VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Octaplex is indicated for the treatment of bleeding and perioperative prophylaxis of bleeding in acquired deficiency of the prothrombin complex coagulation factors. Octaplex includes the blood clotting factors II, VII, IX and X. In the US, approximately 3 million patients per year receive oral anticoagulant therapy. A UK study investigated warfarin-related bleeding and found that the overall incidence of first-time, idiopathic bleeding was 15.2 per 100 patient-years of current warfarin exposure: the incidence of fatal/hospitalised and referred bleeding was 3.5 and 2.6 per 100 patient-years, respectively.

Octaplex is also indicated in the treatment of bleeding and perioperative prophylaxis in congenital deficiency of the vitamin-K-dependent coagulation factors II and X when purified specific coagulation factor product is not available. Congenital bleeding disorders of vitamin-K-dependent coagulation factors represent only about 15–20% of all congenital bleeding disorders.

Factor X deficiency is a rare disorder, with only 1 in 500 000 people affected. Congenital Factor II deficiency is one of the rarest congenital coagulation disorders.

VI.2.2 Summary of Treatment Benefits

Prothrombin complex concentrate (PCC) preparations, like Octaplex, are primarily used to prevent or control bleeding episodes in patients under anticoagulant treatment (e.g., warfarin). Octaplex may also be used for the treatment of bleeding and perioperative prophylaxis in congenital deficiency of any of the vitamin K dependent coagulation factors when a purified specific coagulation factor product is not available.

Several studies were conducted by Octapharma to assess the efficacy of Octaplex in patients with acquired deficiency and one study assessed the efficacy of Octaplex in patients with congenital deficiency.

Efficacy in patients with congenital deficiency

Study LEX-201 included 6 patients suffering from haemophilia B and 4 patients suffering from factor VII deficiency who were treated with Octaplex for a period of 6 months. The median number of bleeding episodes per patient was 9 for a median period of 26.1 weeks of treatment. Efficacy was reported as “excellent” for 96% of all administrations and as “good” for the remaining 4%. In addition, Octaplex administration was safe and effective in controlling blood loss in three patients who underwent surgical procedures in the course of this study.

Efficacy in patients with acquired deficiency

Study LEX-202 included 20 patients (10 with bleeding episodes and 10 with surgical interventions). All enrolled patients received one Octaplex infusion. The efficacy of Octaplex treatment was considered as “excellent” for 17 patients and as “moderate” for 3 patients.

Study LEX-203 included 60 patients under oral anticoagulant therapy undergoing surgery or invasive procedures. The overall efficacy of the surgeries performed with regard to bleeding was assessed as “excellent” by the investigators for 59 patients.

Study LEX-206 included 59 patients with intracranial haemorrhage related to oral anticoagulant therapy. Octaplex was given as a single dose in the majority of cases. Two

dose groups were studied. The overall clinical response at 48 hours was reported as "excellent" in most (68%) patients without significant difference between the dose groups.

Overall, based on the studies performed by Octapharma, other studies with prothrombin complex concentrates as investigational product available in the published literature and the experience on the international market, it can be concluded that Octaplex is efficacious in the approved indications.

VI.2.3 Unknowns Relating to Treatment Benefits

Efficacy data in pregnant and breast feeding women and in paediatric population are limited. There is no evidence to suggest that results would be any different in these populations.

VI.2.4 Summary of Safety Concerns

Important identified risks

Risk	What is known	Preventability
Thrombogenicity (embolism and thrombosis)	May be serious or even fatal, depending on the site and type of thrombosis. Risk factors include obesity, advanced age, hypertension, diabetes mellitus, hyperlipidaemia, a history of vascular disease, a history of thrombotic episodes, acquired or inherited thrombophilic disorders, prolonged periods of immobilisation, hypovolaemia, renal insufficiency, liver disease, atrial fibrillation, haemophilia (with severe muscle haemorrhage, crush injury, or orthopaedic surgery), increased blood viscosity.	• Careful risk-benefit evaluation in at-risk patients • Ensure adequate hydration prior to infusion • Accurate diagnosis for the use of PCC • Relevant coagulation parameters should be carefully measured prior to the use of PCC, including antithrombin (AT) activity • In case of antithrombin deficiency, AT concentrate should be administered • Heparin should be administered if not contraindicated • Individual dosage calculations to avoid overdosing • Infusion rate <1 mL/minute • Monitor patients for signs and symptoms of thromboembolic events and the effect of PCC therapy o Appropriate warning in the SmPC and product labelling.
General tolerability (hypersensitivity and allergic	May be serious (very rarely). Usually patients recover following treatment. Risk factors include a history of	• Premedication (antihistamines and intravenous hydrocortisone) • Assessment of individual

Risk	What is known	Preventability
reactions)	hypersensitivity, immunoglobulin A (IgA) deficiency, presence of anti-IgA antibodies, previous severe systemic reactions to the administration of human plasma-derived products.	patient risk • Slow infusion rates o Appropriate warning in the SmPC and product labelling.

Important potential risks

Risk	What is known
Transmission of viruses	Serious with respect to human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV) and hepatitis A virus (HAV) and potentially serious with respect to Parvovirus B19 in immunocompromised patients and in pregnant women.
Heparin-induced thrombocytopenia	May be serious or even fatal, depending on the site and type of thrombosis. Risk groups include patients with type II heparin-induced thrombo-cytopenia (HIT) and HIT patients who develop thrombotic complications.

Important missing information

Risk	What is known
Limited information on use in pregnant and breast feeding women	There is no data on Octaplex use in pregnant and breast feeding women.
Limited information on use in paediatric population	There is insufficient evidence available to allow a recommendation for use of this product in this patient population. However, in the scientific literature there are several reports indicating that PCC may be successfully used in paediatrics.

VI.2.5 Summary of Additional Risk Minimisation Measures by Safety Concern

No additional risk minimisation measures are necessary.

VI.2.6 Planned Post-authorisation Development Plan

Not applicable, nothing is planned.

Studies which are a condition of the marketing authorisation

No such studies are required. The above study is not a condition of the marketing authorisation.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
01	31-May-2008	**Identified risks:** Thromboembolic events Anaphylactic reaction **Potential Risks:** Virus safety in general **Missing information:** None	First edition of RMP for Octaplex.
02	03-Dec-2012	**Identified risks:** Thrombogenicity Hypersensitivity and allergic reactions **Potential Risks:** Virus safety in general Heparin-induced thrombocytopenia (HIT) **Missing information:** Use in pregnant and breast feeding women Use in paediatric population	Second edition of RMP for Octaplex updated according to Guidance on format of the risk management plan in the EU - GVP Module V.
03	20-Mar-2013	**Identified risks:** Thrombogenicity Hypersensitivity and allergic reactions **Potential Risks:** Virus safety in general Heparin-induced thrombocytopenia (HIT) **Missing information:** Use in pregnant and breast feeding women Use in paediatric population	Section SVI 4.4 discussing medication errors and section SVII.3 together with Part III.1 discussing proposed routine and additional PhV activities (search criteria for potential risk "virus safety in general": HLT "Infectious transmissions" (MedDRA Code 10027684)) have been updated.
04	26-June-2013	**Identified risks:** Thrombogenicity Hypersensitivity and allergic reactions **Potential Risks:** Virus safety in general Heparin-induced thrombocytopenia (HIT) **Missing information:** Use in pregnant and breast feeding women Use in paediatric population	Update according to US requirements
05	22-Oct-2013	**Identified risks:** Thrombogenicity	Update according to

Version	Date	Safety Concerns	Comment
		Hypersensitivity and allergic reactions **Potential Risks:** Virus safety in general Heparin-induced thrombocytopenia (HIT) **Missing information:** Use in pregnant and breast feeding women Use in paediatric population	FDA requirements