octaplex®

Prothrombin Complex Concentrate

Accurate prevention and fast control of life-threatening bleeding

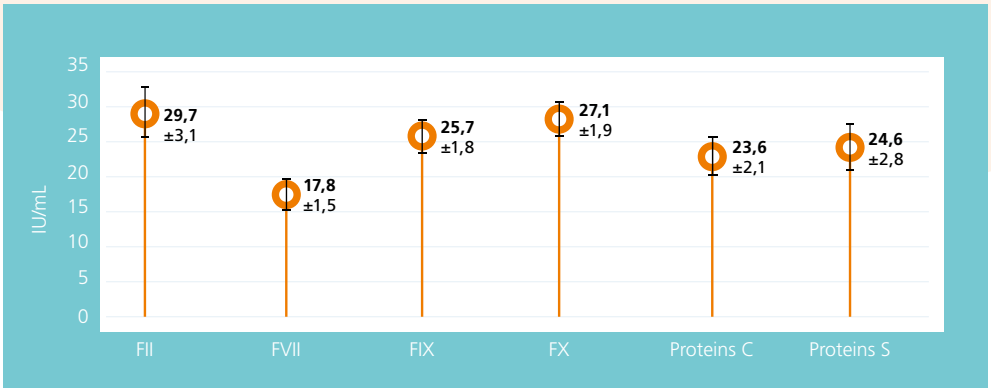
octapharma®

For the safe and optimal use of human proteins

octaplex® is the 4 factor PCC with balanced composition[14]

octaplex® is a lyophilized prothrombin complex concentrate (PCC) containing therapeutic and balanced levels of vitamin k-dependent coagulation factors (FII, FVII, FIX and FX) and inhibitory proteins C, and S.[1,14]

Balanced and reproducible content of coagulation factors and inhibitory proteins in octaplex®



Analysis of 88 consecutive batches of octaplex®. Octapharma data on file.

octaplex® reduces the time to achieve INR reversal due to:

- Low volume of infusion: 20mL (500IU) or 40 mL (1000IU)[1]
- Quick reconstitution and easy administration[1]
- Storage at room temperature[1]
- No need for blood type identification[1]

octaplex® provides a high level of pathogen safety by dedicated production steps:

- Solvent detergent (SD) treatment to inactivate possible enveloped viruses[2]
- Nanofiltration to remove viruses[2]
- Ion exchange chromatography for further reduction of non-enveloped viruses[3]

Current international guidelines on bleeding management recommend the use of octaplex® to prevent and control life-threatening bleeding.[4,5,6,7]

Minimising delay in initiating treatment is of crucial importance[8] not only in serious bleeding like intracranial haemorrhage (ICH), but also in emergency surgery or invasive procedure.[9]

octaplex® replaces pro-coagulant factors and inhibitory proteins in a fast and balanced way[14]

octaplex® is indicated for:

The treatment of bleeding and perioperative prophylaxis of bleeding in acquired deficiency of prothrombin complex coagulation factors or in congenital deficiency of factors II and X when purified specific coagulation factor products are not available.[1]

The efficacy and tolerability of octaplex® has been demonstrated in relevant clinical settings:

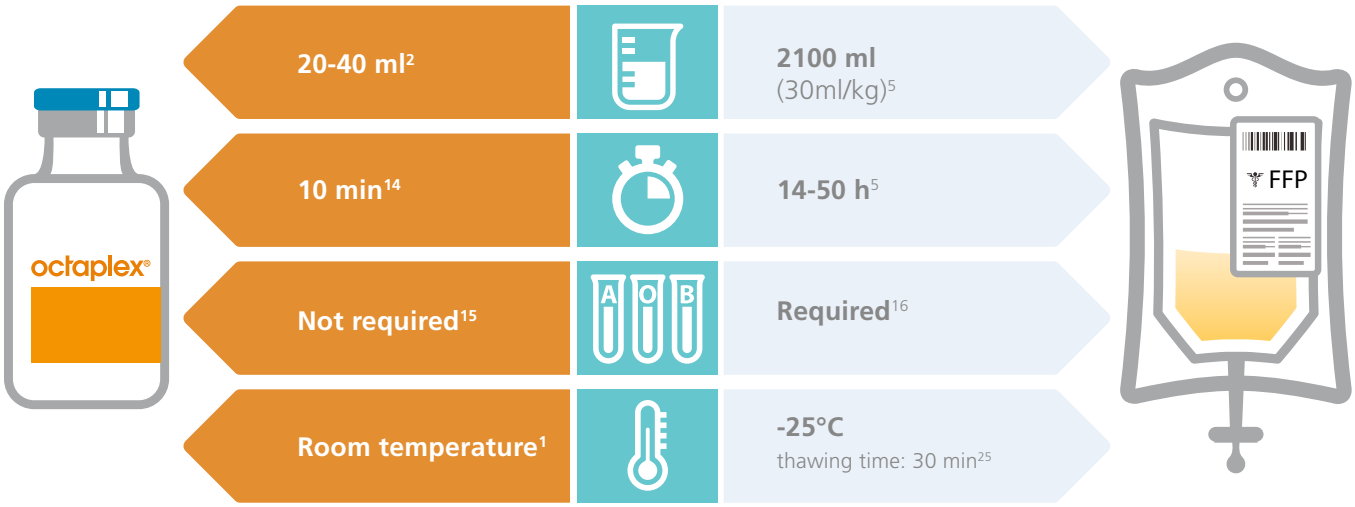
Prothrombin complex concentrates reverse INR faster, resulting in better clinical outcome compared to FFP.[5]

octaplex® quickly reverts anticoagulant therapy[2,14]

octaplex® provides a rapid and complete reversal of vitamin K antagonists (VKA) induced coagulopathy due to:

- Easy storage at room temperature and quick availability[1]
- Small infusion volume with no risk of fluid overload[11,12]
- Short infusion time[1]
- No need for blood type matching[1]
- Balanced content of vitamin K coagulation factors and inhibitory proteins[14]

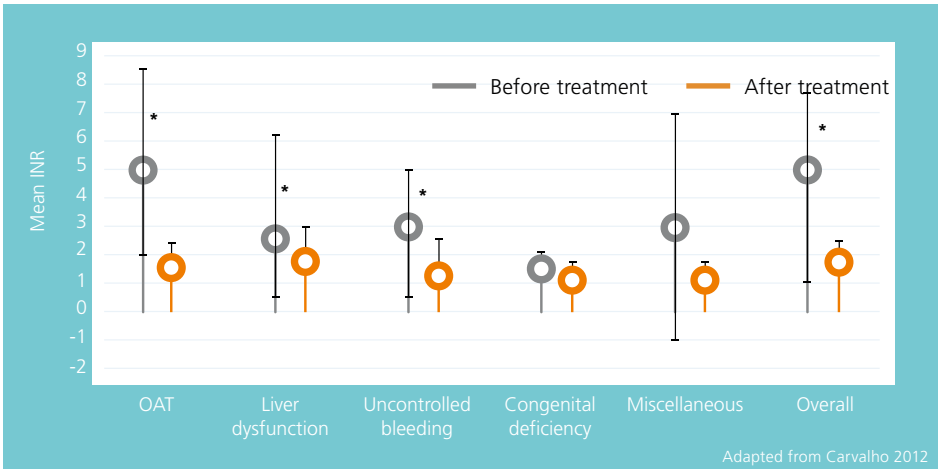
octaplex® is ready to be used in life-threatening bleeding, unlike FFP:



Compared with FFP, octaplex® as a 4-factor PCC provides quicker and more controlled correction of INR, improving bleeding control.[5]

octaplex® is effective in bleeding control[2]

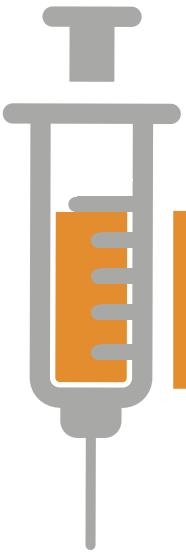
Mean INR before and after octaplex®



Treatment of all evaluable patients by indication and in total. Bars represent mean values, lines represent standard deviation. *P< 0.01. INR, international normalized ration; OAT, oral anticoagulation.

octaplex® allows INR reversal in all relevant clinical settings including intracranial haemorrhage, cardiac surgery, orthopaedic surgery and trauma.
In a multicenter study, including 1152 patients, octaplex® achieved an overall significant reduction of INR (p<0.01) without any adverse drug reactions or thromboembolic events reported.[12]

Only 1 dose of octaplex® to reverse INR



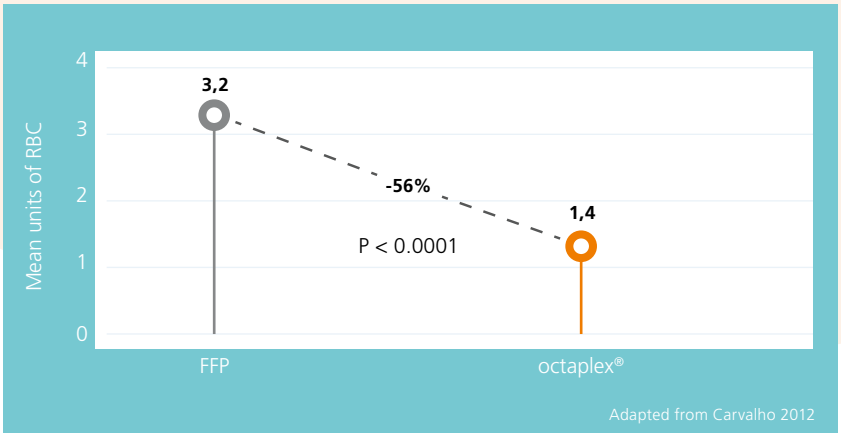
95% of patients require **1 dose** to reverse INR[12]

A single dose of octaplex® effectively controls bleeding. In 95% of the cases, a single dose of octaplex® was required to reverse INR. The percentage reached 100% in patients with very high INR and high risk of haemorrhage.[12]

octaplex®

octaplex® reduces red blood cell requirements[17]

Mean units of RBC required with octaplex® or FFP



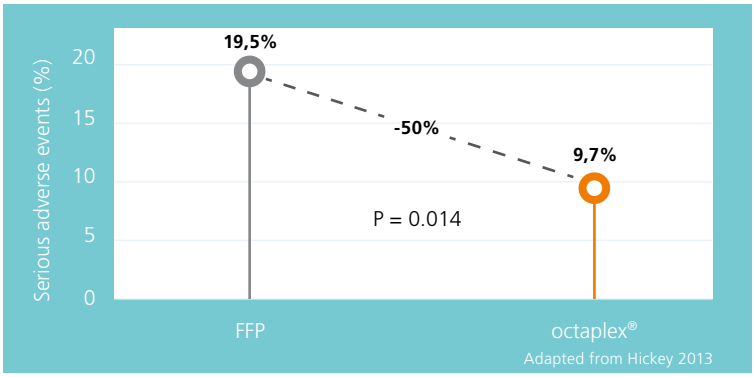
octaplex® used for urgent warfarin reversal reduces the need for RBC transfusions.
The retrospective analysis of 314 patients showed that octaplex® achieved full oral anticoagulant treatment (OAT) reversal with significantly lower requirements for red blood cell (RBC) transfusion compared with FFP.[17]

Strict transfusion protocols involving point of care testing (POC) and PCC, have been related to a reduction of transfusion requirements, mortality and overall costs.[18]

octaplex® is well tolerated and shows low thrombogenicity[9]

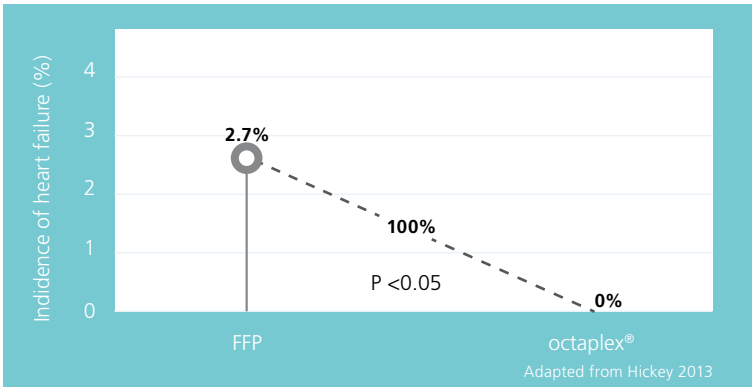
Due to the lower incidence of adverse events when compared to FFP, octaplex® should be considered a first-line treatment for OAT reversal.[17]

Serious adverse events after warfarin reversal with octaplex® or FFP (%)



octaplex® has shown OAT reversal with significantly lower incidence of serious adverse events (p=0.014) when compared to FFP, in a study involving 314 patients.[17]

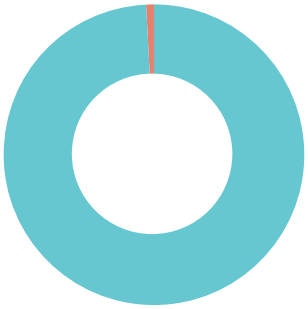
Incidence of heart failure after warfarin reversal with octaplex or FFP (%)



In the same analysis, **the use of octaplex® was associated with a significantly lower incidence of heart failure** compared to FFP (2.7% vs. 0%; P<0.05).[17]

Low risk of thrombotic events

Incidence of thrombotic events



In **99.4%** of cases patients do not develop any thrombotic event[19]

No cases

Thrombotic events

In a retrospective study, only 4 out of 686 patients treated with octaplex® to reverse OAT showed an incidence of thrombotic events,confirming the low thrombotic risk.[19]

Compared to other PCCs, octaplex® contains consistently lower FVIIa/FVII ratio as well as balanced levels of coagulation factors and haemostasis-controlling proteins C and S.[20]

The use of **octaplex®** is recommended

Current guidelines recommend the use of a 4-factor PCC for urgent VKA reversal:[21]

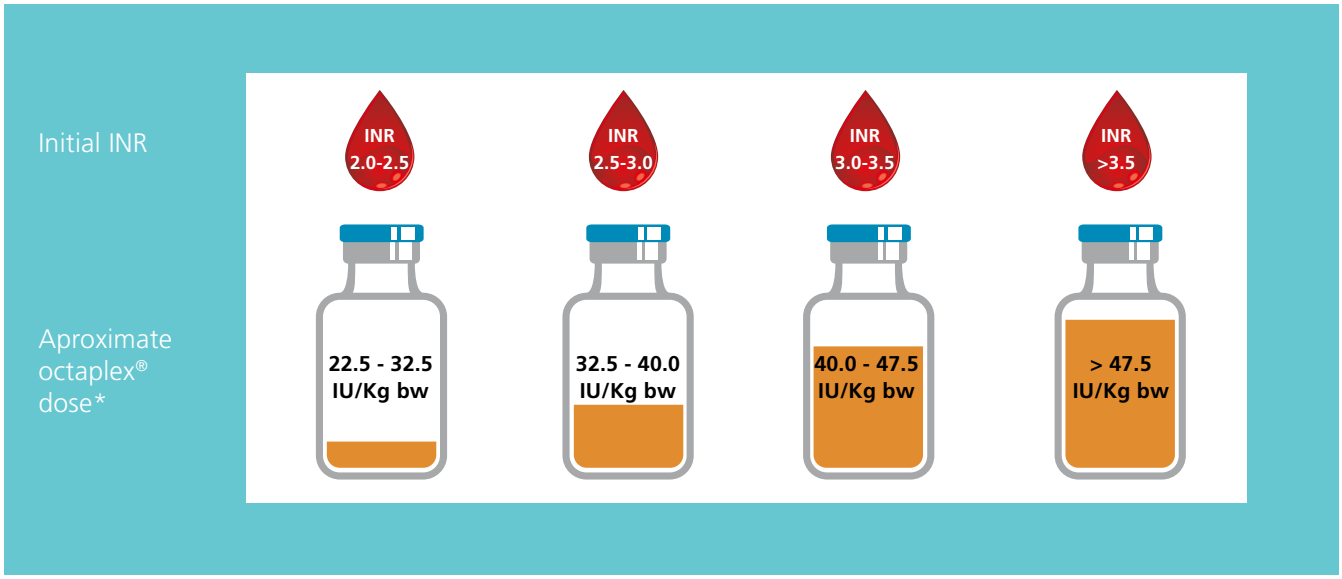
- The British Committee for Standards in Haematology[22]
- The American College of Chest Physicians[23]
- The French clinical practice guidelines[24]
- The Board of the German Medical Association[25]
- The European guidelines on the management of perioperative bleeding[5]
- The European guideline on management of major bleeding and coagulopathy following trauma[28]

These recommendations reflect findings from a range of studies showing that PCCs are effective in lowering INR for prompt VKA reversal.[21]

Individualised dosage of octaplex®[1]

The amount and frequency of administration should be calculated on an individual patient basis. The dose will depend on baseline INR and the defined target value.

Approximate doses required for normalisation of INR (≤ 1.2 within 1 hour) at different initial INR levels.



In orthopaedic and neurosurgery, a dose of 20-40 IU/kg, supplemented with vitamin K (10 mg), is recommended for emergency VKA reversal in patients with INR > 1.5 and life-threatening bleeding or ICH.[5]

Accurate prevention and fast control of life-threatening bleeding

- **Haemostatic balance of prothrombin complex coagulation factors[26]**
- **Therapeutic concentrations of protein C and protein S[26]**
- **Rapid INR reversal within 10 minutes[14]**
- **Low thrombogenic profile[2,9]**
- **Small volume and short infusion time[21]**

octaplex®

Name of the medicinal product: octaplex® 500 IU, containing Human Prothrombin Complex. **Presentation:** Powder and solvent for solution for infusion. Each vial contains coagulation factors II (280 - 760 IU), VII (180 - 480 IU), IX (500 IU) and X (360 - 600 IU), Protein C (260 - 620 IU), Protein S (240 - 640 IU) and total protein (260 - 820mg). FIX specific activity ≥ 0.6 IU/mg proteins. **Indications:** Treatment and perioperative prophylaxis of bleeding in 1) acquired deficiency of prothrombin complex coagulation factors when rapid correction of the deficiency is required and 2) congenital deficiency of the vitamin K dependent coagulation factors II and X when purified specific coagulation factor product is not available. **Dosage and Method of Administration:** The dosage and duration of substitution therapy depends on the severity of the coagulation disorder, location and extent of bleeding, half-life of the different coagulation factors and patient's clinical condition. Guidance for bleeding and bleeding prophylaxis during vitamin K antagonist treatment: Dose will depend on INR before treatment and target INR. Guidance for initial dosage for congenital deficiency: 1 IU/kg body weight raises the activity of factor II by 0.02 IU/ml and factor X by 0.017 IU/ml. For intravenous administration start infusion rate at 1 ml/min followed by 2 - 3 ml/min. **Contraindications:** Hypersensitivity to active substance, excipients or heparin. History of heparin induced thrombocytopenia. **Special Warnings and Precautions:** Stop infusion if allergic or anaphylactic reactions occur. Despite measures to prevent infections, possibility of infective transmission cannot be totally excluded - record patient name and product batch number. Appropriate vaccination (hepatitis A and B) is recommended for patients in regular/repeated receipt. Infusion of prothrombin complex may exacerbate underlying hypercoagulable state in patients receiving vitamin K antagonists. Repeated dosing in patients with congenital or acquired bleeding defect is associated with a risk of thrombosis or disseminated intravascular coagulation (DIC). Closely monitor when administering to patients: with a history of coronary heart disease or liver disease, at risk of thrombosis or DIC, neonates, and peri- or post-operative patients. octaplex® contains 75 - 125 mg sodium per vial and this should be considered in patients on controlled sodium diet. **Undesirable Effects:** Risk of thromboembolic episodes, headache, transient rise in liver transaminases, allergic or anaphylactic reactions, including increase in body temperature, may occur rarely. Replacement therapy may rarely lead to inhibitor formation, manifesting as poor clinical response. octaplex® contains heparin, therefore, sudden allergy induced thrombocytopenia may occur. For further information on side effects please refer to SmPC. **Fertility, pregnancy and lactation:** The safety of human prothrombin complex for use in human pregnancy and during lactation has not been established and should be used only if clearly indicated. **Overdose:** The risk of development of thromboembolic complications or DIC is enhanced.

Issue information: April 2015. Octapharma AG, Lachen Switzerland.

Registered Product Information may differ in your country. For further information and before prescribing please refer to the nationally approved SmPC.

Adverse events should be reported to octapharma®: cdsu@octapharma.com

References

1. Summary of Product Characteristics of octaplex®
2. Varga C et al. The effectiveness and safety of fixed low-dose prothrombin complex concentrates in patients requiring urgent reversal of warfarin. Transfusion 2013; 53:1451-1458
3. Biesert L et al. Viral safety of a prothrombin complex concentrate (octaplex®): Combination of solvent/detergent (SD) treatment with nanofiltration. J Thromb Haemost 2005; 3, Supplement 1: P0655
4. Goodnough T, Shander A. How I treat warfarin-associated coagulopathy in patients with intracerebral hemorrhage. Blood 2011; 117 (23)
5. Kosek-langenecker S et al. Management of severe perioperative bleeding - Guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol 2013; 30:270–382
6. American Society of Anesthesiologists. Practice Guidelines for Perioperative Blood Management - An Updated Report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management. Anesthesiology 2015; 122:241-275
7. Holbrook A et al. Evidence-Based management of anticoagulant therapy antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2)(Suppl):e152S–E184s
8. Hirri HM, Green PJ. Audit of warfarin reversal using a new octaplex® reduced dose protocol. Transfus Apher Sci 2014; 51(2): 141–145
9. Desmesttre T et al. Emergency reversal of anticoagulation: The real use of prothrombin complex concentrates - A prospective multicenter two year French study from 2006 to 2008. Thromb Res 2012; 130 (3): e178–e183
10. Kerebel D et al. A French multicenter randomised trial comparing two dose-regimens of prothrombin complex concentrates in urgent anticoagulation reversal. Critical Care 2013, 17(1):R4
11. Dowlatshahi D et al. Poor prognosis in warfarin-associated intracranial hemorrhage despite anticoagulation reversal. Stroke 2012;43: 1812-1817
12. Carvalho M et al. Prothrombin complex concentrate (octaplex®): a Portuguese experience in 1152 patients. Blood Coagul Fibrinolysis 2012; 23 (3):222–228
13. Arnekian V et al. Use of prothrombin complex concentrate for excessive bleeding after cardiac surgery. Interact Cardiovasc Thorac Surg 2012; 15(3):382-389
14. Lubetsky A et al. Efficacy and safety of a prothrombin complex concentrate (Octaplex®) for rapid reversal of oral anticoagulation. Thromb Res 2004; 113(6):371-378
15. Sorensen B et al. Clinical review: Prothrombin complex concentrates - evaluation of safety and thrombogenicity. Crit Care 2011; 15(1):201
16. Fresh Frozen Plasma and Variants Podcast. www.bbguy.org/podcast/0310/0310notes.pdf (accessed 28 April 2015).
17. Hickey M et al. Outcomes of urgent warfarin reversal with frozen plasma versus prothrombin complex concentrate in the emergency department. Circulation 2013;128:360-364
18. Gill R. Practical management of major blood loss. Anaesthesia 2015; 70 (Suppl. 1): 54–57
19. Desmesttre T et al. Reversal of vitamin K antagonist (VKA) effect in patients with severe bleeding: a french multicenter observational study (Optiplex) assessing the use of prothrombin complex concentrate (PCC) in current clinical practice. Crit Care 2012, 16 (5):R185
20. Hoffer L et al. Consistent manufacturing of 50 consecutive octaplex® 500 lots: Biochemical characteristics of a prothrombin complex concentrate. J Thromb Haemost 2005; 3 (Suppl. 1): P0656
21. Sarode R. Four-factor prothrombin complex concentrate versus plasma for urgent vitamin K antagonist reversal: New evidence. Clin Lab Med 2014; 34 (3): 613–621
22. Baglin TP et al. Guidelines on oral anticoagulation (warfarin): third edition-2005 update. Br J Haematol 2006;132(3):277-285
23. Ansell J et al. Pharmacology and management of vitamin K antagonists: American College of Chest Physicians Evidence-based Clinical Practice Guidelines (8th edition). Chest 2008; 133:160S-198S
24. Pernod G et al. French clinical practice guidelines on the management of patients on vitamin K antagonists in at-risk situations (overdose, risk of bleeding, and active bleeding). Thromb Res 2010;126(3):e167-e174
25. Board of German Medical Association. Cross-sectional guidelines for therapy with blood components and blood derivatives; plasma for therapeutic use. Transfus Med Hemother 2009; 26:388-397
26. Josic D, et al. Manufacturing of a Prothrombin Complex Concentrate Aiming at Low Thrombogenicity. Thromb Res 2000; 100: 433-441
27. Steiner T et al. Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. Lancet Neurol 2016; 15: 566–73
28. Rossaint R et al. The European guideline on management of major bleeding and coagulopathyfollowing trauma. Critical Care 2016; 20:100

Headquartered in Lachen, Switzerland, Octapharma is one of the largest human protein manufacturers in the world, developing and producing human proteins from human plasma and human cell lines. As a family-owned company, Octapharma believes in investing to make a difference in people's lives and has been doing so since 1983; because it's in our blood. Octapharma employs more than 6,200 people worldwide to support the treatment of patients in 105 countries with products across three therapeutic areas:

- Critical Care
- Haematology (coagulation disorders)
- Immunotherapy (immune disorders)

Octapharma owns five state-of-the-art production facilities in Austria, France, Germany, Mexico and Sweden.

We work to the highest standards of quality and safety set by physicians, patients and regulatory authorities.

For more information visit
www.octapharma.com

752_CCUBROPLX_2015v002

Exclusive Sole Agent in Lebanon:
Mediterranean Pharmaceutical Company
Airport Road, Al Kital Street, Beirut - Lebanon
Tel. 44 55 54 1 961+ - Fax. 45 54 54 1 961+
Website: www.mpc-pharma.com

Octapharma AG, Seidenstrasse 2
8853 Lachen, Switzerland
www.octapharma.com
Date of preparation: June 2016.

For healthcare professionals only.

octapharma®

For the safe and optimal use of human proteins