Review of Data for Monoclonal Antibody-purified Plasma-derived Factor IX

Massimo Morfini[1] and Wolfhart Kreuz[2]

1. Director, Agency for Haemophilia and Regional Reference Centre for Inherited Bleeding Disorders, Careggi University Hospital, Florence;
2. Associate Professor and Head, Comprehensive Care Centre for Haemophilia, Coagulation Disorders and Immunodeficiencies, Johann Wolfgang Goethe University Hospital, Frankfurt

Abstract

Haemophilia B is attributed to a mutation in the gene that produces coagulation factor IX (FIX), resulting in FIX deficiency. Treatment of haemophilia B currently consists of replacing the deficient FIX by intravenous administration of exogenous FIX. There are two major treatment strategies: prophylactic FIX administration (to prevent recurrent bleeding episodes in patients), and on-demand FIX administration (to control existing bleeding in patients when it occurs). Prothrombin complex concentrates (PCCs), which were initially used to treat haemophilia B patients, have been available for approximately 40 years. However, PCCs have been largely replaced by highly purified plasma-derived FIX and recombinant FIX, which have benefited from improvements in purification and viral inactivation, reduction or elimination methods. Monoclonal antibody-purified plasma-derived FIX (MAb pd-FIX) has been extensively evaluated in clinical trials and has proved to be safe and efficacious for surgical prophylaxis and for on-demand and prophylactic treatment in previously untreated and previously treated patients. While intermittent dosing is the conventional method of administration, MAb pd-FIX is also suitable for continuous intravenous infusion; this dosing method has been shown to result in normal haemostasis in patients with haemophilia B. This article reviews the data available for MAb pd-FIX.

Keywords

Factor IX (FIX), haemophilia B, plasma-derived factor IX, monoclonal antibody-purified plasma-derived factor IX (MAb pd-FIX)

Disclosure: Massimo Morfini has acted as a paid consultant for Bayer, Novo Nordisk and Pfizer, and has served on advisory boards for, and received a fee as invited speaker from, Baxter and CSL Behring. Wolfhart Kreuz has received research support from Abbott, Baxter, Bayer, Biotest, Boehringer Ingelheim, CSL Behring, Grifols, Intersero, Janssen, Jerini, Novo Nordisk, Octapharma, Pfizer and Shire; he has received meeting sponsorship from Baxter, has served on advisory boards for Baxter, Bayer, Biotest, CSL Behring, Novo Nordisk, Octapharma, Pfizer and Viropharma, and has received travel grants from Baxter, Bayer, Biotest, CSL Behring, Octapharma and Viropharma.
Acknowledgements: Editorial support was funded by CSL Behring LLC and provided by Touch Medical Communications.
Received: 19 September 2011 **Accepted:** 31 October 2011 **Citation:** *European Oncology & Haematology*, 2011;7(4):257–62 *DOI: 10.17925/EOH.2011.07.04.257*
Correspondence: Massimo Morfini, Agenzia per l'Emofilia, Azienda Ospedaliero Universitaria Careggi, Viale GB Morgagni 85, 50134 Florence, Italy.
E: Massimo Morfini (massimo.morfini@unifi.it) or Wolfhart Kreuz (w.kreuz@gmx.de)

Support: The publication of this article was funded by CSL Behring LLC. The views and opinions expressed are those of the authors and not necessarily those of CSL Behring LLC.

Haemophilia B is an X-linked recessive coagulation disorder with an estimated incidence of 1 in 60,000 people.[1,2] It is characterised by repeated bleeding, particularly into the joints and muscles, which can initiate a cascade of events leading to destruction of the synovium due to synovitis, breakdown of cartilage, development of fibrosis and, eventually, severe and disabling arthropathy.[3–6] Pain associated with joint bleeding and arthropathy can have a significant impact on the patient's quality of life (QoL).[7,8] Muscle bleeding represents a major problem in the haemophiliacs owing to the increased risk of life-threatening bleeding. Some recent studies have suggested that haemophilia B may be a less severe form of the disease than haemophilia A because, at the same degree of disease severity (indicated by the baseline level of clotting factor), there appeared to be less joint damage and fewer bleeds over time in haemophilia B than in haemophilia A.[9–11] However, to date, there are no large-scale studies to support this view.

Haemophilia B is attributed to a mutation in the gene coding for coagulation factor IX (FIX), resulting in FIX deficiency. Treatment of haemophilia B currently consists of replacing the deficient FIX by intravenous administration of exogenous FIX. There are two major treatment strategies:

- prophylactic FIX administration (see *Table 1*),[12] either as primary or secondary prophylaxis – to prevent recurrent bleeding episodes in patients – reinforced by short-term anticipatory prophylaxis, for example, for preventing uncontrolled bleeding in those patients undergoing surgery; and
- on-demand FIX administration – to control existing bleeding in patients when it occurs.[13,14]

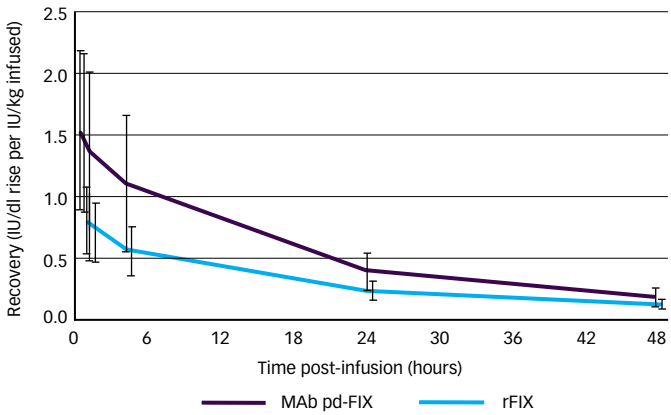
Currently available FIX concentrates include the human plasma-derived FIX (pd-FIX) concentrates and one recombinant FIX (rFIX) (see *Table 2*). Two prothrombin complex concentrates (PCCs), Bebulin® VH and Profilnine® SD, are also approved for treating haemophilia B. While they have been available for approximately 40 years, PCCs have since been largely replaced by highly purified pd-FIX (HP-FIX) and rFIX, which have

Table 1: Definitions of Primary, Secondary and Short-term Prophylaxis

Model	Definition
Primary prophylaxis determined by age	Long-term continuous* treatment started before the age of two years and prior to any clinical evidence of joint bleeding
Primary prophylaxis determined by first bleed	Long-term continuous* treatment started prior to the onset of joint damage (presumptively defined as having had no more than one joint bleed) irrespective of age
Secondary prophylaxis	Long-term continuous* treatment not fulfilling the criteria for primary prophylaxis
Short-term prophylaxis	Short-term treatment to prevent bleeding

**With the intent of treating 52 weeks per year up to adulthood and receiving treatment for a minimum of 46 weeks per year. Adapted from Berntorp et al., 2003.[12]*

Figure 1: Mean Recovery (± Standard Deviation) of Factor IX Clotting Activity over Time



The time course of recovery after infusion of MAb pd-FIX and rFIX from 0 to 48 hours. IU = international unit; MAb pd-FIX = monoclonal antibody-purified plasma-derived factor IX; rFIX = recombinant factor IX. Adapted from Ewenstein et al., 2002.[42]

benefited from improvements in purification and viral inactivation, reduction or elimination methods. HP-FIX concentrates include monoclonal antibody (MAb)-purified pd-FIX (MAb pd-FIX; Mononine®, CSL Behring) and ion-exchange chromatography purified pd-FIX (Alphanine® SD, Alpha). This article will focus on the efficacy, safety and pharmacokinetic profile of the MAb pd-FIX concentrate, which has been approved in the US since 1992 and in Europe from 1993 onwards for the prevention and control of bleeding in haemophilia B patients.

Classification of Haemophilia B

Classification of the severity of haemophilia B has traditionally been based on the plasma level of FIX clotting activity (FIX:C). Mild haemophilia B is generally classified as FIX:C >5 international unit (IU)/dl; moderate haemophilia B as FIX:C ≥1–5 IU/dl; and severe haemophilia B as FIX:C <1 IU/dl.[4] In a 1995 study of 1,967 haemophilia B patients, the proportions of patients with mild, moderate and severe disease were approximately 30 %, 33 % and 37 %, respectively.[15,16] In patients with mild or moderate haemophilia B, typical joint and soft tissue bleeding is usually experienced only after a traumatic event. However, patients with severe haemophilia B may experience two to five spontaneous bleeding episodes per month, even without a preceding injury or trauma. The severity of haemophilia B can also be classified by the frequency and severity of bleeding episodes – due to the lack of a direct correlation between the clotting factor levels and the frequency of bleeding in some patients.

The choice of treatment and treatment schedule are partly determined by the severity of the disease. In haemophilia A, severe haemophilia is associated with a substantially reduced QoL in both adults and children.[8,17] To limit or even prevent complications such as joint bleeds, prevention and management of bleeding in patients should be started before any joint bleeding or at least after the first joint bleeding in severe haemophilia, through either prophylaxis or on-demand treatment – prophylactic treatment with clotting factor concentrates is the recommended strategy.[6,13,18–20] Prophylaxis may also be useful in patients with a 'moderate' deficiency of clotting factor levels if they have frequent recurrent or serious bleeding episodes.

Improvements in Human Plasma-derived Factor IX Concentrates

PCCs were among the first plasma-derived concentrates to be developed. These concentrates contained not only FIX but also varying amounts of other clotting factors, some in their activated form, and extraneous proteins.[21] While PCCs have been shown to be effective in reducing bleeding in patients with haemophilia B, they have also been associated with serious adverse events (AEs) in this population.[21–32]

Safety concerns associated with the early PCCs led to the development and introduction of HP-FIX concentrates, including those purified using MAbs.[33] The HP-FIX concentrates are prepared from large pools of human plasma, and advanced purification and viral inactivation methods ensure a highly purified FIX concentrate, with a specific activity of up to 250 IU/mg (see *Table 2*). The safety profiles of FIX concentrates have been improved using these purification and viral inactivation steps that remove extraneous plasma proteins and activated coagulation factors and enable the inactivation and removal of potentially contaminating viruses. Indeed, preclinical and laboratory studies have shown these HP-FIX concentrates to contain only FIX and to be free of other vitamin K-dependent coagulation factors, fibronectin, fibrinogen, immunoglobulins and proteins C and S.[33–37] Preclinical studies demonstrated MAb pd-FIX had no thrombogenicity in the Wessler venous stasis assay in rabbits, whereas a marketed activated PCC – i.e., factor eight inhibitor bypass activity (FEIBA) – caused 3+ and 4+ thrombi.[33] Furthermore, HP-FIX concentrates (tested in clinical trials with small sample sizes) do not generate inappropriate activation of coagulation after infusion *in vivo*.[35,37] Furthermore, since their introduction, international surveys have indicated no transmission of blood-borne viruses from MAb-purified FIX concentrates.[38,39]

Current guidelines recommend the use of a pd-FIX concentrate, such as MAb pd-FIX (Mononine®, CSL Behring) or rFIX (BeneFIX®, Pfizer).[40,41]

Pharmacokinetic Profile of Monoclonal Antibody-purified Plasma-derived Factor IX

The comparative pharmacokinetic profiles of MAb pd-FIX versus rFIX in previously treated patients (PTPs) undergoing prophylactic treatment with clotting factor concentrates have been evaluated in clinical studies. Ewenstein et al. evaluated the pharmacokinetics and recovery rates of MAb pd-FIX and rFIX concentrates in a double-blind, two-period cross-over study.[42] In the first treatment period, patients were randomised to receive a single bolus infusion (50 IU/kg) of either MAb pd-FIX or rFIX. Following a washout period, patients were given the other treatment. Forty-three PTPs received a single bolus injection of FIX concentrate (50 IU/kg) in the non-bleeding state. Measurement of FIX:C levels over 48 hours post-infusion showed the presence of wide product- and

Table 2: Factor IX Concentrates Currently Approved in Europe and the US

Brand Name	Company	Plasma Source	Purification	Viral Reduction/Inactivation/Elimination
Human Plasma-derived Purified Factor IX Concentrates				
Mononine®	CSL Behring	Paid apheresis	MAb affinity chromatography	Immunoaffinity chromatography, sodium thiocyanate and ultrafiltration (19 nm)
Aimafix®*	Kedrion	Voluntary donors	Ion-exchange chromatography adsorption	TNBP polysorbate 80; dry heat 100 °C, 30 minutes; nanofiltration 35 + 15 nm (registration pending for nanofiltration)
Alphanine® SD	Alpha	Paid apheresis	CHO ligand chromatography Ion-exchange chromatography	Solvent detergent (360 minutes), nanofiltration regenerated multilayered structured cellulose membranes 35 + 15 nm
Recombinant Factor IX Product				
BeneFIX®	Pfizer	None	Recombinant	Membrane nanofiltration retaining molecules >70,000 Da (e.g., large proteins and viral particles)

**Available only in Hungary. CHO = carbohydrate; DEAE = diethylaminoethyl; MAb = monoclonal antibody; TNBP = tri-n-butyl phosphate. Source: Burnouf-Radosevich et al., 1994.*[62]

patient-related variability in recovery. The mean *in vivo* recovery was significantly higher in the MAb pd-FIX group than in the rFIX group (1.71 ± 0.73 IU/dl per IU/kg versus 0.86 ± 0.31 IU/dl per IU/kg, respectively; p≤0.0001) (see *Figure 1*). Furthermore, a significant positive correlation (Pearson's r=0.62; p≤0.0001; 95 % confidence interval 0.37 ± 0.78) was reported between the recoveries of the two FIX concentrates.[42] The results of this study also showed that the terminal half-life for MAb pd-FIX was similar to that for rFIX (14.9 hours and 16.8 hours, respectively, p=0.10).[42] The dosage needed to maintain a prophylactic level of FIX (≥2 IU/dl) was determined in a modelling analysis based on data from the earlier double-blind, two-period cross-over study by Ewenstein et al. described above. The study used single-dose pharmacokinetic data from 15 non-inhibitor severe (≤1 % FIX) FIX-deficient subjects to determine the dosing required to achieve and maintain a prophylactic level of ≥2 %.[43] From this study it was estimated that a lower dose of MAb pd-FIX than rFIX would be required to maintain the prophylactic trough level of 2 IU/dl for 30 days, regardless of whether the concentrates were administered continuously, every day, every second day or every third day (see *Table 3*). The results also demonstrated significantly higher *in vivo* recovery in the MAb pd-FIX group than in the rFIX group (median *in vivo* recovery: 1.67 ± 1.07 IU/dl per IU/kg, versus 0.86 ± 0.32 IU/dl per IU/kg, respectively; p=0.0002). The higher recovery associated with MAb pd-FIX accounts for the lower dose required to achieve prophylaxis. The results also showed similar values of median half-life for MAb pd-FIX and rFIX (p=0.016). The pharmacokinetic data for both MAb pd-FIX and rFIX are summarised in *Table 4*.

These results emphasise the importance of individualising treatment to incorporate both inter-patient and inter-product variability in recovery and half-life. These results are consistent with those results from studies by Kim et al., and White et al. that evaluated the recovery of MAb pd-FIX concentrate following infusion, either for pharmacokinetic analysis prior to surgery or during treatment.[35,44] The latter study also highlighted the wide intra- and inter-patient variability in recovery values observed for MAb pd-FIX with repeated dosing;[44] median population data cannot be used to predict the pharmacokinetic profile of an individual patient.

Greater understanding of drug pharmacokinetics offers the opportunity to tailor therapy, optimise treatment outcomes and, possibly, improve cost-effectiveness. Pharmacokinetic analyses and/or recovery studies may be carried out in individual patients, particularly prior to surgery, as there may be wide product- and patient-specific variability in recovery, which could impact treatment outcomes. White et al. demonstrated, however, that the *in vivo* recovery values obtained in pharmacokinetic studies performed for approximately a week prior to surgery did not predict recovery values when MAb-purified HP-FIX was administered just prior to surgery.[44] Nevertheless, knowledge of pharmacokinetics could allow the evaluation of the most effective treatment strategy, in terms of dosing schedule for optimum efficacy, safety and cost-effectiveness. For example, a low *in vivo* recovery of FIX would

Table 3: Estimated Amounts of Factor IX Concentrate Needed to Maintain a Prophylactic Trough Level of 2 IU/dl

Dosing Schedule	Monoclonal Antibody-purified Plasma-derived Factor IX (n=15) Median (range) (IU/kg)	Recombinant Factor IX (n=15) Median (range) (IU/kg)
Continuous infusion	61 (24–105)	104 (52–209)
Dosing every day	119 (60–262)	194 (87–522)
Dosing every two days	262 (160–1,147)	470 (154–2,383)
Dosing every three days	677 (388–6,005)	1,168 (268–13,085)

IU = international unit. Adapted from Kisker et al., 2003.[43]

Table 4: Major Pharmacokinetic Parameters for Subjects Treated with Factor IX Concentrates

Parameter	Monoclonal Antibody-purified Plasma-derived Factor IX Median (range) (IU/kg)	Recombinant Factor IX Median (range) (IU/kg)
Recovery (IU/dl per IU/kg)	1.67 (0.85–4.66)	0.86 (0.39–1.48)
Volume of distribution (dl/kg)	0.61 (0.24–1.27)	1.18 (0.80–2.71)
Elimination rate (l/hr)	0.054 (0.049–0.085)	0.051 (0.035–0.087)
Half-life (hr)	12.9 (8.1–14.1)	13.7 (7.9–20.0)
Estimated C_{max} (IU/dl)	78 (39–212)	42 (20–62)
Area under the curve (IU/dl/hr)	1,199 (696–3,094)	703 (372–1,400)
Clearance [(IU/kg)/(IU/dl/hr)]	0.042 (0.016–0.072)	0.071 (0.036–0.143)

C_{max} = maximum plasma concentration. Adapted from Kisker et al., 2003.[43]

Table 5: Studies Evaluating the Clinical Efficacy and Safety of Monoclonal Antibody-purified Plasma-derived Factor IX (MAb pd-FIX)

Authtor	Outline
Kim et al.[35]	MAb pd-FIX for on-demand control of bleeding in haemophilia B patients
Kurczynski et al.[48]	MAb pd-FIX for either surgical prophylaxis or for spontaneous or trauma-induced bleeding in previously treated children
Warrier et al.[49]	MAb pd-FIX for major surgery, trauma or severe spontaneous bleeding in previously treated haemophilia B patients
White et al.[44]	MAb pd-FIX for management of spontaneous or trauma-induced bleeding, or as prophylaxis with surgery
Shapiro et al.[45]	On-demand treatment with MAb pd-FIX in previously untreated patients with mild, moderate or severe haemophilia B MAb pd-FIX for surgical prophylaxis in previously untreated patients with mild, moderate or severe haemophilia B
Shapiro et al.[47]	MAb pd-FIX for surgical prophylaxis in patients with mild, moderate or severe haemophilia B
Hoots et al.[46]	MAb pd-FIX, administered through continuous intravenous infusion, in patients with mild, moderate or severe haemophilia B undergoing surgery, exposed to trauma, or experiencing severe spontaneous haemorrhage

indicate the need to infuse a higher dose to achieve the desired plasma levels necessary for achieving haemostasis. Similarly, the dosing frequency and the dosage would be influenced by the half-life and the recovery of the factor in an individual patient; a shorter half-life would necessitate more frequent dosing and, perhaps, a higher dose than would a product with a longer half-life in that individual patient. Clearly, treatment of each patient must be individualised and be based on repeated monitoring of the factor levels achieved during treatments.

Clinical Efficacy and Safety of Monoclonal Antibody-purified Plasma-derived Factor IX

The clinical efficacy and safety of the MAb pd-FIX concentrate have been extensively evaluated in both on-demand treatment and surgical prophylactic settings for previously untreated patients (PUPs) and PTPs (see *Table 5*).[35,44–49]

On-demand Treatment in Previously Untreated Patients

Two trials, enrolling patients with mild, moderate or severe haemophilia B, evaluated the efficacy and safety of MAb pd-FIX.[45] In the first trial, on-demand MAb pd-FIX was administered to 24 PUPs whereas, in the second trial eight patients were enrolled who needed surgery with FIX replacement. Patients in both trials were evaluated every two weeks for the first 24 weeks and at 9 months and 12 months. Haemostasis was rated as 'excellent' in the eight patients with mild haemophilia B who received MAb pd-FIX concentrate as prophylaxis for surgery. In none of the patients was therapy ineffective or were additional doses of MAb pd-FIX concentrate required to stop bleeding after the initial treatment, demonstrating the efficacy of MAb pd-FIX for on-demand treatment and for surgical coverage. No patient treated with MAb pd-FIX developed seroconversion to hepatitis C or HIV, or to non-A, non-B, non-C hepatitis. Furthermore, no patient evaluable for non-A, non-B, non-C hepatitis developed elevated alanine aminotransferase (ALT) levels (normally taken as a surrogate marker of post-transfusion hepatitis). AEs that may have been related to treatment were few (n=8) and most (63 %; 5/8 AEs) were mild in severity. The relationships of three of these mild events to the treatment were considered to be remote. A major problem with replacement therapy for treating haemophilia in general is the production of inhibitor antibodies that neutralise the replacement factor. However, the PUP study showed the rate of inhibitor development in PUPs with haemophilia B, treated with MAb pd-FIX concentrate, to be very low (3 %). The low incidence of inhibitor development in this study is consistent with the results of an inhibitor prevalence study in a larger sample of PUPs with haemophilia B (2 % in the haemophilia B population, 4 % in severely affected patients; n=365).[50]

Surgical Prophylaxis in Patients with Haemophilia B

Two studies were conducted to investigate the efficacy of MAb pd-FIX in patients with haemophilia B who required extensive FIX replacement for surgery, trauma or spontaneous bleeding (73 unique subjects and eight subjects enrolled twice – a total of 81 treatment episodes).[47,51] In all instances (n=75) where efficacy was systematically evaluated, investigators rated the haemostatic efficacy of MAb pd-FIX as 'excellent'. There were no reports of inadequate therapy in patients in whom haemostasis was not determined.[47] This study illustrated the safety and effectiveness of MAb pd-FIX for surgical prophylaxis in patients with haemophilia B, including those who have experienced previous thromboembolic complications with PCCs. Moreover, even at relatively high dosages, MAb pd-FIX did not lead to thromboembolic events.[49,51]

Results in Previously Treated Children with Haemophilia B

The safety and efficacy of MAb pd-FIX were evaluated in previously treated children using data from patients recruited to a larger controlled trial.[44,48] Data from the 18 patients aged three months to 20 years who received MAb pd-FIX for either surgical prophylaxis or for spontaneous or trauma-induced bleeding were analysed separately.[48] Pharmacokinetic data were available for ten of the patients; the average maximum post-infusion FIX level was 62.4 % (range 45–149 %), and the average *in vivo* recovery was 1.13 U/dl rise per U/kg of FIX infused (range 0.41–2.53 IU/dl). Again, all patients treated with MAb pd-FIX experienced excellent haemostasis.[44] No patient experienced thromboembolic complications; two AEs possibly related to treatment (venospasm and burning at injection site) resolved spontaneously.

Continuous Infusion of Monoclonal Antibody-purified Plasma-derived Factor IX

Management of bleeding in haemophilia B patients involves maintaining plasma FIX at specified levels, which will achieve haemostasis.[52] Plasma levels of FIX achieved may be affected by dosing method and schedule. The conventional method involves the administration of a loading dose of pd-FIX followed by intermittent bolus maintenance doses. However, this method is associated with the presence of plasma level trough and peak levels. These fluctuations mean that the concentrate needs to be re-administered frequently enough to maintain plasma levels high enough to achieve and maintain haemostasis.[52] In addition, a high peak plasma concentration of the factor concentrate may occur when using less frequent infusions, because the dose must also be sufficient to avoid trough plasma concentrations falling

below the minimum level needed for haemostasis.[52,53] In contrast to the conventional method, continuous intravenous (CIV) infusion administration of HP-FIX may offer several advantages.[54] CIV infusion could be a practical method of HP-FIX administration when sustained FIX activity is desired, rather than intermittently therapeutic and sub-therapeutic levels; for example, during peri-operative periods or for the management of life-threatening bleeds. Data for FIX and for other factor concentrates suggest that CIV infusion is able to sustain a constant level of circulating factor, thereby reducing the quantity of the coagulation factor required and, consequently, reducing treatment costs.[55–58] An example based on a 70 kg patient was calculated by Bjorkman (see *Table 6*).[59]

Table 6: Continuous Infusion – Assessment of Factor IX Dosage Based on a 70 kg Patient

	Plasma-derived Factor IX	Recombinant Factor IX
Clearance (ml/hr/kg)	3.8–4.3	8.4
Trough level (IU/ml)	0.01	0.01
Body weight (kg)	70	70
Infusion rate (IU/day/70kg)	2,555–2,890	5,645

Rationale for assessment of dosage by repeated administration. Dosing rate = Cl x Css x Tau. Cl = clearance; Css = concentration at steady state; Tau = interval between bolus administrations in case of continuous infusion, where Tau is the lowest possible. Calculated from data from White et al. by Bjorkman, 2011.[59]

Highly purified MAb pd-FIX concentrate has been approved for CIV infusion. Rood et al. had shown that the MAb pd-FIX concentrate remains sterile and stable, without significant loss of FIX activity, when delivered through a simulated CIV infusion apparatus for 24 hours.[60] The pharmacokinetics and efficacy of MAb pd-FIX via CIV infusion for the treatment of patients with haemophilia B were assessed in a prospective, multicentre, open-label study.[46] The study included 28 patients with mild, moderate or severe haemophilia B who were undergoing surgery, exposed to trauma or experiencing spontaneous haemorrhage. A group of 13 patients underwent a pre-operative pharmacokinetic analysis, prior to elective surgery in order to allow tailoring of continuous infusion. The remaining 15 patients underwent emergency surgery without a prior pharmacokinetic analysis. Patients received a therapeutic bolus dose followed by maintenance of FIX activity levels by CIV infusion of concentrate. Data from the 24 patients who completed the 72–120-hour CIV infusion showed that 96 % (23/24) of the evaluable patients achieved normal haemostasis. The median FIX activity level was between 72 % and 86 % for all patients receiving CIV FIX on all days. In terms of safety, 13 AEs possibly related to the study medication were reported in nine patients, although these events were not deemed serious by the investigator and were largely due to local irritation at the infusion site. Only the highly purified FIX concentrates appear to meet the optimal criteria for continuous infusion – defined as one-week stability with no signs of degradation.[61] Based on these findings, MAb pd-FIX (Mononine®) was approved for continuous administration in addition to an intravenous bolus injection in patients with haemophilia B.

Summary and Conclusions

While previous treatment options for haemophilia B have been associated with safety concerns (such as thromboembolic complications), improvements in purification and viral inactivation techniques have led to the development of high-purity FIX products, such as MAb pd-FIX and rFIX concentrates. In terms of pharmacokinetic profile, MAb pd-FIX has a higher recovery than rFIX, resulting in a lower dose being required to achieve a prophylactic plasma level of FIX. Furthermore, both the terminal and media half-lives of MAb pd-FIX have been shown to be similar to the respective half-lives of rFIX. MAb pd-FIX has been extensively evaluated in clinical trials and has proved to be safe and efficacious for surgical prophylaxis and for on-demand treatment of both PUPs and PTPs. While intermittent dosing is the conventional method of administration, MAb pd-FIX is also suitable for CIV infusion; this dosing method has been shown to result in normal haemostasis in patients with haemophilia B. To conclude, HP-FIX concentrates, such as MAb pd-FIX, are suitable for use in previously untreated and previously treated haemophilia B patients as well as in a variety of clinical situations such as for surgical prophylaxis, following trauma or to treat spontaneous bleeding. ■

1. Mannucci PM, Tuddenham EG, The hemophilias—from royal genes to gene therapy, *N Engl J Med*, 2001;344:1773–9.
2. Mannucci PM, Tuddenham EG, The hemophilias: progress and problems, *Semin Hematol*, 1999;36:104–17.
3. Rodriguez-Merchan EC, Haemophilic synovitis: basic concepts, *Haemophilia*, 2007;13:1–3.
4. White GCI, Rosendaal F, Aledort LM, Lusher JM, Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. Factor VII and Factor IX Subcommittee, *Thromb Haemost*, 2001;85:560.
5. Gilbert MS, Musculoskeletal complications of haemophilia: the joint, *Haemophilia*, 2000;6(Suppl. 1):34–7.
6. Van den Berg HM, Dunn A, Fischer K, Blanchette VS, Prevention and treatment of musculoskeletal disease in the haemophilia population: role of prophylaxis and synovectomy, *Haemophilia*, 2006;12(Suppl. 3):159–68.
7. Ahlberg A, Haemophilia in Sweden VII. Incidence, treatment and prophylaxis of arthropathy and other musculo-skeletal manifestations of haemophilia A and B, *Acta Orthop Scand*, 1965;77:5–99.
8. Fischer K, Bom JG, Mauser-Bunschoten EP, et al., Effects of haemophilic arthropathy on health-related quality of life and socio-economic parameters, *Haemophilia*, 2005;11:43–8.
9. Pai KM, Walker I, Almonte T, Chan AK, Comparing bleed frequency and factor concentrate use between haemophilia A and haemophilia B, *J Thromb Haemost*, 2005;3:Abstract P0807.
10. Tagariello G, Iorio A, Santagostino E, et al., Comparison of the rates of joint arthroplasty in patients with severe factor VIII and IX deficiency: an index of different clinical severity of the 2 coagulation disorders, *Blood*, 2009;114:779–84.
11. Biss TT, Chan AK, Blanchette VS, et al., The use of prophylaxis in 2663 children and adults with haemophilia: results of the 2006 Canadian national haemophilia prophylaxis survey, *Haemophilia*, 2008;14:923–30.
12. Berntorp E, Astermark J, Bjorkman S, et al., Consensus perspectives on prophylactic therapy for haemophilia: summary statement, *Haemophilia*, 2003;9(Suppl. 1):1–4.
13. Lofqvist T, Nilsson IM, Berntorp E, Pettersson H, Haemophilia prophylaxis in young patients—a long-term follow-up, *J Intern Med*, 1997;241:395–400.
14. Gutierrez C, Vendrell J, Broch M, et al., [Apolipoprotein AI-CIII, B, and CII gene polymorphisms in patients with non-insulin dependent diabetes mellitus. Association with hyperlipemia], *Med Clin (Barc)*, 1996;107:561–5.
15. Katz J, Prevalence of FIX inhibitors among patients with hemophilia B: results of a large scale North American survey, *Haemophilia*, 1996;2:28–31.
16. Warrier I, Immune tolerance therapy in hemophilia B: possibilities and problems, *Haemophilia Monitor*, 2000;8:3–6.
17. Shapiro AD, Donfield SM, Lynn HS, et al., Defining the impact of hemophilia: the Academic Achievement in Children with Hemophilia Study, *Pediatrics*, 2001;108:E105.
18. MASAC, MASAC Recommendation Concerning Prophylaxis (Regular Administration of Clotting Factor Concentrate to Prevent Bleeding), *National Hemophilia Foundation*, 2007.
19. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al., Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia, *N Engl J Med*, 2007;357:535–44.
20. Kreuz W, Escuriola-Ettingshausen C, Funk M, et al., When should prophylactic treatment in patients with haemophilia A and B start?–The German experience, *Haemophilia*, 1998;4:413–7.
21. Lusher JM, Thrombogenicity associated with factor IX complex concentrates, *Semin Hematol*, 1991;28:3–5.
22. Warrier I, Management of haemophilia B patients with inhibitors and anaphylaxis, *Haemophilia*, 1998;4:574–6.
23. Cederbaum AI, Blatt PM, Roberts HR, Intravascular coagulation with use of human prothrombin complex concentrates, *Ann Intern Med*, 1976;84:683–7.
24. Sandler SG, Rath CE, Wickerhauser M, et al., Post-Konyne hepatitis: the ineffectiveness of screening for the hepatitis B antigen (HBAg), *Transfusion*, 1973;13:221–4.
25. Campbell EW, Neff S, Bowdler AJ, Therapy with factor IX concentrate resulting in DIC and thromboembolic phenomena, *Transfusion*, 1978;18:94–7.
26. Kasper CK, Thromboembolic complications, *Thromb Diath Haemorrh*, 1975;33:640–4.
27. Blatt PM, Lundblad RL, Kingdon HS, et al., Thrombogenic materials in prothrombin complex concentrates, *Ann Intern Med*, 1974;81:766–70.
28. Rosenberg PS, Goedert JJ, Estimating the cumulative incidence of HIV infection among persons with haemophilia in the United States of America, *Stat Med*, 1998;17:155–68.
29. Menache D, Roberts HR, Summary report and recommendations of the task force members and consultants, *Thromb Diath Haemorrh*, 1975;33:645–7.
30. Ehrlich HJ, Henzl MJ, Gomperts ED, Safety of factor VIII inhibitor bypass activity (FEIBA): 10-year compilation of thrombotic adverse events, *Haemophilia*, 2002;8:83–90.
31. Hampton KK, Makris M, Kitchen S, Preston FE, Potential thrombogenicity of heat-treated prothrombin complex concentrates in Haemophilia B, *Blood Coagul Fibrinolysis*, 1991;2:637–41.
32. Lusher JM, Myocardial necrosis after therapy with prothrombin-complex concentrate, *N Engl J Med*, 1984;310:464.
33. Hrinda ME, Huang C, Tarr GC, et al., Preclinical studies of a monoclonal antibody-purified factor IX, Mononine, *Semin Hematol*, 1991;28:6–14.
34. Hampton KK, Preston FE, Lowe GD, et al., Reduced coagulation activation following infusion of a highly purified factor IX concentrate compared to a prothrombin complex

concentrate, *Br J Haematol*, 1993;84:279–84.
35. Kim HC, McMillan CW, White GC, et al., Purified factor IX using monoclonal immunoaffinity technique: clinical trials in hemophilia B and comparison to prothrombin complex concentrates, *Blood*, 1992;79:568–75.
36. Kim HC, McMillan CW, White GC, et al., Clinical experience of a new monoclonal antibody purified factor IX: half-life, recovery, and safety in patients with hemophilia B, *Semin Hematol*, 1990;27:30–5.
37. Mannucci PM, Bauer KA, Gringeri A, et al., Thrombin generation is not increased in the blood of hemophilia B patients after the infusion of a purified factor IX concentrate, *Blood*, 1990;76:2540–5.
38. Tabor E, The epidemiology of virus transmission by plasma derivatives: clinical studies verifying the lack of transmission of hepatitis B and C viruses and HIV type 1, *Transfusion*, 1999;39:1160–8.
39. CDC. From the Centers for Disease Control and Prevention, Blood safety monitoring among persons with bleeding disorders, *JAMA*, 2003;289:541–4.
40. Keeling D, Tait C, Makris M, Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. A United Kingdom Haemophilia Center Doctors' Organisation (UKHCDO) guideline approved by the British Committee for Standards in Haematology, *Haemophilia*, 2008;14:671–84.
41. Santagostino E, Mannucci PM, Bianchi Bonomi A, Guidelines on replacement therapy for haemophilia and inherited coagulation disorders in Italy, *Haemophilia*, 2000;6:1–10.
42. Ewenstein BM, Joist JH, Shapiro AD, et al., Pharmacokinetic analysis of plasma-derived and recombinant F IX concentrates in previously treated patients with moderate or severe hemophilia B, *Transfusion*, 2002;42:190–7.
43. Kisker CT, Eisberg A, Schwartz B, Prophylaxis in factor IX deficiency product and patient variation, *Haemophilia*, 2003;9:279–84.
44. White GC 2nd, Shapiro AD, Kurczynski EM, et al., Variability of in vivo recovery of factor IX after infusion of monoclonal antibody purified factor IX concentrates in patients with hemophilia B. The Mononine Study Group, *Thromb Haemost*, 1995;73:779–84.
45. Shapiro AD, Ragni MV, Lusher JM, et al., Safety and efficacy of monoclonal antibody purified factor IX concentrate in previously untreated patients with hemophilia B, *Thromb Haemost*, 1996;75:30–5.
46. Hoots WK, Leissinger C, Stabler S, et al., Continuous intravenous infusion of a plasma-derived factor IX concentrate (Mononine) in haemophilia B, *Haemophilia*, 2003;9:164–72.
47. Shapiro AD, White GC, Kim HC, et al., Efficacy and safety of monoclonal antibody purified factor IX concentrate in haemophilia B patients undergoing surgical procedures, *Haemophilia*, 1997;3:247–53.
48. Kurczynski EM, Lusher JM, Pitel P, et al., Safety and efficacy of monoclonal antibody-purified Factor IX concentrate for management of bleeding and surgical prophylaxis in previously treated children with hemophilia B, *Int J Ped Hemat/Oncol*, 1995;2:211–6.
49. Warrier I, Kasper CK, White GC 2nd, et al., Safety of high doses of a monoclonal antibody-purified factor IX concentrate. The Mononine Study Group, *Am J Hematol*, 1995;49:92–4.
50. Sultan Y, Prevalence of inhibitors in a population of 3435 hemophilia patients in France. French Hemophilia Study Group, *Thromb Haemost*, 1992;67:600–2.
51. LLC Behring CB, Mononine Package Insert, 2009.
52. Shord SS, Lindley CM, Coagulation products and their uses, *Am J Health Syst Pharm*, 2000;57:1403–20.
53. Varon D, Martinowitz U, Continuous infusion therapy in haemophilia, *Haemophilia*, 1998;4:431–5.
54. Morfini M, Secondary prophylaxis with factor IX concentrates: continuous infusion, *Blood Transfus*, 2008;6(Suppl. 2):s21–5.
55. Campbell PJ, Rickard KA, Continuous and intermittent infusion of coagulation factor concentrates in patients undergoing surgery: a single centre Australian experience, *Aust N Z J Med*, 1998;28:440–5.
56. Goldsmith JC, Gordon EM, Treatment of hemophilia B: serendipitous use of continuous infusion coagulation factor IX, *Thromb Res*, 1993;70:265–7.
57. Kurczynski EM, Moncino MD, Monoclonal-antibody-purified factor IX, *Lancet*, 1993;341:1148.
58. Schulman S, Wallensten R, White B, Smith OP, Efficacy of a high purity, chemically treated and nanofiltered factor IX concentrate for continuous infusion in haemophilia patients undergoing surgery, *Haemophilia*, 1999;5:96–100.
59. Bjorkman S, A commentary on the differences in pharmacokinetics between recombinant and plasma-derived factor IX and their implications for dosing, *Haemophilia*, 2011;17:179–84.
60. Rood GS, Thill W, Flanigan E, Stability and sterility of dilute solutions of monoclonal antibody purified factor IX (Mononine) concentrate prepared for continuous infusion, *Blood*, 1995;86(Suppl 1):886a (Abstract 3530).
61. Martinowitz UP, Schulman S, Continuous infusion of factor concentrates: review of use in hemophilia A and demonstration of safety and efficacy in hemophilia B, *Acta Haematol*, 1995;94(Suppl. 1):35–42.
62. Burnouf-Radosevich M, Appourchaux P, Huart JJ, Burnouf T, Nanofiltration, a new specific virus elimination method applied to high-purity factor IX and factor XI concentrates, *Vox Sang*, 1994;67:132–8.