and also provided efficacy data using the surrogate endpoint maximum clot firmness (MCF) and safety data.
For each subject, the MCF was determined before (baseline) and one hour after a single dose administration of 70 mg/kg body weight of Haemocomplettan. Haemocomplettan was found to be effective in increasing clot firmness in patients with congenital fibrinogen

deficiency (afibrinogenaemia) as measured by thromboelastometry. Haemostatic efficacy in acute bleeding episodes, and its correlation with MCF, are being verified in a postmarketing study.

5.2 Pharmacokinetic properties

Human fibrinogen is a normal constituent of the human plasma and acts like endogenous fibrinogen. In plasma, the biological half-life of fibrinogen is 3 to 4 days. Regarding degradation Haemocomplettan behaves like the endogenous fibrinogen.

Haemocomplettan is administered intravenously and is immediately available in a plasma concentration corresponding to the dosage administered.

A pharmacokinetic study evaluated the single-dose pharmacokinetics before and after administration of human fibrinogen concentrate in subjects with congenital afibrinogenaemia. This prospective, open label, uncontrolled, multicentre study consisted of 5 females and 10 males, ranging in age from 8 to 61 years (2 children, 3 adolescents, 10 adults). The median dose was 77.0 mg/kg body weight (range 76.6 – 77.4 mg/kg).

Blood was sampled from 15 subjects (14 measurable) to determine the fibrinogen activity at baseline and up to 14 days after the infusion was complete. In addition, the incremental *in vivo* recovery (IVR, defined as the maximum increase in fibrinogen plasma levels per mg/kg body weight dosed), was determined from levels obtained up to 4 hours post-infusion. The median incremental IVR was 1.7 (range 1.30-2.73) mg/dl per mg/kg body weight. The following table provides the pharmacokinetic results:

Pharmacokinetic results for fibrinogen activity

Parameter (n=14)	**Mean ± SD**	**Median (range)**
$t_{1/2}$ [h]	78.7 ± 18.13	77.1 (55.73-117.26)
C_{max} [g/l]	1.4 ± 0.27	1.3 (1.00-2.10)
AUC for dose of 70 mg/kg [h•mg/ml]	124.3 ± 24.16	126.8 (81.73-156.40)
Extrapolated part of AUC [%]	8.4 ± 1.72	7.8 (6.13-12.14)
Cl [ml/h/kg]	0.59 ± 0.13	0.55 (0.45-0.86)
MRT [h]	92.8 ± 20.11	85.9 (66.14-126.44)
V_{ss} [ml/kg]	52.7 ± 7.48	52.7 (36.22-67.67)
IVR [mg/dl per mg/kg bw]	1.8 ± 0.35	1.7 (1.30-2.73)

$t_{1/2}$ = terminal elimination half-life
h = hour
C_{max} = maximum fibrinogen concentration in plasma within 4 hours
AUC = area under the plasma concentration curve
Cl = clearance
MRT = mean residence time
V_{ss} = volume of distribution at steady state
SD = standard deviation

IVR = in vivo recovery
bw= body weight

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single dose toxicity and safety pharmacology.

Preclinical studies with repeated dose applications (chronic toxicity, cancerogenicity and mutagenicity) cannot be reasonably performed in conventional animal models due to the development of antibodies following the application of heterologous human proteins.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin,
L-arginine hydrochloride,
sodium chloride,
sodium citrate

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products, diluents, or solvents except those mentioned in section 6.6. A standard infusion set is recommended for intravenous application of the reconstituted solution at room temperature.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

The physico-chemical stability for the reconstituted product has been demonstrated for 8 hours at room temperature (max. +25 °C). From a microbiological point of view the product should be used immediately following reconstitution. If the reconstituted product is not administered immediately, storage shall not exceed 8 hours below 25 °C. The reconstituted product should not be stored in the refrigerator.

6.4 Special precautions for storage

Store in a refrigerator ($2\ ^0$ C – $8\ ^0$C). Do not freeze!
Keep the vial in the closed outer carton, in order to protect from light.

Stability for the reconstituted product see section 6.3.

6.5 Nature and contents of container

Vial of colourless glass (Type II Ph. Eur.) closed with a latex-free stopper (bromobutyl rubber), and sealed with an aluminium / plastic crimp cap.

Pack with 1 or 2 g *(Figure 1)*

1. One vial containing 1 or 2 g human fibrinogen
2. Filter: Pall® Syringe Filter
3. Dispensing pin: Mini-Spike® Dispensing Pin

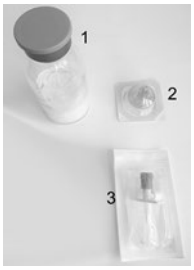


Figure 1

6.6 Special precautions for disposal and other handling

General instructions

- Reconstitution and withdrawal should be carried out under aseptic conditions.
- Reconstituted product should be inspected visually for particulate matter and discoloration prior to administration.
- The solution should be almost colourless to yellowish, clear to slightly opalescent and of neutral pH. Do not use solutions that are cloudy or contain residues (deposits/particles).

Reconstitution

- Warm both the solvent and the powder in unopened vials to room or body temperature (not above 37 °C).
- Haemocomplettan should be reconstituted with water for injections (50 ml for 1 g and 100 ml for 2 g, respectively, not included).
- Wash hands or use gloves before reconstituting the product.
- Remove the cap from the Haemocomplettan vial to expose the central portion of the infusion stopper.
- Treat the surface of the infusion stopper with antiseptic solution and allow it to dry.
- Transfer the solvent with an appropriate transfer device into the infusion vial. Ensure to push straight down centrally through the infusion stopper. Transfer the solvent completely. The powder should be completely wet.
- Gently swirl the vial until the powder is reconstituted and the solution is ready for administration. Avoid strong shaking which causes formation of foam. The powder should be completely reconstituted within max. 15 minutes (generally within 5 to 10 minutes).

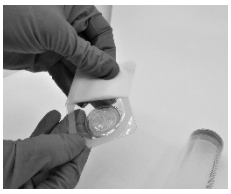
- Open the plastic blister containing the dispensing pin (Mini-Spike® Dispensing Pin) provided with Haemocomplettan (Figure 2).

 Figure 2

- Take the provided dispensing pin and insert it into the stopper of the vial with the reconstituted product (Figure 3).

 Figure 3

- After the dispensing pin is inserted, remove the cap. After the cap is removed, do not touch the exposed surface.
- Open the blister with the filter (Pall® Syringe Filter) provided with Haemocomplettan (Figure 4).

 Figure 4

- Screw the syringe onto the filter (Figure 5).

Figure 5

- Screw the syringe with the mounted filter onto the dispensing pin (Figure 6).

Figure 6

- Draw the reconstituted product into the syringe (Figure 7).


Figure 7

- When completed, **remove the filter, dispensing pin and empty vial from the syringe,** dispose of properly, and proceed with administration as usual.
- Reconstituted product should be administered immediately by a separate injection / infusion line (see section 6.3).
- Take care that no blood enters syringes filled with product.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

CSL Behring GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

8. REGISTRATION HOLDER:

Genmedix,
12 Beit Harishonim St., Emek-Heffer 3877701.

9. REGISTRATION NUMBERS

141 35 31819
141 36 31820

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