

## DATA SHEET

### PRONATIV

#### NAME OF DRUG

PRONATIV, Human Prothrombin Complex, powder and solvent for solution for injection.

#### DESCRIPTION

PRONATIV is a sterile, freeze dried powder containing purified coagulation factors II, VII, IX and X. It is prepared from blood collected from donors.

1 vial of PRONATIV nominally contains the following:

<b>Ingredient</b>	<b>PRONATIV Quantity per vial (20 mL)</b>	<b>PRONATIV Quantity per mL reconstituted solution</b>
Total protein:	260 - 820 mg	13 - 41 mg
<b><i>Active substances</i></b>		
Human coagulation factor II	220 - 760 IU	11 - 38 IU
Human coagulation factor VII	180 - 480 IU	9 - 24 IU
Human coagulation factor IX	500 IU	25 IU
Human coagulation factor X	360 - 600 IU	18 - 30 IU
<b><i>Further active ingredients</i></b>		
Protein C	140 - 620 IU	7 - 31 IU
Protein S	140 - 640 IU	7 - 32 IU
<b><i>Excipients</i></b>		
Heparin	100-250 IU	5-12.5 IU
Sodium Citrate	130 mg	6.5 mg

Factor IX specific activity is  $\geq 0.6$  IU/ mg proteins.

Factors II, VII, IX, X, and protein C and S are all of human origin. The heparin is of porcine origin.

PRONATIV does not contain any antimicrobial or preserving agents.

#### PHARMACOLOGY

##### *Pharmacodynamic properties*

Pharmacotherapeutic group: antihemorrhagics, blood coagulation factors IX, II, VII, and X in combination.

ATC code: B02BD01

The coagulation factors II, VII, IX and X, which are synthesised in the liver with the help of vitamin K, are commonly collectively called the Prothrombin Complex.

Factor VII is the inactive precursor of the active serine protease factor VIIa by which the extrinsic pathway of blood coagulation is initiated. The tissue factor-factor VIIa complex activates coagulation factors X and IX, whereby factor IXa and Xa are formed. With further activation of the coagulation cascade prothrombin (factor II) is activated and transformed to thrombin. By the action of thrombin, fibrinogen is converted to fibrin, which results in clot formation. The normal generation of thrombin is also of vital importance for platelet function as a part of primary haemostasis.

Isolated severe deficiency of factor VII leads to reduced thrombin formation and a bleeding tendency due to impaired fibrin formation and impaired primary haemostasis. Isolated deficiency of factor IX is one of the classical haemophilias (haemophilia B). Isolated deficiency of factor II or factor X is very rare but in severe form they cause a bleeding tendency similar to that seen in classical haemophilia.

Acquired deficiency of the vitamin K dependant coagulation factors occurs during treatment with vitamin K antagonists. If the deficiency becomes severe, a severe bleeding tendency results, characterised by retroperitoneal or cerebral bleeds rather than muscle and joint haemorrhage. Severe hepatic insufficiency also results in markedly reduced levels of the vitamin K dependant coagulation factors and a clinical bleeding tendency which, however, is often complex due to a simultaneous ongoing low-grade intravascular coagulation, low platelet levels, deficiency of coagulation inhibitors and disturbed fibrinolysis.

The administration of human prothrombin complex provides an increase in plasma levels of the vitamin K dependent coagulation factors, and can temporarily correct the coagulation defect of patients with deficiency of one or several of these factors.

### ***Pharmacokinetic properties***

The pharmacokinetic properties of PRONATIV were assessed in 6 haemophilia B patients and in 4 FVII deficient patients in Study I. Apart from 2 FVII deficient patients, all had a repetitive pharmacokinetic analysis after 6 months treatment with PRONATIV.

Ranges of recovery and half-life are shown in the following table. Because of the low number of patients per group, no mean values are presented.

### **Recovery and half-life of FVII and FIX**

	<b>Recovery def 1<sup>1</sup></b> <b>(% IU/kg-1)</b>	<b>Recovery def 2<sup>2</sup></b> <b>(%)</b>	<b>Elimination t<sub>1/2</sub></b> <b>(hours)</b>
FVII <sup>3</sup>	0.84 - 1.24 (n=4)	35.5 - 53.4 (n=4)	5.4 - 8.3 (n=3)
FIX	0.8 - 1.42 (n=6)	38.6 - 61.0 (n=6)	28.7 - 49.1 (n=6)

<sup>1</sup>(C<sub>max</sub>-C<sub>0</sub>) x (body weight)/dose, <sup>2</sup>(C<sub>max</sub> -C<sub>0</sub>) x (bodyweight) x (1-HCT/100)/dose, <sup>3</sup> Recovery based upon measured potency

The plasma half-life ranges are as follows:

<b>Coagulation factor</b>	<b>Half life</b>
Factor II	48 - 60 hours
Factor VII	1.5- 6 hours
Factor IX	20 - 24 hours
Factor X	24 - 48 hours
Protein C	1.5 - 6 hours
Protein S	24 - 48 hours

The half-lives of coagulation factors may be significantly reduced in the case of extended catabolic metabolism, severe liver cell damage or disseminated intravascular coagulation (DIC).

Pronativ is administered intravenously and therefore immediately available in the organism.

## **CLINICAL TRIALS**

Three clinical studies with PRONATIV have been conducted. In total, 90 patients have been enrolled and the patients received a total of about 569,000 IU of PRONATIV. All studies used an open design and were uncontrolled.

### **Overview of Demographic Data by Study**

	<b>Study I</b>	<b>Study II</b>	<b>Study III</b>
Number of patients	10	20	60
Population studied	Haemophilia B (n=6) FVII deficient (n=4)	Control of bleeding (n=10) Surgical intervention (n=10)	Major surgery (n=19) Minor surgery (n=38) Control bleeding (n=3)
Mean age, years (range)	21 (11-67)	68 (43-83)	67 (24-93)

### ***Acquired deficiency of the prothrombin complex coagulation factors***

#### ***Study II***

This was a prospective, non-randomised, non-controlled, open-labelled, multi-centre study. The primary objective of the study was to assess the efficacy of PRONATIV in patients suffering from major bleeds or who had to undergo emergency surgical procedures during treatment with anticoagulants of coumarin or indandion type.

The primary efficacy variables were PT (expressed in percent of normal plasma) and International Normalised Ratio (INR). The results are shown in the following table.

**Arithmetic means  $\pm$  standard deviations (range) of PT and INR**

Time Points	n	PT (%)	n	INR
<b>Baseline</b>	20	14.6 $\pm$ 5.7 (10.0 – 34.0)	20	6.1 $\pm$ 2.8 (2.1 – 12.8)
<b>10 min</b>	20	55.4 $\pm$ 16.9 (33.0 – 102.0)	20	1.5 $\pm$ 0.3 (1.0 – 2.1)
<b>30 min</b>	20	53.9 $\pm$ 14.4 (32.0 – 84.0)	20	1.6 $\pm$ 0.3 (1.1 – 2.2)
<b>1 h</b>	20	51.4 $\pm$ 14.4 (31.0 – 80.0)	20	1.6 $\pm$ 0.3 (1.1 – 2.3)
<b>2 h</b>	6	53.5 $\pm$ 11.4 (39.0 – 65.0)	6	1.5 $\pm$ 0.2 (1.3 – 1.9)
<b>3 h</b>	20	47.0 $\pm$ 12.9 (25.0 – 71.0)	20	1.7 $\pm$ 0.4 (1.2 – 2.7)
<b>24 h</b>	7	34.3 $\pm$ 16.8 (19.0 – 57.0)	7	2.5 $\pm$ 0.9 (1.4 – 3.7)

**Study III**

This was a prospective, non-randomised, non-controlled, open-labelled, Phase III study. The primary objective of the study was to investigate the efficacy of PRONATIV in correcting the PT in patients undergoing surgical or invasive procedures being under treatment with anticoagulants. The secondary objective of the study was to investigate the safety and tolerability of PRONATIV.

The results of the PT are presented in the following table.

**PT(%) profile (PerProtocol population, N=56)**

Time point	Mean $\pm$ SD [range]
Pre-infusion	22.1 $\pm$ 11.8 [4.0 - 48.0]
10 min post	79.7 $\pm$ 17.4 [36.0 - 106.0]
30 min post	78.7 $\pm$ 17.2 [33.0 - 117.0]
1 hr post	78.8 $\pm$ 17.9 [31.0 - 111.0]
Post	79.1 $\pm$ 17.2 [33.3 - 111.2]

Of the 56 patients in the PP population, 51 (91 %) showed an efficacy response, i.e. the mean of post-infusion PT values was equal to or larger than the pre-defined target PT value based on the actual administered dose.

At baseline the median INR was 2.8 (1.5 – 9.5); 10, 30 and 60 minutes after infusion with PRONATIV the median INR decreased to 1.1 (1.0 – 1.9), 1.1 (0.9 – 1.9) and 1.1 (1.0 – 1.9), respectively. In summary a decrease in INR of about 0.06 was achieved per unit PRONATIV per kg BW.

## ***Congenital deficiency of any of the vitamin K dependent coagulation factors***

### ***Study I***

This was a prospective, non-randomised, open, non-controlled, Phase II/III study. Previously treated patients suffering from severe prothrombin complex factor deficiencies were treated for a period of 6 months.

During the study 285 exposure days were documented in 10 patients. In total, 84 bleeding episodes were reported during the study. The mean duration of these episodes was 1.2 days. The median dose administered by exposure days (for the treatment of bleeding episodes) was 26.3 IU FIX per kg BW.

All PK and efficacy data available for this study indicates that PRONATIV is suitable for the substitutive chronic treatment of FIX- or FVII-deficient patients. All bleeding episodes could be controlled with PRONATIV.

### **INDICATIONS**

- Treatment of bleeding and perioperative prophylaxis of bleeding in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required.
- Treatment of bleeding and perioperative prophylaxis in congenital deficiency of any of the vitamin K dependent coagulation factors when purified specific coagulation factor product is not available.

### **CONTRAINDICATIONS**

- Hypersensitivity to the active substance or to any of the excipients
- Known allergy to heparin or history of heparin induced thrombocytopenia.

### **PRECAUTIONS**

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 inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood and plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses or other pathogens and theoretically to Creutzfeldt-Jacob Disease (CJD) agents. The risk of transmission of infective agents is however reduced by:

- i. selection of donors by a medical interview and screening of individual donations and plasma pool for specific markers of infection
- ii. inactivation/ removal procedures included in the production process that have been validated using model viruses.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV. The measures taken may be of limited value against non-enveloped viruses such as

HAV and parvovirus B19. Parvovirus B19 may cause serious reactions in pregnant women who are sero-negative (foetal infection) and for individuals with immunodeficiency or increased red cell production (e.g. in haemolytic anaemia).

The manufacturing process for PRONATIV has been investigated for its capacity to remove prion proteins using an experimental agent of transmissible spongiform encephalopathy (TSE), considered to be a model for the CJD and vCJD agents. The manufacturing process of PRONATIV has been shown to significantly decrease the amount of this experimental model agent. The TSE reduction steps are chromatography adsorption, purification steps and nanofiltration.

Appropriate vaccination (hepatitis A and B) is recommended for patients in regular/repeated receipt of human plasma-derived prothrombin complex products.

It is strongly recommended that every time that PRONATIV 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.

The advice of a specialist experienced in the management of coagulation disorders should be sought.

In patients with acquired deficiency of the vitamin K dependent coagulation factors (e.g. as induced by treatment with vitamin K antagonists), PRONATIV should only be used when rapid correction of prothrombin complex levels is necessary, such as major bleeding or emergency surgery. In other cases, reduction of the dose of the vitamin K antagonist and/or administration of vitamin K is usually sufficient.

Patients receiving a vitamin K antagonist may have an underlying hypercoagulable state and infusion of prothrombin complex concentrate may exacerbate this.

In congenital deficiency of any of the vitamin K dependent factors, specific coagulation factor product should be used when available.

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

Treatment with plasma derived products that contain factors II, VII, IX, and X has been associated with thrombosis.

There is a risk of thrombosis or disseminated intravascular coagulation when patients, with either congenital or acquired deficiency are treated with human prothrombin complex particularly with repeated dosing. The risk may be higher in treatment of isolated factor VII deficiency, since the other vitamin K dependant coagulation factors, with longer half-lives, may accumulate to levels considerably higher than normal. Patients given human prothrombin complex should be observed closely for signs or symptoms of intravascular coagulation or thrombosis. Because of the risk of thromboembolic complications, close monitoring should be exercised when administering human prothrombin complex to patients with a history of coronary heart disease, to patients with liver disease, to peri- or postoperative patients, to neonates, or to patients at risk of thromboembolic events or disseminated intravascular coagulation. In each of these situations, the potential benefit of treatment should be weighed against the risk of these complications.

No data are available regarding the use of PRONATIV in case of perinatal bleeding due to vitamin K deficiency in the new born.

#### ***Use in pregnancy and lactation***

The safety of human prothrombin complex for use in human pregnancy and during lactation has not been established.

Animal studies are not suitable to assess the safety with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Therefore, human prothrombin complex should be used during pregnancy and lactation only if clearly indicated.

#### ***Interactions with other medicines***

Human prothrombin complex products neutralise the effect of vitamin K antagonist treatment, but no interactions with other medicinal products are known.

#### ***Effects on laboratory tests***

When performing clotting tests which are sensitive to heparin in patients receiving high doses of human prothrombin complex, the heparin as a constituent of the administered product must be taken into account.

#### ***Effects on ability to drive and use machines***

No studies on the effects on the ability to drive and use machines have been performed.

### **ADVERSE REACTIONS**

Adverse reactions for PRONATIV are rare. In case of severe reactions, the infusion should be stopped and an appropriate treatment should be initiated.

The following adverse reactions have been observed with PRONATIV:

Rarely (> 0.01% and < 0.1%):

#### ***Immune system disorders:***

Replacement therapy may rarely lead to the formation of circulating antibodies inhibiting one or more of the human prothrombin complex factors. If such inhibitors occur, the condition will manifest itself as a poor clinical response.

Allergic or anaphylactic-type reactions and an increase in body temperature have not been observed in clinical studies with PRONATIV but may rarely occur.

#### ***Vascular disorders:***

There is a risk of thromboembolic episodes following the administration of human prothrombin complex (see **PRECAUTIONS**).

#### ***General disorders and administration site conditions:***

Increase in body temperature has not been observed with PRONATIV but may rarely occur.

*Nervous system disorders:*

Headache may rarely occur.

*Investigations:*

A transient increase in liver transaminases have been rarely observed.

For information on viral safety, see **PRECAUTIONS**.

## **DOSAGE AND ADMINISTRATION**

### ***Posology***

Only general dosage guidelines are given below. Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders. The dosage and duration of the substitution therapy depend on the severity of the disorder, on the location and extent of the bleeding and on the patient's clinical condition.

The amount and the frequency of administration should be calculated on an individual patient basis. Dosage intervals must be adapted to the different circulating half-life of the different coagulation factors in the prothrombin complex (see **PHARMACOLOGY**).

Individual dosage requirements can only be identified on the basis of regular determinations of the individual plasma levels of the coagulation factors of interest, or on global tests of the prothrombin complex levels (prothrombin time, INR), and continuous monitoring of the clinical condition of the patient.

In case of major surgical interventions, precise monitoring of the substitution therapy by means of coagulation assays is essential (specific coagulation factor assays and/or global tests for prothrombin complex levels).

### ***Bleeding and perioperative prophylaxis of bleeding during vitamin K antagonist treatment:***

The dose will depend on the INR before treatment and the targeted INR. In the following table approximate doses (ml/kg body weight of the reconstituted product) required for normalisation of INR ( $\leq 1.2$  within 1 hour) at different initial INR levels are given.

#### **Doses Required for Normalisation of INR**

Initial INR	2 – 2.5	2.5 – 3	3 – 3.5	> 3.5
Approximate dose * (mL PRONATIV/ kg body weight)	0.9 – 1.3	1.3 – 1.6	1.6 – 1.9	> 1.9

\* The single dose should not exceed 3,000 IU (120 mL PRONATIV).

The correction of the vitamin K antagonist induced impairment of haemostasis persists for approximately 6-8 hours. However, the effects of vitamin K, if administered simultaneously, are usually achieved within 4-6 hours. Thus, repeated treatment with human prothrombin complex is not usually required when vitamin K has been administered.

As these recommendations are empirical and recovery and the duration of effect may vary, monitoring of INR treatment is mandatory.

***Bleeding and perioperative prophylaxis in congenital deficiency of any of the vitamin K dependent coagulation factors when specific coagulation factor product is not available:***

The calculated required dosage for treatment is based on the empirical finding that approximately 1 IU of factor VII or factor IX per kg body weight raises the plasma factor VII or IX activity, respectively, by 0.01 IU/mL, 1 IU of factor II or X per kg body weight raises the plasma factor II or X activity by 0.02 and 0.017 IU/mL, respectively.

The dose of a specific factor administered is expressed in International Units (IU), which are related to the current WHO standard for each factor. The activity in plasma of a specific coagulation factor is expressed either as a percentage (relative to normal plasma) or in IUs (relative to the international standard for the specific coagulation factor).

One IU of a coagulation factor activity is equivalent to the quantity in one mL of normal human plasma.

For example, the calculation of the required dosage of factor X is based on the empirical finding that 1 IU of factor X per kg body weight raises the plasma X activity by 0.017 IU/mL. The required dosage is determined using the following formula:

**Required units = body weight (kg) x desired factor X rise (IU/mL) x 59**

where 59 (mL/kg) is the reciprocal of the estimated recovery.

Required dosage for factors II, VII, IX:

**Required units = body weight (kg) x desired factor II rise (IU/mL) x 50**

**Required units = body weight (kg) x desired factor VII rise (IU/mL) x 100**

**Required units = body weight (kg) x desired factor IX rise (IU/mL) x 100**

If the individual recovery is known that value should be used for calculation.

***Administration***

Reconstitute the product as described under **INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL**.

PRONATIV should be administered intravenously. The infusion should start at a speed of 1 mL per minute, followed by 2-3 mL per minute, using an aseptic technique.

***Incompatibilities***

PRONATIV must not be mixed with other medicinal products or administered simultaneously with other intravenous preparations in the same infusion set.

Only the provided injection/infusion sets can be used because treatment failure can occur as a consequence of adsorption of coagulation factors to the internal surfaces of some infusion equipment.

## **INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL**

The powder should be reconstituted only directly before injection. The product does not contain any antimicrobial agent. After reconstitution the solution should be used immediately.

The reconstituted solution should be used on one occasion only. Any solution remaining should be discarded appropriately.

Please read all the instructions and follow them carefully!

During the procedure described below, aseptic technique must be maintained!

The product reconstitutes quickly at room temperature.

The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Reconstituted products should be inspected visually for particulate matter and discoloration prior to administration.

### ***Instructions for reconstitution:***

1. Warm the solvent (Water for Injections) and the concentrate (powder) in the closed vials up to room temperature. This temperature should be maintained during reconstitution.  
If a water bath is used for warming, care must be taken to avoid water coming into contact with the rubber stoppers or the caps of the vials. The temperature of the water bath should not exceed 37°C.
2. Remove the caps from the concentrate vial and the water vial and clean the rubber stoppers with an alcohol swab.
3. Remove the protective cover from the short end of the double-ended needle, making sure not to touch the exposed tip of the needle. Then perforate the centre of the water vial rubber stopper with the vertically held needle.  
In order to withdraw the fluid from the water vial completely, the needle must be introduced into the rubber stopper in such a way that it just penetrates the stopper and is visible in the vial.
4. Remove the protective cover from the other, long end of the double-ended needle, making sure not to touch the exposed tip of the needle. Hold the water vial upside-down above the upright concentrate vial and quickly perforate the centre of the concentrate vial rubber stopper with the needle. The vacuum inside the concentrate vial draws in the water.
5. Remove the double-ended needle with the empty water vial from the concentrate vial, then slowly rotate the concentrate vial until the concentrate is completely dissolved. PRONATIV dissolves quickly at room temperature to a colourless to slightly blue solution.

If the concentrate fails to dissolve completely or an aggregate is formed, do not use the preparation.

### ***Instructions for injection:***

As a precautionary measure, the patients pulse rate should be measured before and during the injection. If a marked increase in the pulse rate occurs, the injection speed must be reduced or the administration must be interrupted.

1. After the concentrate has been reconstituted in the manner described above, remove the protective cover from the filter needle and perforate the rubber stopper of the concentrate vial.
2. Remove the cap of the filter needle and attach the 10 mL syringe.
3. Turn the vial with the attached syringe upside-down and draw up the solution into the syringe.
4. Remove the syringe from the filter needle and attach the infusion set (butterfly) to the syringe instead.
5. Disinfect the intended injection site with an alcohol swab.
6. Inject the solution intravenously at a slow speed: Initially 1 mL per minute, not faster than 2 - 3 mL per minute.
7. Remove the syringe from the infusion set (butterfly) and attach it to the filter needle instead.
8. Turn the vial with the attached syringe upside-down and draw up the solution into the syringe.
9. Remove the syringe from the filter needle and attach the infusion set (butterfly) to the syringe instead.
10. Inject the solution intravenously at a slow speed: Initially 1 ml per minute, not faster than 2 - 3 ml per minute.

The filter needle is for single use only. Always use a filter needle when drawing up the preparation into a syringe. No blood must flow into the syringe due to the risk of formation of fibrin clots.

### **OVERDOSAGE**

The use of high doses of human prothrombin complex products has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. Therefore, in case of overdose, the risk of development of thromboembolic complications or disseminated intravascular coagulation is enhanced.

### **PRESENTATION**

PRONATIV is supplied as a combination package consisting of two cartons held together with a clear plastic strip.

One carton contains a vial of PRONATIV (powder) and a vial of solvent (20 mL Water for Injections).

The other carton contains the following devices for administration:

- 1 disposable syringe
- 1 transfer set [1 double-ended needle and 1 filter needle]

- 1 infusion set
- 2 alcohol swabs

**STORAGE CONDITIONS**

Shelf life is 2 years.

Store at 2°C to 8°C (Refrigerate. Do not freeze).

Protect from light.

Do not use after expiry date.

After reconstitution the solution must be used immediately.

***Medicine Classification***

Prescription Medicine

**NAME AND ADDRESS OF SPONSOR**

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