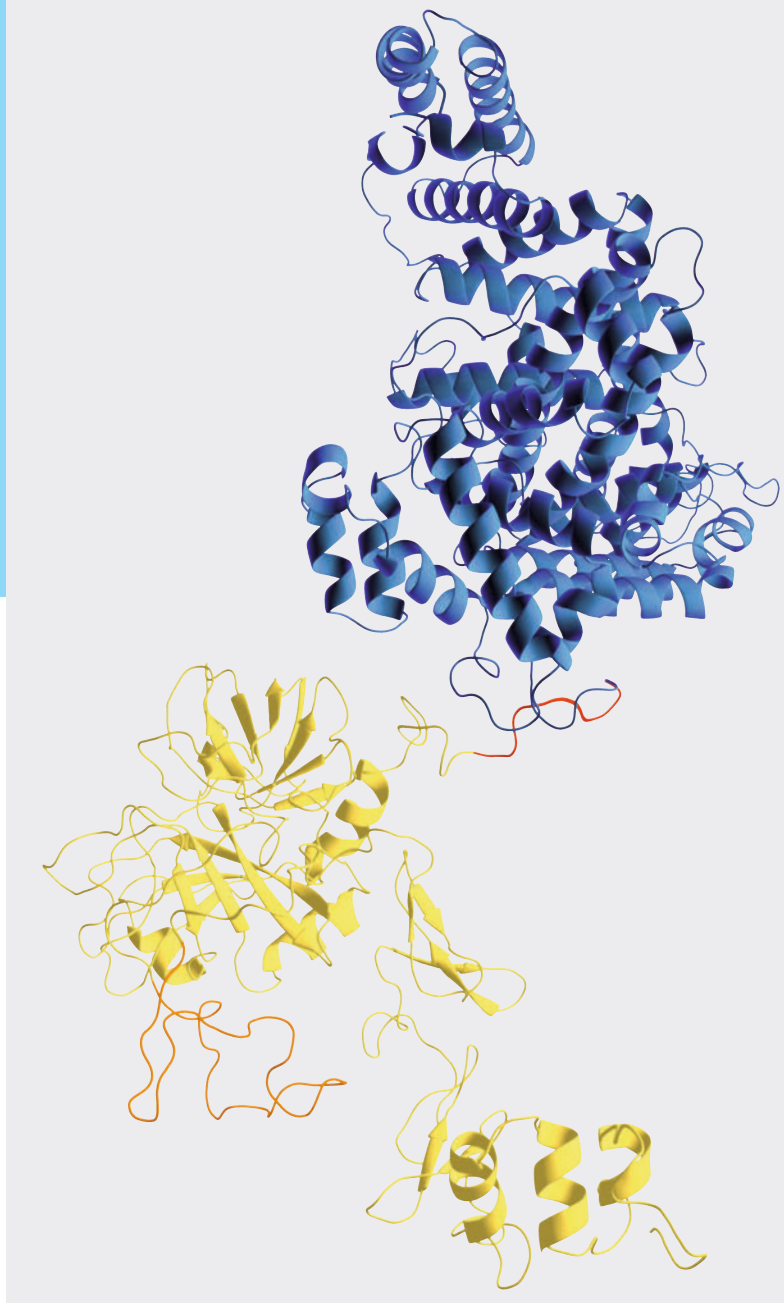
Case Report



Idelvion®

as a modern treatment option for haemophilia B

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Case Report
Idelvion® as a modern treatment option for haemophilia B
January 2020
ISSN 1611-7875

This Case Report is attached to the journal Thrombosis and Haemostasis. This issue of the Thieme Case Report has been produced with the kind support of CSL Behring GmbH, Hattersheim.

This publication is published outside the responsibility of the editors of the journal Thrombosis and Haemostasis.

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Publisher
Georg Thieme Verlag KG Stuttgart · New York
Rüdigerstr. 14, 70469 Stuttgart
Postfach 30 11 20, 70451 Stuttgart
Tel. 07 11 / 89 31-0, Fax 07 11 / 89 31-2 98
www.thieme.de

Print
W. Kohlhammer Druckerei GmbH + Co. KG, Augsburger Straße 722, 70329 Stuttgart

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Case Report

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Editorial

Extended half-life (EHL) factor IX (FIX) products, such as recombinant fusion protein linking FIX with albumin (albutrepenonacog alfa; Idelvion®), can allow prophylaxis intervals of one or even two weeks.* This could be beneficial for patients in whom prophylaxis for severe or moderate haemophilia B has proved inadequate for various reasons. Some patients are unable to fit frequent injections and the associated burden into an active, largely normal lifestyle, while other patients struggle to maintain compliance with their prophylaxis regimen. It is clear that individualised prophylaxis, ensuring a continuous and appropriate trough level of FIX activity, is vastly superior to on-demand treatment for bleeding episodes. Unfortunately, non-adherent patients with haemophilia may not achieve the benefits conferred by individual prophylaxis. There are also patients who, after years of injections, have increasingly limited venous access. Elderly haemophilia patients may also experience additional challenges: for example, manual dexterity and mobility may be restricted due to previous joint bleeds, making self-administration difficult, and the need for frequent visits to the doctor may prove challenging. You will meet all of these patients in the following five case reports. These include a young boy whose desire for movement is hard to curb despite his haemophilia. Furthermore, two case reports demonstrate how perioperative prophylaxis can be successfully managed with an EHL FIX product. We hope you will benefit greatly from reading these interesting cases.

* Some patients who are well-controlled on a once-weekly regimen might be treated with up to 75 IU/kg every 10 or 14 days.

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Introduction

Idelvion® as a modern treatment option for haemophilia B

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ABSTRACT

Idelvion® (albutrepenonacog alfa, rIX-FP) is a long-acting recombinant factor IX (FIX) albumin fusion protein indicated for the treatment and prophylaxis of bleeding in patients with haemophilia B. It allows prophylaxis intervals of up to 14 days.* Compared with previous therapy, this fusion protein allows for a significant reduction in injection frequency while maintaining a favourable efficacy and safety profile.

Haemophilia B

Haemophilia B is an X-chromosome-linked hereditary bleeding disorder caused by the absence or deficiency of functionally active coagulation FIX. Depending on the endogenous FIX activity level, haemophilia is classified into three degrees of severity: mild 5–40 %, moderate 1–5 % and severe < 1 % [1]. Patients with severe or moderate haemophilia B may experience spontaneous or traumatic bleeding into the joints, muscles or internal organs. Therefore, they require prophylactic FIX replacement therapy aimed at increasing FIX activity levels and thus reducing disease severity to a milder phenotype.

Product technology

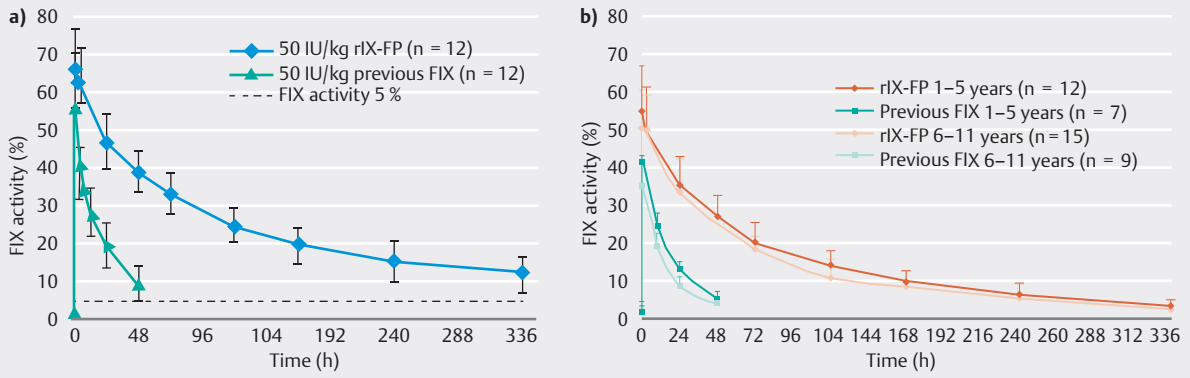
Idelvion® is manufactured through the genetic fusion of recombinant FIX (rFIX) to human recombinant albumin. Albumin bestows many advantages as a fusion partner, of which the most important is the extended half-life ($t_{1/2}$) of around 20 days [2, 3]. One novel feature of this fusion protein is the innovative linker sequence between FIX and albumin. Since this is derived from the natural activation peptide of human FIX, FIX is both activated and cleaved from albumin by the same protease [4] (▶ **Fig. 1**).

Pharmacokinetics

Maintaining an adequately high or elevated FIX level at the end of a prophylaxis interval (trough level) is considered an important determinant of prophylaxis efficacy in patients with haemophilia B [5]. The pharmacokinetics (PK) of Idelvion® was evaluated in 63 previously treated patients (PTPs) (12–61 years) with severe and moderately severe haemophilia B (FIX activity ≤ 2 %). After administration of a single dose of 50 IU/kg, mean FIX activity remained above 5 % for at least 14 days. Idelvion® demonstrated a significantly improved PK profile compared with previously used FIX products (▶ **Fig. 2a**). At steady state, mean FIX trough levels were markedly above 5 %. In adults treated with 75 IU/kg Idelvion® every 14 days, mean trough FIX activity was 12.4 %, and in those treated

▶ **Fig. 1** Activation of Idelvion® with cleavable linker (red) results in release of albumin (blue) and an activated FIX molecule (yellow). FIX = factor IX; FXIa = activated factor XI; FVIIa = activated factor VII; TF = tissue factor [4].

* Some patients who are well-controlled on a once-weekly regimen might be treated with up to 75 IU/kg on an interval of 10 or 14 days.



▶ **Fig. 2** Factor IX activity after injection of a single dose of Idelvion® or previous FIX product **a)** in patients ≥ 12 years [6], **b)** in children < 12 years [7].

with 40 IU/kg every 7 days, mean FIX activity was 20 % [6].

The PK of Idelvion® was also evaluated in 27 previously treated male **paediatric** patients **(**1–11 years**)** with endogenous FIX activity ≤ 2 % [7]. In this population, Idelvion® also demonstrated a significantly improved PK profile compared with previously used FIX product (▶ **Fig. 2b**). As expected, the mean $t_{½}$ in **paediatric patients** was shorter than in adolescents/adults [7].

Efficacy in prophylaxis and treatment

The clinical efficacy and safety of rIX-FP was investigated in 107 **patients aged 1–61 years** with severe or moderate haemophilia B (FIX activity ≤ 2 %), including 27 patients aged 1–11 years [6–8]. The **adolescent/adult** patients received Idelvion® once every 7 days as routine prophylaxis with a starting dose of 35–50 IU/kg, as determined by the treating physician. Patients who were well-controlled on that regimen were able to switch to a prophylaxis treatment interval of 10 or 14 days with a dose of up to 75 IU/kg [6]. **Paediatric** patients were treated with a dose of 35–50 IU/kg once weekly [7]. FIX consumption with Idelvion® was markedly lower for all regimens compared with prophylactic FIX consumption with previous FIX therapy. For adult patients, the median consumption on prophylaxis with standard FIX products was 256.5 IU/kg per month. After switching to 7- or 14-day prophylaxis with Idelvion®, patients had a median monthly consumption of 194.7 and 162.3 IU/kg, respectively [6]. In paediatric patients, the mean weekly consumption of Idelvion® was more than 50 % lower than weekly consumption for routine prophylaxis with standard FIX products prior to study entry; 47 and 107 IU/kg, respectively [7]. At steady state, mean trough FIX activity of > 12 % was achieved for all age groups with rIX-FP [6, 7].

The median annualised spontaneous bleeding rate was 0 for all Idelvion® prophylaxis regimens. Likewise, the median total annualised bleeding rate was very low in **paediatric patients** (3.12) and **adolescent/adult patients (**0 [7- or 10-day prophylaxis regimen] or 1.08 [14-day regimen]). More than 97 % of bleeding episodes were successfully treated with 1–2 infusions of Idelvion® [6, 7].

PERIOPERATIVE ADMINISTRATION

The perioperative efficacy and safety of Idelvion® was evaluated in 21 surgical procedures performed in 19 patients with severe and moderately severe haemophilia B (FIX activity ≤ 2 %) [9]. Haemostatic efficacy was rated as excellent in 17 surgeries (incl. 7 major surgeries) and as good in 4 (incl. 2 major surgeries) surgical procedures.

For major surgeries, a single bolus dose of Idelvion® was administered pre-operatively to target a FIX activity level of 80–100 %. Intraoperative dosing of Idelvion® was dependent on FIX activity and surgery type.

In 20 of 21 procedures, intraoperative haemostasis was maintained with a single preoperative dose of Idelvion®. Postoperative dosing aimed to maintain FIX activity levels according to the World Federation of Hemophilia guidelines [10]. The majority of patients maintained the desired FIX activity level with dosing every 2 days during the postoperative period [9].

The safety of Idelvion® was evaluated in four clinical studies in 107 PTPs [5–8]. These studies reported 13 adverse events (all mild or moderate) in 7 subjects [11]. No inhibitors against FIX were detected in any patient in the pivotal study programme receiving Idelvion®. Furthermore, no non-neutralizing antibodies against Idelvion® or Chinese hamster ovary host cell proteins were detected. Similarly, there were no reports of thromboembolic events or anaphylaxis, hence Idelvion® was demonstrated to be effective and well-tolerated.

CONCLUSIONS FOR EVERYDAY PRACTICE

- The administration of Idelvion® up to every 14 days allows for longer prophylaxis dosing intervals and thus could facilitate individualised dosing regimens.
- Trough activity levels of 5 % are exceeded in most patients, even with a 14-day prophylaxis dosing interval.
- Idelvion® can be successfully used for maintaining haemostasis during and after surgery.

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Case 1

7-year-old boy with severe haemophilia B and a desire for freedom and adventure with only 1 injection per week

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ABSTRACT

A boy with severe haemophilia B and a strong desire for physical activity who is about to start school wished to receive only once-weekly injections rather than three times per week. Therefore the patient was switched to Idelvion®.

Patient history and symptoms

This 7-year-old boy was diagnosed with severe haemophilia B (< 1 % endogenous factor IX [FIX] activity) at the age of 15 months after he was found to have numerous major haematomas. There was no family history of haemophilia and the patient's haemophilia was found to be caused by a point mutation (missense c.1230T > G).

Treatment regimen prior to switch

Immediately after diagnosis of haemophilia B, once-weekly prophylaxis was initiated with recombinant factor IX (rFIX); subsequently, prophylaxis was incrementally intensified. The boy was very active and experienced episodes of both traumatic muscle bleeds (left paravertebral and gluteal) and bleeding into the left ankle joint. Despite these bleeds, the boy's orthopaedic status up to the time of switching was unremarkable, apart from mild scoliosis, with no need for surgery. Before switching to Idelvion® (rIX-FP), the boy was receiving 35 IU/kg rFIX three times per week.

Switch to rIX-FP

The patient was switched to rIX-FP at the age of 5 ½ years; baseline data is shown in ▶ **Table 1**. The main reason for switching was the boy's desire to reduce the injection frequency, while at the same time maintaining high FIX activity for protection against bleeds, so that physical activities with the family could continue as normal.

At the time of switch, the patient received 35 IU/kg Idelvion® once weekly. In order to achieve the target activity level of > 10 %, this dose was increased to 43 IU/kg once weekly; following a few minor injuries, this was further increased to 47 IU/kg once weekly.

Upon switching to a once-weekly dose the family initially lost some of their previous independence. For example, up until switch, the parents always knew when and for which injuries an infusion was needed. During this period, they called the haemophilia treatment centre's emergency number mainly to obtain reassurance from the treating physicians and for their information. After switching, telephone consultation increased as both the family and the doctors had to gain experience of the new medication. For example, at first it was difficult to decide whether a minor injury occurring 2 days after the last scheduled prophylactic dose necessitated administration of additional factor replacement therapy. Over time, these initial uncertainties were overcome. Population pharmacokinetic-based estimation of the patient's individual pharmacokinetics (WAPPS; www.wapps-hemo.org) as well as simple clinical observation proved useful to that effect. In addition, experience sharing with colleagues who had also switched patients to long-acting FIX concentrates was invaluable.

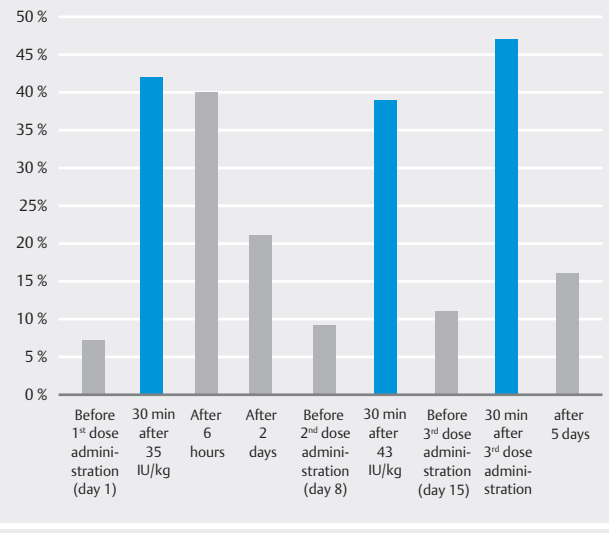
▶ **Table 1** Baseline data at the time of switch to rIX-FP at age 5 ½ years.

Patient	Baseline values
Age	5 ½ years
Gender	Male
BMI	Normal weight
Diagnosis	Severe haemophilia B (< 1 %)
Comorbidities	Scoliosis, status post left paravertebral muscle bleeding, status post gluteal muscle bleeding, status post bleeding into the left ankle joint

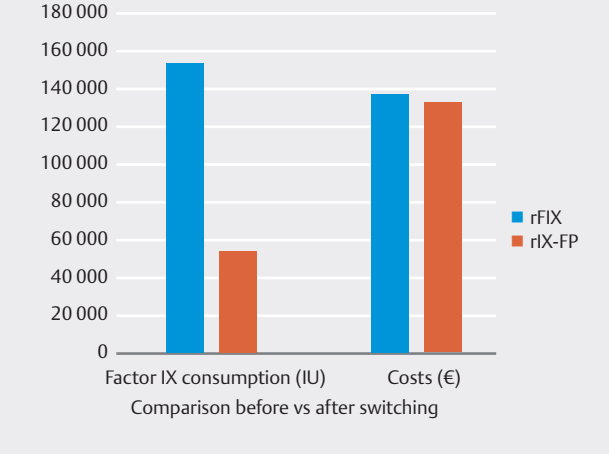
Both the one-stage and chromogenic assays were used for monitoring FIX activity. ▶ **Fig. 1** illustrates the course of FIX activity during the first 3 weekly Idelvion® injections.

Disease course after switching to rIX-FP

The patient and his parents are satisfied with treatment with rIX-FP. Once-weekly prophylaxis is usually sufficient and the reduction in injection frequency is perceived as particularly beneficial. There have also been periods where Idelvion® was given more frequently and injections may have occasionally been too frequent, particularly at the beginning before the family and physicians had built up sufficient first-hand experience. Another observation is that because of the reduced injection frequency, the family's everyday life is no longer dominated by the boy's haemophilia. Overall, the child is more active and, at the same time, a little less careful because at times he forgets about his haemophilia. Therefore, everyone has to get accustomed to the new situation.



▶ **Fig. 1** Measured factor IX activity on rIX-FP.



▶ **Fig. 2** Comparison of consumption and costs of previous therapy vs rIX-FP.

For minor injuries the patient typically administers an additional single dose of 35 IU/kg rIX-FP and for major injuries an additional single dose of 47 IU/kg rIX-FP, which in certain cases may be repeated the next day.

Costs

Comparison of FIX consumption and costs between previous therapy (rFIX) and therapy with Idelvion® showed that factor consumption was higher for rFIX. The costs incurred after switching to Idelvion® were similar to those of therapy prior to switching. The ratio between attainment of the treatment goal and the incurred costs for Idelvion® is rated as good.

Summary

For a boy with a strong desire for physical activity and once-weekly injections, weekly prophylaxis with Idelvion® resulted in FIX activity levels > 10 %, providing good protection. Initial uncertainties about its administration for the treatment of injuries were gradually dispelled thanks to regular consultation and growing experience with the product. The patient and his parents are satisfied with the treatment.

CONCLUSIONS FOR EVERYDAY PRACTICE

- For an active boy, a good FIX activity level can be achieved with Idelvion®.
- Individualisation of treatment is necessary and advisable.
- Regular consultation on the treatment of injuries is useful and possibly cost-saving.

Case 2

18-year-old patient with severe haemophilia B

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ABSTRACT

This patient with recurrent joint bleeds and increasingly limited venous access was switched to 14-day prophylaxis with the extended half-life factor IX product Idelvion®.

Patient history and symptoms

The patient is currently 18 years old and was diagnosed with severe haemophilia B at age 7 months (< 1 % endogenous factor IX [FIX] activity). Haemophilia B was caused by a single-base deletion in the FIX gene. As his family history was negative for haemophilia and maternal carrier status was ruled out, this represents a de novo mutation.

From the age of 1 year, the patient received twice weekly prophylaxis with a recombinant FIX product. Despite this, from infancy to school age, episodes of bleeding into the ankle joints (more pronounced in the left than in the right), right knee joint, and suspected bleeding into the left hip joint were observed. Congenital patellar and trochlear dysplasia caused the patient to develop habitual dislocation of the patella as an adolescent, which in turn resulted in recurrent bilateral bleeding into the knee joints. At age 14, the patient sustained bleeding of the upper gastrointestinal tract due to a stomach ulcer, requiring transfusion. Retrospectively, the stomach ulcer was attributed to the intensive analgesia following an episode of patellar dislocation.

Treatment regimen prior to switch

At age 15, the patient was treated with a recombinant FIX product when he underwent corrective surgery with medial reconstruction of the left patella. In the postoperative period, higher FIX levels were needed until healing was complete; intensified prophylaxis was also required with concomitant physiotherapy. However, due to an episode of re-bleeding into the left knee joint, the injection frequency was increased to three times per week.

Before switching to Idelvion® (rIX-FP) the patient received prophylaxis with 25 U of a recombinant FIX product every 3–4 days. On this prophylaxis regimen his FIX trough levels were 3–7 %. The annualised bleeding rate (ABR) was 4, while the annualised spontaneous bleeding rate (AsBR) was 2.

Switch to rIX-FP

Despite intensified prophylaxis with recombinant FIX the patient experienced recurrent bleeding. Therefore, to address the need for higher FIX activity levels, the patient was switched to rIX-FP in June 2016. Furthermore, the patient's venous access was increasingly limited, leading to frequent unsuccessful venous puncture, thus accentuating the need for less frequent injections. The patient's baseline data prior to switch are shown in ▶ **Table 1**.

Initially, the patient received 35 IU/kg body weight (BW) Idelvion® once weekly. After 2 weeks he was switched to 47 IU/kg BW every 2 weeks. His trough levels were then 9–10 %. ▶ **Table 2** illustrates the trough levels at various doses and time points. A one-stage assay (Siemens) was used for monitoring FIX activity.

Switching to Idelvion® did not present any difficulties. The patient was very satisfied from the outset, no longer experienced joint bleeds and thanks to less frequent injections, venous access was facilitated. How-

▶ **Table 1** Baseline data at the time of switch to rIX-FP (June 2016).

Patient	Baseline data
Age	16 years
Gender	Male
BMI	Underweight
Diagnosis	Severe haemophilia B (<1 %)
Comorbidities	Repeated knee joint and patellar dislocations with recurrent bleeding into the knee

▶ **Table 2** Trough levels after various rIX-FP doses.

	2016			2018	
Dose	35 IU/kg BW	47 IU/kg BW	47 IU/kg BW	38 IU/kg BW	57 IU/kg BW
Time since injection (days)	6.7	12.7	14	14	14
FIX levels (%)	16	10	9	3	n.a.

n.a. patient switched, no trough level data available

ever, having less frequent opportunities to check trough levels (in this case once every 2 weeks) for monitoring the treatment response to Idelvion® initially felt unusual to the treating physician.

Disease course after switching to rIX-FP

After switching to Idelvion® the patient no longer experienced joint bleeds. There were still sporadic episodes of traumatic subcutaneous soft tissue bleeding, but these were less pronounced than on the previous therapy. The patient's satisfaction with the 14-day prophylaxis interval continues to be very high. It was possible to reduce the bleeding rate as well as the injection frequency while assuring higher FIX levels. Sustained healing of previous bleeding was possible.

To date, there has been no need for treatment of acute bleeding. The patient was given the following instructions: in the event of bleeding he should bring the next prophylaxis dose forward; if there is bleeding within the first few days after his regular prophylaxis dose he should consult with his treating physician (in this situation, the patient would possibly administer two-thirds of his usual prophylaxis dose).

Summary

The switch to Idelvion® has been successful in all respects. Sustained high FIX activity was achieved, accompanied by complete control of bleeding, and markedly reduced injection frequency. Patient satisfaction is high.

In the future, extended half-life FIX products will make it possible to ensure continuously high FIX trough levels from infancy for children with haemophilia B. From a paediatric perspective, reduced injection frequency greatly facilitates treatment. An interesting consideration is whether, and to what extent, better joint status can be achieved with high FIX levels. This improved therapy has the potential to consistently reduce morbidity and the need for intervention.

CONCLUSIONS FOR EVERYDAY PRACTICE

- The patient's bleeding has been well controlled on Idelvion® now for over 2 years
- He can be treated effectively with the 14-day regimen which, given his poor venous access, has resulted in a marked improvement.

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Case 3

A young man with inconsistent treatment adherence and breakthrough bleeds before switching to Idelvion®

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ABSTRACT

A 21-year-old man with severe haemophilia B was struggling with adherence to his factor IX (FIX) replacement therapy and experienced breakthrough bleeds. He was therefore switched to Idelvion®.

Patient history and symptoms

The patient is currently 21 years old and was diagnosed with haemophilia B the day after his birth. His mother's bleeding tendency was known; her carrier status was not. There was already one case of severe haemophilia B in the family. The patient likewise had severe haemophilia B with a residual FIX activity of < 1 IU/dl or < 1 %. Baseline data is shown in ▶ **Table 1**.

Until the patient was 10 years of age, he was mainly treated on-demand for several episodes of joint bleeding. At approximately 4 years old, the patient experienced an episode of bleeding into the hip joint and has since suffered from hip problems. Although forbidden by his mother, he played football with his friends, giving rise to repeated joint problems.

The patient's mother was taught to administer FIX therapy at home when the patient was 9 years of age, and the patient was taught to self-administer at the age of 11. Since then, he has received prophylaxis therapy (see below); however, it has not always been administered regularly. No inhibitors have developed during FIX therapy so far.

There have been repeated episodes of haematuria over a period of 4 years.

The patient exhibits heterotopic ossification in the region of the right hip after bleeding into the right rectus femoris muscle. In addition to hip joint complaints, the patient presents with bilateral reduced elbow extension. Currently, the patient reports no other joint problems. The most recent Hemophilia Joint Health Score (HJHS Version 2.1) was 4.

Treatment regimen prior to switch

Prior to the switch, the patient received prophylaxis with recombinant FIX, which was prescribed at a dose of 2000 IU in the morning every 3–4 days. However, the patient did not always regularly administer as prescribed, tending to forget administration in the morning, particularly if he was not reminded by his mother. On several occasions, at the paediatric clinic, a more intensive therapy had been tried with much enthusiasm but little success. With this irregular, low-dose prophylaxis, the patient experienced occasional renal bleeds and rarely, joint bleeds.

When first presenting to the Haemophilia Treatment Centre, the patient reported frequent episodes of renal bleeding (haematuria), each of which he treated with three doses of 2000 IU recombinant FIX (rFIX) over several days. At his second routine visit, the patient was switched to Idelvion® (rIX-FP).

▶ **Table 1** Baseline data

Patient	Baseline data
Age	21 years
Gender	Male
BMI	Overweight
Diagnosis	Severe haemophilia B
Comorbidities	Obesity Haemophilic arthropathy (right hip, both elbows)

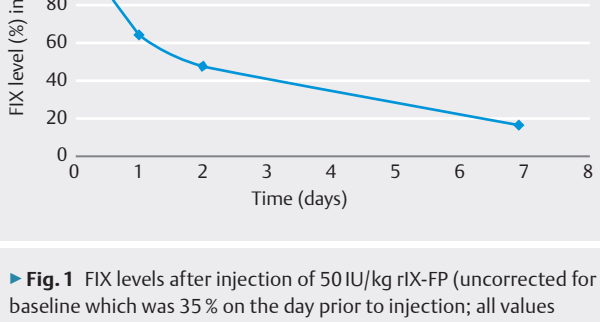
Switch to rIX-FP

The breakthrough bleeds experienced on the previous, irregularly administered therapy triggered the patient switching to rIX-FP in the autumn of 2016. The initial prophylaxis dose was 50 IU/kg once weekly and that dose was maintained over time. Switching did not present any difficulties. A one-stage assay from Hyphen Biophen was used for monitoring of FIX activity.

Disease course after switching to rIX-FP

Overall, there was a good response to treatment with rIX-FP, resulting in high factor levels. At the time of switching, the patient received 50 IU rIX-FP/kg. Prior to switching, his FIX trough level was 35 %. Forty minutes after the initial dose of 50 IU/kg rIX-FP his FIX trough level was 113 %, after 24 h it was 65 %, and after 7 days it was 15 %. The patient then received a second dose of rIX-FP; 7 days later his FIX levels were 18 %. At his next routine visit in March 2017, FIX levels were 48 % 2 days after administration of 50 IU/kg rIX-FP (▶ **Fig. 1**).

The patient is very satisfied with the treatment and since switching has administered replacement therapy every 7–8 days, not always exactly on the scheduled day, but without missing a weekly dose. The patient's mother confirmed that the situation has improved; her son has now taken the initiative to reliably manage his prophylaxis therapy. This has also positively influenced the general atmosphere in the family. Overall, this has assured a better quality of life for the patient and for those around him.



▶ **Fig. 1** FIX levels after injection of 50 IU/kg rIX-FP (uncorrected for baseline which was 35 % on the day prior to injection; all values measured with the one-stage assay from Hyphen Biophen).

Since switching there has been one episode of minimal haematuria 5 days after administering prophylaxis and no additional factor replacement therapy was administered. Bleeding had already resolved by the next scheduled replacement therapy. The patient did not report any side effects on prophylaxis with Idelvion®.

Summary

The patient has clearly derived clinical benefit from switching to Idelvion®. Prior to the switch, adherence was poor and he experienced numerous episodes of bleeding that required treatment. The clinical picture and his treatment adherence have greatly improved since switching. Additionally, management is now easier for the patient and the treating physicians. It is important to gather more experience with the new product in routine clinical use in order to be able to gradually and satisfactorily address all related practical considerations.

CONCLUSIONS FOR EVERYDAY PRACTICE

- Bleeding has occurred less frequently after switching to higher dose prophylaxis with Idelvion®.
- The patient's treatment adherence has improved, in particular, due to the longer prophylaxis intervals.
- The treatment reduces burden and improves the quality of life of the patient and of those around him.

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Case 4

Safe surgical management with Idelvion® replacement therapy

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ABSTRACT

A 31-year-old patient with mild haemophilia B and mild von Willebrand syndrome underwent surgery of the ankle joint. Extended half-life factor IX (FIX) product Idelvion® was used for perioperative replacement therapy.

Patient history and symptoms

The 31-year-old patient was diagnosed in 1993 with mild haemophilia B (residual FIX activity ≥ 8 %) following prolonged bleeding after milk tooth extraction. His maternal grandfather was known to have haemophilia B. Baseline data is shown in ▶ **Table 1**.

The patient also had mild von Willebrand syndrome (genetically confirmed type 2B). After a dental extraction in 2012, his von Willebrand factor (vWF) activity and vWF antigen level were measured as 76 %, and 63 %, respectively. This was caused by a heterozygous missense mutation in exon 28 p. (Arg1341Trp).

In 2006, the patient sustained lower gastrointestinal tract bleeding (source could not be identified colonoscopically), which was treated in the intensive care unit by means of massive transfusion. Otherwise, there were no bleeding stigmata, no nasal or gum bleeding, and no predisposition to haematoma or haematuria episodes. Patient history is shown in ▶ **Table 2**.

Surgery while using rIX-FP

The patient's indication for surgery was osteoarthritis of the right ankle joint with ventral impingement and osteophytic outer edge spurs. Surgical resection of these osteophytes was carried out in December 2016. Idelvion® (rIX-FP) was used for perioperative management. FIX activity levels were monitored with a one-stage assay; Pathromtin® SL (Siemens). The patient had no inhibitors against FIX.

Preoperative management

▶ **Table 3** illustrates the preoperative laboratory test results obtained via the Haemostaseology Outpatient Clinic; the results are within the normal range apart from a low FIX activity level.

FIX activity on the day before surgery was 21 %; this guided the individualised preoperative dosing strategy. A single dose of 2000 IU Idelvion® was administered on the day prior to surgery. Eight hours follow-

▶ **Table 1** Baseline data.

Patient	Baseline data
Age	31 years
Gender	Male
BMI	Normal weight
Diagnosis	Mild haemophilia B Mild von Willebrand syndrome (type 2B)
Comorbidities	Osteoarthritis of the right ankle joint with osteophytes

▶ **Table 2** Patient history.

Date	Event	Remarks
1993	Milk tooth extraction	Prolonged bleeding, haemostasis with tamponade, FIX 8 %
2006	Lower gastrointestinal bleeding	ICU treatment with massive transfusion
2010	Extraction of wisdom teeth	Administration of tranexamic acid and plasma-derived FIX concentrate
2012	Dental extraction	Administration of plasma-derived FIX product (FIX before extraction 8 %)

FIX = Factor IX

▶ **Tab. 3** Preoperative laboratory test results.

Parameter	Value
FIX activity	14 %
vWF activity	56 %
vWF antigen	74 %
Quick's thromboplastin time	100 %
INR	1.02
Thrombin time	16 sec
Fibrinogen	276 mg/dl
D-dimer	<0.2 mg/l
Cross reactive protein	0.4 mg/l
Platelets	197/nl
Leucocytes	5.4/nl
Haemoglobin	16 g/dl

FIX, factor IX; INR, International Normalized Ratio; vWF, von Willebrand Factor

ing Idelvion® administration, FIX activity was 57 %, and after 20 hours, it was 52 %, demonstrating dose adequacy.

Surgery

On the day of surgery, the patient (who had a FIX level of 52 % on the day before) received a dose of 2000 IU rIX-FP; 12 hours later, the patient had a FIX activity level of 57 %. ▶ **Fig. 1** illustrates the perioperative dosing regimen of rIX-FP and the resulting FIX activity levels. Since vWF activity was in the normal range, there was no need to administer a vWF-containing concentrate.

Surgery was performed under general anaesthesia. The osteophytes were carefully resected. Assurance of an impingement-free dorsal extension of around 10° was followed by meticulous wound irrigation, final haemostasis, drain placement, wound closure and X-ray examination.

Postoperative course

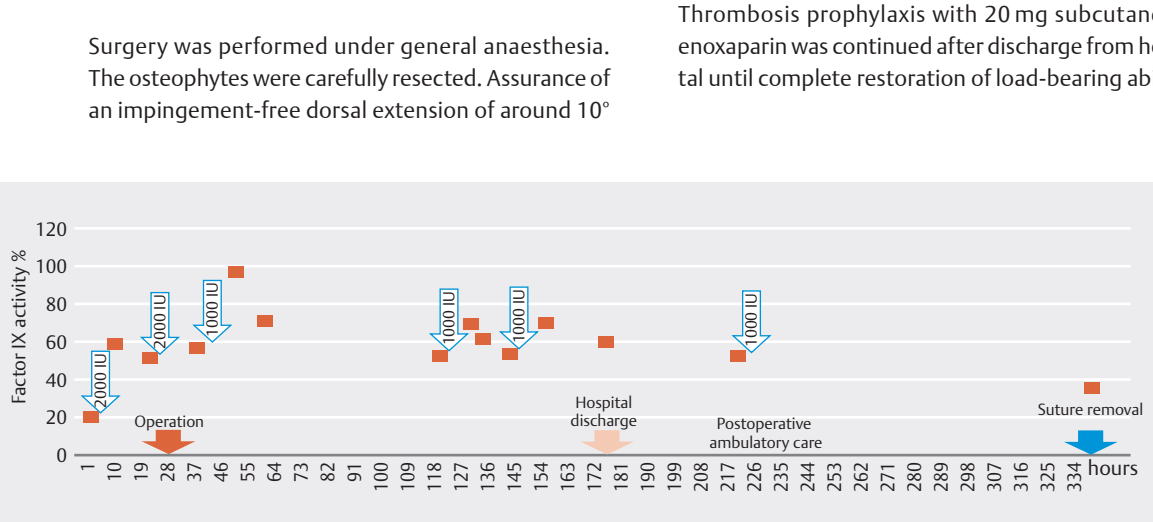
The patient's postoperative course under FIX replacement therapy was free of complications. The FIX target trough level of > 50 % was achieved (▶ **Fig. 1**). On postoperative day 6, the patient was discharged after checking his FIX activity levels were adequate (60 %). Subsequent follow-up and replacement therapy were managed in the outpatient setting.

On postoperative day 9, the patient presented in the outpatient clinic for routine assessment of his coagulation status, including FIX activity levels; subsequently he received 1000 IU of Idelvion®.

On postoperative day 14, he attended for follow-up examination and suture removal. He was doing well, had little discomfort and the wound was unremarkable and free of irritation. With a FIX activity of 34 %, it was possible to remove the sutures without having to readminister FIX replacement therapy. Afterwards, he received tranexamic acid (3 × 1 g orally) for 2 days. Henceforth, he was able to engage in load-bearing movement without having to wear a splint.

At his follow-up appointment, 6 weeks after surgery, the patient was very satisfied with the surgical outcome, had no complaints and complete restoration of load-bearing ability. Clinical examination of the scar was unremarkable. Extension-flexion and pro-supination were still slightly limited.

Thrombosis prophylaxis with 20 mg subcutaneous enoxaparin was continued after discharge from hospital until complete restoration of load-bearing ability.



▶ **Fig. 1** Perioperative dosage of rIX-FP and the resulting FIX activity levels.

Costs

There are potential cost savings due to the reduced need for replacement therapy during postoperative ambulatory care.

Summary

The perioperative management of a 31-year-old patient with mild haemophilia B was successfully managed with extended half-life (EHL) FIX concentrate under inpatient conditions and regular laboratory monitoring. High-dose preoperative replacement therapy resulted in effective perioperative bleeding management. Replacement therapy with an EHL factor concentrate resulted in stable postoperative FIX levels, which were crucial to the healing process. With Idelvion®, it was possible to maintain trough levels of > 50 % for over one week. This is the greatest advantage over conventional products that result in fluctuating factor levels.

CONCLUSIONS FOR EVERYDAY PRACTICE

- High preoperative dosing enables a stable postoperative course with a reduced need for postoperative replacement therapy.
- Treatment costs are lower due to a reduced need for postoperative replacement therapy and laboratory testing.
- Stable and predictable postoperative factor levels could reduce the need for frequent laboratory monitoring, thus enabling operative management at outpatient clinics or community hospitals.

Thieme

Case 5

61-year-old patient with severe haemophilia B and problems administering intravenous injections

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ABSTRACT

Treatment management of a 61-year-old patient with severe haemophilia B and increasingly restricted physical abilities had to be tailored to his specific life circumstances. Switching to a once-weekly injection with the extended half-life factor IX (FIX) product Idelvion® (rIX-FP) greatly improved clinical outcomes for this patient.

Patient history and symptoms

Following multiple episodes of bleeding during childhood teething, some of which required blood transfusion, and bleeding into the knee joints with subsequent plaster cast treatment, the patient was diagnosed with severe haemophilia B (point mutation). His brother, who also suffered from haemophilia, died at a young age following a bleed. There is no other known family history of haemophilia. Baseline data is shown in ▶ **Table 1**.

Due to recurrent, often inadequately treated, joint bleeds during childhood, the patient has extensive arthropathy of all major joints (both knees, ankles, hips, elbows, right shoulder) and of the right wrist (▶ **Figure 1**). He has a bilateral pes equinus position due to a functional difference in leg length with ankylosis of the ankle joints. In 2004, the patient needed total prosthetic replacement of the right knee and, subsequently, replacement of the left hip in 2005. However, the patient's mobility continues to be greatly reduced.

▶ **Table 1** Baseline data.

Patient	Baseline data
Age	61 years
Gender	Male
BMI	Slightly overweight
Diagnosis	Severe haemophilia B (<1 %)
Comorbidities	Multiple arthropathies

Due to osteoarthritis in his right elbow and wrist reducing his mobility, the patient was restricted in his ability to self-administer coagulation factor. Therefore, he was obliged to visit his general practitioner (GP) regularly. However, due to both his drastically compromised mobility and the long distance to the GP's office, maintaining his treatment regimen became increasingly more challenging and dominated the patient's daily life. This also aggravated the patient's mental state.

Treatment regimen prior to switch

A FIX trough level of 5 % was targeted for prophylactic treatment. To that effect, the patient, who had no known inhibitors, received 28 IU/kg of FIX concentrate every 2 days. The dose was increased up to 2 doses of 41 IU/kg/d in the event of bleeds or for surgery. Regular follow-up examinations took place at the Haemophilia Centre and included orthopaedic assessment.

Switch to rIX-FP

The patient's overall situation made it necessary to change his treatment. During a detailed discussion, several options were put forward including relocation, caregiver services, and a change of medication. He decided to try switching to an extended half-life FIX product. This meant that his infusion frequency was reduced by around two-thirds with once-weekly prophylaxis treatment. The switch in October 2016 resulted in a sustained improvement of his overall situation.

The patient received 35 IU/kg of rIX-FP once weekly. So far (until July 2017) there have been no bleeding events during prophylaxis with rIX-FP. A dental surgi-

cal procedure was carried out problem free using this prescribed prophylaxis regimen.

The switch to Idelvion® presented no clinical difficulties, and the patient received the first two weekly doses at the Haemophilia Centre. It was possible to adapt or confirm the dosage by measuring the peak level 30 minutes after infusion and the trough level one week later (▶ **Table 2**).The one stage assay with Pathromtin SL was used for monitoring FIX activity.

Since prophylaxis has proved to be effective and was to be administered on a fixed day of the week, the dose and prophylaxis interval have been maintained to date. If warranted by the patient's social situation, that interval could possibly be prolonged up to 14 days (up to 75 IU/kg every 10–14 days).

Dental extraction on rIX-FP

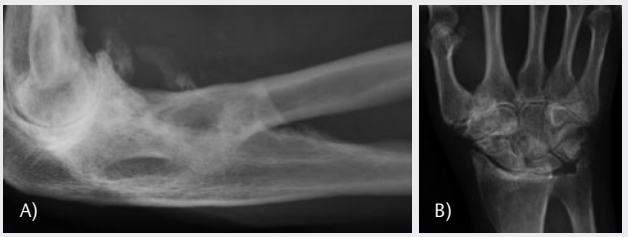
The surgical procedure was performed on the day of prophylaxis. The patient received a prophylaxis dose (35 IU/kg) immediately before the dental extractions; 24 hours later a second dose of 35 IU/kg was administered, and then 35 IU/kg every other day (postoperative days 3 and 5). Standard prophylaxis (35 IU/kg) was resumed two days later (1 week after the procedure). As such, a total of three additional injections were administered for the procedure. The clinical response was very good.

Disease course after switching to rIX-FP

The patient attends regular follow-up examinations at the Haemophilia Centre where factor levels are monitored. Thanks to the once-weekly long-term treatment, the patient is spared more than 130 exposure days annually. With his previous product, he had to administer replacement therapy on 186 days per year; however, with Idelvion® he only administers replacement therapy on 52 days per year. Switching has significantly improved the patient's overall situation, allowing more time for other activities.

Consumption

The total monthly consumption of FIX has been reduced to around 33 % of the dose of the previous FIX therapy. An even greater reduction in consumption is expected for treatment of bleeds and for therapy prior to invasive procedures.



▶ **Fig. 1** Haemophilic osteroarthritis in the A) Elbow joint, right, and B) Wrist joint, causing restriction of fine motor control needed for the administration of intravenous replacement therapy.

▶ **Table 2** Peak and trough levels as well as activated partial thromboplastin time (aPTT) after the first administration of rIX-FP.

Interval since injection	FIX level	aPTT
30 min (peak level)	58.3 %	27.3
7 days (trough level)	5.8 %	34.6

Summary

This patient with reduced mobility who was dependent on his GP for help with administration, experienced a significant improvement in his quality of life following a switch to a once-weekly injection of Idelvion®, while maintaining effective bleeding prophylaxis. Additionally, he now visits his GP less due to the reduction in injection frequency. To date, the Haemophilia Treatment Centre of University Clinic Bonn has gained experience from switching 20 patients to Idelvion®.

These case studies have revealed:

- easy switching,
- very effective bleeding prophylaxis and treatment,
- no development of inhibitors and
- high patient satisfaction.

CONCLUSIONS FOR EVERYDAY PRACTICE

- Switching to Idelvion® can significantly improve the circumstances of many patient groups by reducing the number of injections.
- Switching should always be performed under medical supervision with monitoring of trough and peak FIX activity levels.
- Switching can lead to a marked reduction in total factor consumption.

Thieme

Conclusions

Idelvion® – A valuable treatment option in many cases

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ABSTRACT

Using the long-acting recombinant factor IX (FIX) product Idelvion®, it is possible to greatly reduce injection frequency whilst assuring a high level of efficacy and safety compared with previous therapies. This can be particularly advantageous for certain patient cohorts.

These case reports demonstrate that Idelvion® represents an opportunity for haemophilia patients of all age groups: paediatric patients who prefer not to be reminded about their haemophilia and who will not allow their desire for physical activity to be curbed by their condition; adolescents with inconsistent treatment adherence and who have experienced major difficulties in reliably administering their previous FIX prophylaxis; younger patients with already greatly limited venous access; and elderly patients with reduced manual dexterity and compromised mobility as a sequela of arthropathy who are neither able to inject themselves nor, without considerable inconvenience, frequently visit their general practitioner.

Case 1 by Christoph Bidlingmaier, relates to a 7-year-old boy who, despite severe haemophilia B, gives free rein to his desire for freedom and adventure. He is delighted to receive only one weekly injection, allowing him the freedom to forget about his condition. On weekly prophylaxis with Idelvion® it has been possible to achieve a FIX level > 10 % for this patient and assure effective protection against bleeding. His parents' initial uncertainties about its administration for injuries were gradually dispelled thanks to regular consultation and growing experience with the product.

Case 2 by Wolf-Achim Hassenpflug, focuses on an adolescent who required higher FIX levels because of recurrent bleeding despite intensified prophylaxis; this presented a challenge with his increasingly limited venous access. He was then switched to a 14-day injection interval with Idelvion®, greatly facilitating his treatment and reducing his bleeding frequency. After two years, the patient continues to be very satisfied with the 14-day prophylaxis interval.

In Case 3 by Michaela Stemberger, a young man with inconsistent treatment adherence experienced frequent breakthrough renal and joint bleeds requiring treatment. He has adapted well to once-weekly prophylaxis with Idelvion®, and is now better protected against bleeding. There has been a marked improvement in treatment adherence and in his clinical picture. Treatment management is now easier for the patient and his treating physicians, improving the quality of life of the patient and of those around him.

Case 4 by Elena Kekukh describes successful perioperative management with Idelvion®. The 31-year-old patient with mild haemophilia B underwent an osteophyte resection in his right ankle joint. On the day prior to surgery, he received 2000 IU rIX-FP, 8 hours later his FIX activity was 57 %. Shortly before start of the surgical procedure (20 hours post-injection) his FIX activity levels were 52 %. On the day of surgery he received 2000 IU rIX-FP and 12 hours later his FIX activity level was 57 %. The postoperative course was free of complications, FIX trough levels were maintained within the target range of > 50 % over one week. This stability is crucial to the healing process and with conventional FIX products can generally only be assured by means of close monitoring and possibly dose adjustments. The author draws attention to the fact that stable factor levels could potentially have the advantage of allowing operative management in community hospitals. Case 5 describes a similarly problem-free case following dental extractions in an elderly patient with severe haemophilia B treated with Idelvion®.

The treatment regimen of a 61-old patient in Case 5 described by Georg Goldmann was tailored to his increasingly restricted physical abilities. The patient with arthropathy of all major joints had greatly reduced mobility. Due to osteoarthritis in his right elbow and wrist,

the patient was no longer able to self-administer his coagulation factor concentrate and was therefore obliged to visit his GP three times weekly. Because of his drastically compromised mobility, that method of administering coagulation factor became increasingly more challenging for the patient, creating enormous mental stress. The subsequent switch to once-weekly Idelvion® presented no clinical difficulties and substantially improved the patient's quality of life. If warranted by the patient's situation, that interval could possibly be prolonged up to 14 days.

Switching to Idelvion® is simple and assures effective bleeding prophylaxis and treatment with high patient satisfaction. This is also demonstrated by a small number of patients who were switched to Idelvion® at the Haemophilia Treatment Centre of University Clinic Bonn under the supervision of Georg Goldmann. Inhibitor development was not observed in any of the patients undergoing switching at that institution nor in any of the patients described here.

ESSENTIAL INFORMATION EU

Idelvion 250/500/1000/2000 IU. Powder and solvent for solution for injection. **Qualitative and quantitative composition**: One vial contains nominally 250/500/1000/2000 IU of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP), (INN = albutrepenonacog alfa). After reconstitution with 2.5 ml water for injections (250/500/1000 IU) the solution contains 100/200/400 IU/ml of albutrepenonacog alfa. When reconstituted with 5 ml water for injections (2000 IU) the solution contains 400 IU/ml of albutrepenonacog alfa. Other ingredients: Tri-sodium citrate dihydrate, Polysorbate 80, Mannitol, Sucrose, HCl. **Solvent:** Water for injections. **Therapeutic indications:** Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency). IDELVION can be used for all age groups. **Contraindications:** Hypersensitivity to the active substance (recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP)) or to any of the excipients. Known allergic reaction to hamster protein. **Special warnings and precautions for use:** Monitoring Laboratory Tests: To confirm adequate factor IX levels have been achieved and maintained, monitor plasma factor IX activity by performing the one-stage clotting assay. Factor IX results can be affected by the type of aPTT reagent used. Measurement with a one-stage clotting assay using a kaolin based aPTT reagent or Actin FS aPTT reagent will likely result in an underestimation of activity level. **Interactions:** No interactions of IDELVION with other medicinal products have been reported. **Fertility, pregnancy and lactation:** Animal reproduction studies have not been conducted with IDELVION. Based on the rare occurrence of haemophilia B in women, experience regarding the use of IDELVION during pregnancy and breast-feeding is not available. Therefore, IDELVION should be used during pregnancy and lactation only if clearly indicated. **Undesirable effects:** Summary of the safety profile: Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed rarely and may in some cases progress to severe anaphylaxis (including shock). In some cases, these reactions have progressed to severe anaphylaxis, and they have occurred in close temporal association with development of factor IX inhibitors. Nephrotic syndrome has been reported following attempted immune tolerance induction in haemophilia B patients with factor IX inhibitors and a history of allergic reaction. With the use of factor IX products obtained from CHO cells very rarely development of antibodies to hamster protein has been observed. No such antibodies have been detected in clinical trials for IDELVION. Patients with haemophilia B may develop neutralising antibodies (inhibitors) to factor IX. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. Inhibitor development was reported in an ongoing clinical study with previously untreated patients. Inhibitor development has been observed in previously treated patients in the post-marketing experience with IDELVION. There is a potential risk of thromboembolic episodes following the administration of factor IX products, with a higher risk for low purity preparations. No thrombotic events were reported during clinical studies for IDELVION. The use of low purity factor IX products has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. The use of high purity factor IX is rarely associated with such adverse reactions. The most frequent adverse reactions in clinical trials include injection site reactions, headache (common, ≥ 1/100 to < 1/10), dizziness, hypersensitivity, rash and eczema (uncommon, ≥ 1/1,000 to < 1/100) followed by factor IX inhibition / inhibitor development (not known, cannot be estimated from the available data). Paediatric population: Frequency, type and severity of adverse reactions in children are similar as in adults. **Prescription status:** Prescription-only drug. **Manufacturer:** CSL Behring GmbH, Emil-von-Behring-Str. 76, 35041 Marburg, Germany. **Date of information:** October 2019