Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2017-B-054 Nonacog beta pegol

Stand: Mai 2017

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Nonacog beta pegol Zur Behandlung der Hämophilie B	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse des G-BA über eine Änderung der Arzneimittel-Richtlinie (AM-RL): - Albutrepenonacog alfa (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 01. Dezember 2016) - Eftrenonacog alfa (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 15. Dezember 2016)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Handelsname **ATC-Code**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Nonacog beta pegol *ATC-Code* Refixia®	Geplantes Anwendungsgebiet laut Beratungsanforderung/Zulassungsantrag: „Refixia® ist indiziert für die Behandlung und Prophylaxe von Blutungen bei Patienten im Alter von 12 Jahren und älter mit Hämophilie B (angeborener Faktor-IX-Mangel).“
Faktor-IX-Präparate	
Plasmatische Präparate	
AlphaNine® Berinin® Mononine® Octanine® B02BD04	Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (angeborener Faktor-IX-Mangel) *bzw.* Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (kongenitaler Faktor-IX-Mangel)
Haemonine® B02BD04	Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (angeborener Faktor-IX-Mangel). Haemonine wird angewendet bei Erwachsenen, Jugendlichen und Kindern im Alter von 6 Jahren und älter.
Immunine® B02BD04	Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (angeborener Faktor-IX-Mangel). IMMUNINE ist für die Anwendung in allen Altersgruppen – bei Kindern älter als 6 Jahre bis hin zu Erwachsenen – indiziert. Die Anwendung von IMMUNINE bei Kindern unter 6 Jahren kann nicht empfohlen werden, da hierzu nur unzureichende Daten vorliegen.
Rekombinante Präparate	
BeneFix® Nonacog alfa B02BD09	Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (kongenitaler Faktor-IX-Mangel). BeneFIX kann bei allen Altersgruppen angewendet werden.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Rixubis Nonacog gamma B02BD29	Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (kongenitalem Faktor-IX-Mangel). RIXUBIS ist für Patienten aller Altersgruppen indiziert.
Alprolix Eftrenonacog alfa B02BD34	Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (angeborener Faktor-IX-Mangel). ALPROLIX kann bei allen Altersgruppen angewendet werden.
Idelvion Albutrepenonacog alfa B02BD33	Therapie und Prophylaxe von Blutungen bei Patienten mit Haemophilie B (kongenitaler Faktor-IX-Mangel). IDELVION kann bei allen Altersgruppen angewendet werden.
Kombination verschiedener Gerinnungsfaktoren	
Beriplex® Cofact® B02BD01	Kombinationspräparate aus den Gerinnungsfaktoren II, VII, IX und X Behandlung von Blutungen und perioperative Vorbeugung bei erblichem Mangel an einem der Vitamin-K-abhängigen Gerinnungsfaktoren, wenn kein gereinigtes spezifisches Gerinnungsprodukt zur Verfügung steht.
Prothromplex® B02BD01	Kombinationspräparat aus den Gerinnungsfaktoren II, VII, IX und X Behandlung und perioperative Prophylaxe von Blutungen bei angeborenem Mangel von Vitamin K-abhängigen Gerinnungsfaktoren, wenn das gereinigte, spezifische Gerinnungsfaktoren-Konzentrat nicht zur Verfügung steht. Prothromplex NF 600 ist indiziert für Erwachsene. Da nur unzureichende pädiatrische Daten vorliegen, kann die Anwendung von Prothromplex NF 600 bei Kindern nicht empfohlen werden.
Feiba NF® B02BD03	Eine mit Faktor VIII-Inhibitor-Bypassing- Aktivität angereicherte Humanplasmafraktion Behandlung und Prophylaxe von Blutungen bei Hämophilie-B-Patienten mit FIXInhibitor

II. Zugelassene Arzneimittel im Anwendungsgebiet

Weitere Präparate	
NovoSeven® Eptacog alfa B02BD08	Rekombinanter Faktor VIIa NovoSeven® wird angewendet zur Behandlung von Blutungen und Prophylaxe von Blutungen im Zusammenhang mit chirurgischen oder invasiven Eingriffen bei folgenden Patientengruppen: • bei Patienten mit angeborener Hämophilie mit Hemmkörpern gegen Blutgerinnungsfaktoren VIII oder IX > 5 Bethesda-Einheiten (BE) • bei Patienten mit angeborener Hämophilie, bei denen mit einem starken Anstieg des Hemmkörpers bei Verabreichung von Faktor VIII oder Faktor IX zu rechnen ist […]

Quelle: Lauer-Taxe, Fachinformation, AMIS

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation Hämophilie B durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 28.04.2017 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 255 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 10 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

„Für die Behandlung und Prophylaxe von Blutungen bei Patienten im Alter von 12 Jahren und älter mit Hämophilie B (angeborener Faktor-IX-Mangel)“

Abkürzungen:

aPCC	Activated prothrombin complex concentrate
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BD	Bodily Pain

BU	Bethesda units
DAHTA	Deutsche Agentur für Health Technology Assessment
ED	Exposure days
EQ-5D	EuroQoL-5-Dimension
EQ-VAS	EuroQoL Visual Analogue Scale
FEIBA NF	Factor Eight Inhibitor Bypassing Activity, Nanofiltered
G-BA	Gemeinsamer Bundesausschuss
GH	General Health
GIN	Guidelines International Network
h	hour
HA	Haemophilia A
HB	Haemophilia B
HRQoL	health-related quality of life
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
m	Month
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NS	Not significant
OD	on-demand treatment
PCC	Prothrombin complex concentrates
PCS	Physical Component Summary
Pro-FEIBA	Prophylaxis with Factor Eight Inhibitor Bypassing Activity
rFVIIa	recombinant factor VII
rFVIX	recombinant factor IX
rFVIXFc	recombinant FVIXFc
RP	Role-Physical
SD	standard deviation
SF	Social Functioning
SIGN	Scottish Intercollegiate Guidelines Network
tiw	thrice-weekly
TRIP	Turn Research into Practice Database
VAS	Visual analogue scale
Vs.	Versus
VT	Vitality
VWD	Von Willebrand Disease
WHO	World Health Organization

IQWiG Berichte/G-BA Beschlüsse

G-BA, 2016 [6]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Eftrenonacog alfa vom 15. Dezember 2016	**Fazit:** **Zugelassenes Anwendungsgebiet (laut Zulassung vom12. Mai 2016):** Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (angeborener Faktor-IX-Mangel). ALPROLIX kann bei allen Altersgruppen angewendet werden. **Ausmaß des Zusatznutzens:** Nicht quantifizierbar
G-BA, 2016 [5]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Albutrepenonacog alfa	**Fazit:** **Zugelassenes Anwendungsgebiet (laut Zulassung vom11. Mai 2016):** Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (kongenitaler Faktor-IX-Mangel). Idelvion® kann bei allen Altersgruppen angewendet werden. **Ausmaß des Zusatznutzens:** nicht quantifizierbar
IQWiG, 2015 [8]. Therapie von Hämophilie-Patienten (Rapid Report, A13-07)	**Fragestellung/Ziele:** 1) Eine Kartierung der Evidenzlage in der langfristigen Behandlung von Patienten mit schwerer Hämophilie A oder B mit Faktorpräparaten. 2) Nutzenbewertung der prophylaktischen gegenüber einer anlassbezogenen Therapiestrategie in der langfristigen Behandlung von Patienten mit schwerer Hämophilie A oder B hinsichtlich patientenrelevanter Endpunkte. **Methoden:** Systematische Literaturrecherche, Ein- und Aussschlusskriterien, Selektion relevanter Studien, Datenextraktion **Ergebnis:** 1) Für Hämophilie B nur 2 Studien identifiziert: (siehe Anlage 1) • Valentino 2014 HB: hochfrequente versus niedrigfrequente Standardprophylaxe mit Faktor 3090A1-400-WW (Valentino 2014 HB) Pfizer. Study comparing on-demand treatment with two prophylaxis regimens of BeneFIX In patients with severe hemophilia B: study results [online]. In: ClinicalTrials.gov. 30.08.2011 [Zugriff: 17.06.2014]. URL:

	https://clinicaltrials.gov/ct2/show/results/NCT00364182. Shafer F, Smith L, Vendetti N, Rendo P, Carr M. Lack of seasonal variation in bleeding and patient-assessed pain patterns in patients with haemophilia B receiving on-demand therapy. Haemophilia 2014; 20(3): 349-353. Valentino LA, Rusen L, Elezovic I, Smith LM, Korth-Bradley JM, Rendo P. Multicentre, randomized, open-label study of on-demand treatment with two prophylaxis regimens of recombinant coagulation factor IX in haemophilia B subjects. Haemophilia 2014; 20(3): 398-406. Wyeth. A multicenter, open-label study to compare on-demand treatment with 2 prophylaxis regimens of recombinant coagulation factor IX (BeneFIX) reformulated drug product (rFIX-R) in subjects with severe hemophilia B: study 3090a1-400-WW (B1821002); final report [unveröffentlicht]. 2011. • Lindvall 2012: Hämophilie A und B: Standardprophylaxe vs. alternatives prophylaktisches Therapieregime; Lindvall K, Astermark J, Björkman S, Ljung R, Carlsson KS, Persson S et al. Daily dosing prophylaxis for haemophilia: a randomized crossover pilot study evaluating feasibility and efficacy. Haemophilia 2012; 18(6): 855-859. 2) keine Studien zu dieser Fragestellung für Hämophilie B identifiziert Suche nach LL: Von den Leitlinien wurden ausschließlich Empfehlungen zur schweren Hämophilie A angegeben. Spezifische Empfehlungen zur Hämophilie B liegen nicht vor. **Fazit:** nur 2 Studien schlossen Patienten mit Hämophilie B ein (Vergleich unterschiedlicher prophylaktischer Therapieregime), allerdings liegen zur Hämophilie B für viele Fragestellungen keine Daten vor: […] Für den Vergleich der prophylaktischen gegenüber der anlassbezogenen Behandlung mit Faktor IX bei Kindern, Jugendlichen und Erwachsenen mit Hämophilie B liegen keine Daten vor.[…]

Cochrane Reviews

Coppola A et al., 2015 [3]. Treatment for preventing bleeding in people with haemophilia or other congenital bleeding disorders undergoing surgery (Review)	Fragestellung To assess the effectiveness and safety of different haemostatic regimens (type, dose and duration, modality of administration and target haemostatic levels) administered in people with haemophilia or other congenital bleeding disorders for preventing bleeding complications during and after surgical procedures.
	Methodik **Population:** Children and adults with a known CBD (Congenital bleeding disorders, any severity) undergoing any surgical intervention, with any follow up available. **Intervention/Komparator:** Any haemostatic treatment regimen compared to no treatment or to another active regimen. **Endpunkt** *Primary outcomes:* • Mortality • Blood loss assessed objectively o during surgery ▪ by variation of haemoglobin levels ▪ by transfusion requirement (number of red blood cell (RBC) units infused) o after surgery ▪ by variation of haemoglobin levels ▪ by transfusion requirement (number of RBC units infused) • Need for re-intervention *Secondary outcomes:* • Need for additional unplanned dosing of the drug under study • Need for alternative haemostatic treatment • Haemostatic effectiveness (as assessed and rated by the surgeon or the treating physician) • Achievement of sustained target haemostatic levels (as measured by lab test during or after surgery) • Duration of replacement treatment • Concentrate consumption • Thromboembolic adverse events • De novo inhibitor development **Suchzeitraum** (Aktualität der Recherche): last search: 20 November 2014 (No restrictions on dates, language, publication type or status) **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 4 RCTs (davon 2 relevant für Hämophilie B), n=53 Qualitätsbewertung der Studien: *Cochrane Risk of Bias tool*

	Ergebnisdarstellung **Pruhti 2007:** • Open-label multicentre RCT • 24 male participants with congenital haemophilia A or B with inhibitors undergoing elective major surgery *[Anmerkung: unklarer Anteil Patienten mit Hämophilie B]* • Age: median (range) 37.4 (10 - 67) years and 26.7 (11 - 53) years in the 2 treatment inhibitor groups • Bolus infusion: 90 µg/kg rFVIIa every 2 hours during surgery through day 5, then every 4 hours for days 6 - 10 • Continuous infusion: 50 µg/kg/hour through day 5, then 25 µg/kg/hour for days 6 - 10 • Sample size not sufficient for adequate statistical power in either efficacy and safety analysis • Unclear to high risk of bias **Shapiro 1998:** • 29 males with haemophilia and inhibitors (25 haemophilia A, 3 haemophilia B, 1 acquired FVIII inhibitor) undergoing elective surgeries (11 major, 18 minor) *[Anmerkung: geringer Anteil Patienten mit Hämophilie B]* • Age: range 0 - 40 years (0 - 4, n = 9; 5 - 16, n = 13; 17 - 40, n = 7) • Haemostatic treatment with rFVIIa as IV bolus at 35 µg/kg or 90 µg/kg, • Low risk of bias **Endpunkte:** *Need for additional unplanned dosing of the drug under Study:* Not statistically significant *Need for alternative haemostatic treatment:* Not statistically significant *Haemostatic effectiveness (as assessed and rated by the surgeon or the treating physician)* • = primary efficacy end-point in the included trials • Pruhti 2007: all time-point efficacy assessments were comparable in the two treatment groups • Shapiro 1998: no difference in the percentage of participants with satisfactory haemostasis was found between the low-dose and high-dose rFVIIa groups in the intra-operative period, at wound closure and in the following 24 hours *Duration of replacement treatment* • Pruhti 2007: median duration of rFVIIa treatment was similar in the bolus and continuous infusion arms • Shapiro 1998: clear reduction in the number of days of dosing (and

	consequently of drug injections) required in the high-dose group than in the low-dose group in participants undergoing major surgery. In minor surgery participants, the number of days dosing was similar in both groups *Thromboembolic adverse events* • […] one participant in the low-dose rFVIIa arm reported a thrombosis of the right internal jugular vein on day three following central venous catheter placement (Shapiro 1998). • In the Pruthi trial, one participant receiving rFVIIa bolus infusion for left total knee arthroplasty developed thrombosis of the left popliteal vein and the proximal peroneal vein on POD 10. […] no site used pharmacological thromboprophylaxis (Pruthi 2007). Referenzen Pruthi RK, Mathew P, Valentino LA, Sumner MJ, Seremetis S, Hoots WK, et al. Haemostatic efficacy and safety of bolus and continuous infusion of recombinant factor VIIa are comparable in haemophilia patients with inhibitors undergoing major surgery. Results from an open-label, randomized, multicenter trial. Thrombosis and Haemostasis 2007;98:726–32. Shapiro AD, Gilchrist GS, Hoots WK, Cooper HA, Gastineau DA. Prospective, randomised trial of two doses of rFVIIa (NovoSeven) in haemophilia patients with inhibitors undergoing surgery. *Thrombosis and Haemostasis* 1998;**80** (5):773–8.
	Anmerkungen/Fazit der Autoren There is insufficient evidence from randomised controlled trials to assess the most effective and safe haemostatic treatment to prevent bleeding in people with haemophilia Hinweise durch FB Med CoI: Dr Antonio Coppola paid lecturer or board member to Bayer, Biotest and Kedrion in the previous 36 months. Dr Matteo Nicola Dario Di Minno paid lecturer or board member and received funds for researches unrelated to the present study from Pfizer, Bayer and Novo Nordisk in the previous 36 months. Dr Jerzy Windyga received fees as speaker, board member, or consultant and funding for clinical trials not related to the present study from Baxter, Bayer, Biogen Idec, CSL Behring, GlaxoSmithKline, LFB, Novo Nordisk, Octapharma and Pfizer in the previous 36 months. Dr Antonella Tufano: none known. Dr Cindy Yeung: none known.
Matino D et al., 2015 [9]. Recombinant factor VIIa concentrate versus plasma-derived	Fragestellung To determine the clinical effectiveness of recombinant factor VIIa concentrate compared to plasma-derived concentrates for treating acute bleeding episodes in people with haemophilia and inhibitors
	Methodik **Population:** Children and adults with haemophilia, of all degrees of severity diagnosed by decreased blood levels of functional procoagulant FVIII or FIX and with FVIII or FIX inhibitors of any titre.

concentrates for treating acute bleeding episodes in people with haemophilia and inhibitors (Review) + **Golestani, M., et al, 2014 [7].** Comparison of bypassing agents in bleeding reduction in treatment of bleeding episodes in patients with haemophilia and inhibitors	**Intervention/Komparator:** Recombinant FVIIa concentrate (rFVIIa) compared to human plasma-derived concentrates (high-dose human or recombinant FVIII or FIX concentrate; PCCs; aPCC). Comparisons with animal-derived products were excluded. **Endpunkte:** *Primary outcomes* • Early cessation of bleeding measured by o changes on any subjective or objective pain and mobility scale or o by the volume of haematoma assessed radiologically at any point in the first 48 hours *Secondary outcomes* • Number of participants requiring additional or alternative treatment • Number of participants with adverse effects (thromboses; allergic reactions) • Correction of abnormal haemostatic laboratory test results **Suchzeitraum/Datenbanken: Anzahl eingeschlossene Studien/Patienten (Gesamt)**: most recent search: 23 September 2015 (No restrictions on dates, language, publication type or status) **Studiendesigns:** Randomised (RCTs) and quasi-randomised controlled clinical trials.
	Ergebnisse **1 relevante Studie: Young 2008:** • Open-label cross-over multicentre 3-tier RCT. • Age: mean 19.5 years (range 1 - 54 years). • The comparison between rFVIIa and aPCC was open label, while the comparison between the two different rFVIIa regimens was concealed • Outcome assessor was blinded. • Individuals with severe haemophilia A and B with inhibitor (the number of participants with A and B was not separately specified). A total of 42 were randomised, with 21 completing all 3 arms of treatment • Activated rrF VII (NovoSeven®) 90mcg/kg as IV bolus administered at 0, 3 and 6 hours. Activated recombinant factorVII (NovoSeven®) 270mcg/kg as single IVbolus (followed by 2 placebo infusions) aPCC (FEIBA®) 75 IU/kg as a single IV bolus <u>Ergebnisse:</u> *changes on any subjective or objective pain and mobility scale:* • no significant difference between the treatment groups *Number of participants requiring additional or alternative Treatment:*

	• A total of eight bleeding episodes for aPCC, two for rFVIIa 270mcg/kg and two for rFVIIa 90mcg/ kg x 3 doses required additional medication. • The difference between rFVIIa 270 mcg/kg versus aPCC was statistically significant (P = 0.032). The efficacy difference between the aPCC treatment group and the rFVIIa 90 mcg/kg x 3 doses did not reach statistical difference (P = 0.069). Referenzen Young G, Shaffer FE, Rojas P, Seremetis S. Single 270 mcg/kg -dose rFVIIa versus standard 90 mcg/kg – dose rFVIIa and APCC for home treatment of joint bleeds in haemophilia patients with inhibitors: a randomized comparison. Haemophilia 2008;14(2):287–94.
	Anmerkungen/Fazit der Autoren: We would like to highlight that we found a relevant difference in treatment efficacy independent of the drug used, i.e. aPCC or rFVIIa, […] (… 40% in the Young trial) However, there is a need for further, well-designed, adequately-powered, randomised controlled trials to assess the relative benefits and risks of using recombinant factor VIIa compared to human plasma derived concentrates in people with haemophilia with inhibitors.

Systematische Reviews

Oladapo AO et al., 2015 [10].

Health-related quality of life assessment in haemophilia patients on prophylaxis therapy: a systematic review of results from prospective clinical trials

Fragestellung

The objective was to examine the methods of HRQoL assessment, summarize the current evidence and to assess whether the findings support the use of prophylaxis in improving HRQoL in haemophilia.

Methodik

Population: subjects had congenital haemophilia A or B, including those with inhibitors

Intervention: prophylaxis in haemophilia

Komparator: keine Angaben

Endpunkt: HRQoL was measured quantitatively using a validated instrument.

Suchzeitraum: (Aktualität der Recherche): PubMed, EMBASE und ClinicalTrials.gov published up to May 15, 2014

Anzahl eingeschlossene Studien/Patienten (Gesamt): 15 publications (10 full-text articles and 5 conference abstracts) of 13 clinical trials

Ergebnisdarstellung

RCTs zu Patienten mit Hämophilie B

First author, year study region(s)	Description	Treatment	Subjects	HRQoL assessment
Windyga [18,23] Europe, Asia and Latin America	Multicentre, controlled, Phase 1/3 trial with 2 comparisons: • Randomized, blinded PK crossover comparison of BAX326 and a licensed comparator rFIX • Randomized (open-label) → OD or prophylaxis for 6 m (or >50 EDs) PK was re-evaluated in subjects receiving prior PK testing	rFIX (nonacog gamma; BAX326; Rixubis®; Baxter Healthcare Corporation, Westlake Village, CA, USA) • Prophylaxis: 40-60 IU kg^{-1} biw • OD: per body weight and desired FIX rise	Open-label phase: • Total, *n* = 73 • Severe (53.4%) or moderately severe HB • Median age, 33.5 y • % with ≥1 target joint at study entry: 65.8%	SF-36v2 at baseline and at week 26 HRQoL outcomes: • Prophylaxis, *n* = 53 • OD, *n* = 13 Sub-analyses: • 42 subjects who switched to prophylaxis from intermittent prophylaxis/OD • 23 subjects with zero bleeding events
Wyrwich, (abstract) and Wyrwich, (abstract) [21,24,27] B-LONG Europe, North America, Australia, Latin America, Asia, Africa	Multicentre, open-label, non-randomized, Phase 2/3 study Patients treated with prior prophylaxis →Group 1 or Group 2. Those treated OD could enrol in any group. Patients requiring major surgery could enter Group 4.	rFIXFc (eftrenonacog alfa; Alprolix™; Biogen Idec, Weston, MA, USA) • Group 1: 50 IU kg^{-1} qw • Group 2: 100 IU kg^{-1} at 10-day intervals with intervals adjusted as needed • Group 3-OD:20-100 IU kg^{-1} • Group 4: rFIXFc for perioperative care	• Total, *n* = 115 • Severe HB • Mean age, 33.6 y • % with ≥1 target joint at study entry: NR	EQ-5D and Haem-A-QoL at baseline and week 26 51 subjects treated with prophylaxis completed the Haem-A-QoL at both baseline and at week 26: • Individualized interval prophylaxis, *n* = 13 • Weekly prophylaxis, *n* = 38

Ergebnisse:

	Windyga et al.:
	• Within-group HRQoL changes at 6 m:
	  • Prophylaxis: PCS significantly improved from baseline (mean change, 2.60; P = 0.019) with statistically and clinically meaningful mean improvements in BP (3.45; P = 0.015) and RP (3.47; P = 0.016). On Demand Treatment (OD): No significant changes
	  • Sub-analyses: Patients switched to prophylaxis from intermittent prophylaxis/OD had statistically and clinically meaningful mean improvements
	  ▪ in PCS (3.21; P = 0.014),
	  ▪ BP (3.71; P = 0.026),
	  ▪ RP (4.43; P = 0.008),
	  ▪ VT (3.71; P = 0.04),
	  ▪ SF (5.06; P = 0.002) and
	  ▪ GH (3.40; P = 0.009).
	• Subjects with zero bleeding events had statistically and clinically meaningful reduction in bodily pain (difference in mean BP, 4.19; P = 0.038) vs. subjects with ≥1 haemorrhages.
	
	Wyrwich et al.: B-Long study
	Analyses were reported for the total Haem-A-QoL score and Physical Health and Sports & Leisure domains only and were limited to only subjects treated with prophylaxis.
	• Comparison of differences in Haem-A-QoL at baseline and at week 26 within treatment arms:
	  • Weekly prophylaxis led to significant improvements from baseline
	  o in the total score (n = 34; mean change ± SD, -6.5 ± 8.7; P = 0.0001)
	  o and scores for Physical Health (n = 38; -12.9 ± 17.6; P < 0.0001)
	  o and Sports & Leisure (n = 30; -12.1 ± 21.2; P = 0.0039),
	  o whereas only Physical Health improved significantly with individualized interval prophylaxis (dosing starting at 10-day intervals; n = 13; -15.8 ± 13.2; P < 0.001).
	
	Referenzen
	18 Windyga J, Lissitchkov T, Stasyshyn O et al. Pharmacokinetics, efficacy and safety of BAX326, a novel recombinant factor IX: a prospective, controlled, multicentre phase I/III study in previously treated patients with severe (FIX level <1%) or moderately severe (FIX level </=2%) haemophilia B. Haemophilia 2014a; 20: 15–24.
	
	23 Windyga J, Lin VW, Epstein JD et al. Improvement in health-related quality of life with recombinant factor IX prophylaxis in severe or moderately severe haemophilia B patients: results from the BAX326 Pivotal Study. Haemophilia 2014b; 20: 362–8.
	
	27 Wyrwich KW, Krishnan S, Auguste P et al. Health-related quality of life data changes over time using Haem-A-QoL scores in the B-LONG clinical study of recombinant factor IX Fc fusion protein. Presented at the World Federation of Hemophilia (WFH) World Congress. 2014. Abstract no. P-M- 221. 2014.
	
	24 Powell JS, Pasi KJ, Ragni MV et al. Phase 3 study of recombinant factor IX Fc fusion protein in hemophilia B. N Engl J Med 2013; 369: 2313–23.
	
	21 Wyrwich K, Auguste P, vonMaltzahn R et al. Psychometric evaluation of healthrelated quality of life assessments from the Along and Blong hemophilia clinical trials. Presented at the 55th American Society of Hematology Annual Meeting and Exposition. 2013. Abstract number: 423. 2013.

	Anmerkungen/Fazit der Autoren

	Improvements in HRQoL following prophylaxis were observed with the EQ-VAS, SF-36 and haemophilia-specific instruments in adult patients and were associated with reduced pain, fewer restrictions in physical activities and better general health. […] Despite study differences, consistent trends suggested that patients previously treated solely on-demand and those who experienced marked reductions in the frequency of bleeding with prophylaxis had a greater improvement in HRQoL. Conclusion: Contrary to findings of observational studies, the results from the majority of prospective trials using validated instruments showed positive trends for improved HRQoL with prophylaxis in adults. *Hinweise zum Review:* • *Aufgrund der limitierten Evidenz wurde dieser SR trotz fehlender Qualitätsbewertung der Primärstudien in die Evidenzsynopse aufgenommen. Das Verzerrungspotential durch unterschiedliche methodische Qualität der Primärstudien kann nicht eingeschätzt werden.*
Coppola A et al., 2012 [2]. Thrombotic adverse events to coagulation factor concentrates for treatment of patients with haemophilia and von Willebrand disease: a systematic review of prospective studies	Fragestellung A systematic review of the published literature data on thrombotic AEs of FVIII/FIX concentrates used for treatment of persons with haemophilia and VWD has been carried out and is reported here.
	Methodik **Population:** patients with haemophilia A (HA), haemophilia B (HB) and von Willebrand Disease (VWD) **Intervention:** FVIII/FIX concentrates, no prothrombin complex concentrates (PCC) or bypassing agents (aPCC and rFVIIa) **Komparator:** k.A. **Endpunkte:** only thrombotic AEs reported as having a highly probable or possible causal relationship with product administration **Suchzeitraum/Datenbanken:** from 1990 until October 2011/ MEDLINE, EMBASE, SCOPUS, reference lists of all included studies manually searched **Eingeschlossene Studien:** prospective studies published in full in English and enrolling at least 10 patients **Anzahl eingeschlossene Studien/Menschen (Gesamt):** 71 studies/n = 5 579
	Ergebnisdarstellung • 15 studies on 748 patients with HB treated with FIX concentrates • type/brand of factor concentrate: plasma derived FIX concentrates (pdFIX)/Alphanine, Mononine, AimaFIX, FIX Grifols, Heamonine, NonaFact – recombinant FIX concentrate (rFIX)/BeneFIX

	Ergebnisse: • number of arterial thrombosis: 0 • number of venous thromboembolism: 0 • number of thrombophlebitis: 11 (all reported in 3 studies, occurred at infusion sites; irritation or phlebitis (lacking further details) reported in nine patients from a single study receiving continuous infusion) • thrombotic AEs/patients (%):11/748 (1,47) • thrombotic AEs/infusions (%):1/17 642 (0,006) - only data from studies reporting total number of concentrate infusions are considered (8 HB) • thrombotic AEs/total AEs (%):2/104 (1,92) - only data from studies providing total number of AEs considered (12 HB)
	Anmerkungen/Fazit der Autoren Data from prospective studies over the last 20 years suggest that the risk of thrombotic AEs from factor concentrate administration is small and mainly represented by superficial thrombophlebitis. These findings support the high degree of safety of products currently used for replacement treatment. *Hinweise zum Review: CoI disclosed, no funding information* • *Aufgrund der limitierten Evidenz wurde dieser SR trotz fehlender Qualitätsbewertung der Primärstudien in die Evidenzsynopse aufgenommen. Das Verzerrungspotential durch unterschiedliche methodische Qualität der Primärstudien kann nicht eingeschätzt werden.* • *Alter der Patienten in Studien zu Hämophilie B nicht identifizierbar.*
Franchini M et al., 2012 [4] Non-thrombotic-, non-inhibitor-associated adverse reactions to coagulation factor concentrates for treatment of patients with	Fragestellung The aim of this systematic review was to screen the published literature data to evaluate the types and frequencies of non-thrombotic-, non-inhibitor associated adverse reactions to coagulation factor concentrates in patients with hemophilia A, hemophilia B and von Willebrand's disease.
	Methodik **Population:** patients with haemophilia A (HA), haemophilia B (HB) and von Willebrand Disease VWD **Intervention:** k.A. **Komparator:** k.A. **Endpunkte:** AEs (having at least a reasonable possibility of a causal relationship between the event and product administration) and laboratory test results (hematology, chemistry, FVIII inhibitor)

hemophilia and von Willebrand's disease: a systematic review of prospective studies	**Suchzeitraum/Datenbanken:** from 1990 until September 2011/ MEDLINE, EMBASE, SCOPUS, reference lists of all included studies manually searched **Eingeschlossene Studien:** prospective studies published in full in English and enrolling at least 10 patients **Anzahl eingeschlossene Studien/Menschen (Gesamt):** 65 studies/n = 5 467
	Ergebnisdarstellung (11 studies on 578 patients with HB) • type/brand of factor concentrate: plasma derived FIX concentrates (pdFIX)/AlphaNine, Mononine, AimaFIX, Heamonine – recombinant FIX concentrate (rFIX)/BeneFIX • 102 AEs recorded in hemophilia B • 2 SAE occurred in hemophilia B patients (most hemorrhagic, minority allergic/anaphylactic reactions and severe febrile episodes and venous access catheter complications) • 100 (14.3%) NSAEs occurred in hemophilia B patients (most frequent local or systemic allergic and other acute reactions, less frequent bleeding, minority venous access catheter complications) • total of 79 AEs among 14 462 infusions (0.55%) in hemophilia B recorded • difference in rate of AEs according to each bleeding disorder was not statistically significant • difference in rate of AEs between studies utilizing recombinant and plasma derived concentrates was not statistically significant [517 AEs/420 893 infusions (0.12%) vs. 79 AEs/34 047 infusions (0.23%)]
	Anmerkungen/Fazit der Autoren On the whole, these data confirm the high degree of safety of the products currently used for replacement therapy. *Hinweise zum Review:* • *CoI disclosed, no funding information* • *Aufgrund der limitierten Evidenz wurde dieser SR trotz fehlender Qualitätsbewertung der Primärstudien in die Evidenzsynopse aufgenommen. Das Verzerrungspotential durch unterschiedliche methodische Qualität der Primärstudien kann nicht eingeschätzt werden.* • *Alter der Patienten nicht identifizierbar.*

Leitlinien

Australian Haemophilia Centre Directors' Organisation, 2016 [1]. **AHCDO** Guidelines for the management of haemophilia in Australia	This document contains several practice statements regarding the clinical management of people with haemophilia
	Methodik Grundlage der Leitlinie • The NBA and AHCDO agreed that the World Federation of Hemophilia (WFH) Guidelines for the management of hemophilia (2nd edition) 5 provided a good basis upon which to develop Australian guidance. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, et al. Guidelines for the management of hemophilia. Haemophilia 2013;19(1):e1-47. (Anmerkung zur LL: Die WFH Leitlinie konnte auf Grund fehlender Angaben zur Methodik nicht in die Synopse aufgenommen werden, u.a. fehlen Angaben zur Literaturrecherche oder Konsentfindung.) • Each chapter of the WFH guidelines was reviewed by at least two AHCDO members, who were asked to appraise the chapter, assess the need for a systematic review and draft additional content. These reviewers were asked to be mindful of the Australian setting, the sustainability of products, the appropriateness of treatment regimens and the need for a consensus approach. • Upon completion of the evidence profile tables, evidence statements were developed for each question and its associated comparisons and outcomes. […] • The revised chapters were then reviewed for consistency, consolidated and circulated to nominated clinical experts as well as to Haemophilia Foundation Australia in a 'critical friends' consultation process. • Suchzeitraum: Februar 2015; EMBASE, Cochrane Library • LoE: GRADE • GoR: […] To ensure consistency of the evidence statements across different questions and outcomes, a standard sentence format was applied in which the strength of the statement reflected the quality of the underlying evidence. *Sonstige methodische Hinweise* *Leitlinie entspricht keiner S3-Leitlinie, wurde aber wegen fehlender höherwertiger Evidenz in die Synopse aufgenommen.*
	Freitext/Empfehlungen/ **1.6 Prophylactic factor replacement therapy** 1.6.1 Prophylaxis is the treatment by intravenous injection of factor concentrate in order to prevent anticipated bleeding […] 1.6.2 Prophylaxis was conceived from the observation that patients with moderate haemophilia with clotting factor level above 1

	international unit (IU)/dl seldom experience spontaneous bleeding and have much better preservation of joint function than those with a lower level of clotting factor.[27-28] 1.6.3 Prophylaxis prevents bleeding and joint destruction, and should be the goal of therapy, to preserve normal musculoskeletal function.[28-29] 1.6.4 Prophylactic replacement of clotting factor has been shown to be useful even when factor levels are not maintained above 1 IU/dl at all times.[29-31] 1.6.5 It is unclear whether all patients should remain on prophylaxis indefinitely as they transition into adulthood. Some data suggest that a proportion of young adults can do well without prophylaxis;[32] however, more studies are needed before a clear recommendation can be made.[33] 1.6.6 In patients with repeated bleeding, particularly into target joints, short-term prophylaxis for 4–8 weeks can be used to interrupt the bleeding cycle. This prophylaxis may be combined with intensive physiotherapy or synoviorthesis.[34-35] 1.6.7 Prophylaxis does not reverse established joint damage; however, it does decrease frequency of bleeding, and it may slow progression of joint disease and improve quality of life. […] Referenzen 27 Fischer K, van der Bom JG, Mauser-Bunschoten EP, Roosendaal G, Prejs R, Grobbee DE, et al. (2001). Changes in treatment strategies for severe haemophilia over the last 3 decades: effects on clotting factor consumption and arthropathy, Haemophilia 7(5):446–452. http://www.ncbi.nlm.nih.gov/pubmed/11554930 28 Aronstam A, Arblaster PG, Rainsford SG, Turk P, Slattery M, Alderson MR, et al. (1976). Prophylaxis in haemophilia: a double-blind controlled trial, British Journal of Haematology 33(1):81–90. http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.1976.tb00973.x/abstract 29 Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, et al. (2007). Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia, The New England Journal of Medicine 357(6):535–544. http://www.nejm.org/doi/full/10.1056/NEJMoa067659#t=abstract 30 Feldman BM, Pai M, Rivard GE, Israels S, Poon MC, Demers C, et al. (2006). Tailored prophylaxis in severe hemophilia A: interim results from the first 5 years of the Canadian Hemophilia Primary Prophylaxis Study, Journal of Thrombosis and Haemostasis 4(6):1228–1236. http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2006.01953.x/abstract 31 Petrini P (2001). What factors should influence the dosage and interval of prophylactic treatment in patients with severe haemophilia A and B?, Haemophilia 7(1):99-102. http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2516.2001.00471.x/abstract 32 Fischer K, Van Der Bom JG, Prejs R, Mauser-Bunschoten EP, Roosendaal G, Grobbee DE, et al. (2001). Discontinuation of prophylactic therapy in severe haemophilia: incidence and effects on outcome, Hemophilia 7(6):544-550. http://onlinelibrary.wiley.com/doi/10.1046/j.1365-2516.2001.00560.x/abstract 33 Hay CRM (2007). Prophylaxis in adults with haemophilia, Hemophilia 13(s2):10-15. http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2516.2007.01500.x/abstract 34 Kavakli K, Aydogdu S, Taner M, Duman Y, Balkan C, Karapinar DY, et al. (2008). Radioisotope synovectomy with rhenium186 in haemophilic synovitis for elbows,

ankles and shoulders, Hemophilia 14(3):518-523. http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2516.2008.01691.x/abstract

35 Luchtman-Jones L, Valentino LA and Manno C (2006). Recombinant therapy workshop participants. Considerations in the evaluation of hemophilia patients for short-term prophylactic therapy: a paediatric and adult case study, Hemophilia 12(1):82-86. http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2516.2005.01171.x/abstract

HAEMOSTATIC AGENTS

4.1 Clotting factor concentrates

4.1.1 The WFH strongly recommends the use of viral-inactivated plasma-derived or recombinant concentrates in preference to cryoprecipitate or FFP for the treatment of haemophilia and other inherited bleeding disorders.[114-115] […]

Purity

[…]

4.1.15 For treatment of FIX deficiency, a product containing only FIX is more appropriate than prothrombin complex concentrates (PCCs), which also contain other clotting factors (e.g. factors II, VII and X), some of which may become activated during manufacture.

Products containing activated clotting factors may predispose to thromboembolism.

Recombinant FIX (rFIX) is available in Australia for the management of FIX deficiency, and is the preferred product to be used in this patient population. PCCs should be used only in emergency situations where recombinant product is not available.[120-121] […]

FIX concentrates

4.1.36 rFIX concentrates are the treatment of choice for haemophilia B.

4.1.38 FIX concentrates fall into two classes:

- pure FIX concentrates, which may be plasma derived or recombinant
- FIX concentrates that also contain factors II, VII, IX and X (i.e. PCC).

4.1.39 The use of a pure FIX concentrate is preferable to the use of PCC for the treatment of haemophilia B.[120-121] Prothrombinex HT, the only PCC currently available in Australia, should only be used for the treatment of haemophilia B where emergency replacement of FIX is required and a pure FIX concentrate is not available.

4.1.40 Pure FIX products are free of the risks of thrombosis or disseminated intravascular coagulation, which may occur with large doses of PCCs.

[…] 4.1.50 Allergic reactions may occur with infusions of FIX concentrates in patients with anti-FIX inhibitors. In such patients, infusions may need to be covered with hydrocortisone.[130] Changing the brand of clotting factor concentrate sometimes reduces symptoms.

Referenzen

	114 Evatt BL, Austin H, Leon G, Ruiz-Saez A and De Bosch N (1999). Haemophilia therapy: assessing the cumulative risk of HIV exposure by cryoprecipitate, *Haemophilia* 5(5):295–300. http://onlinelibrary.w iley.com/doi/10.1046/j.1365-2516.1999.00317.x/abstract 115 Farrugia A (2008). *Guide for the assessment of clotting factor concentrates*, 2nd ed, World Federation of Hemophilia, Montreal. 120 Kim HC, McMillan CW, White GC, Bergman GE, Horton MW and Saidi P (1992). Purified factor IX using monoclonal immunoaffinity technique: clinical trials in hemophilia B and comparison to prothrombin complex concentrates, Blood 79(3):568–575. http://www.bloodjournal.org/content/bloodjournal/79/3/568.full.pdf 121 Lippi G and Franchini M (2008). Pathogenesis of venous thromboembolism: when the cup runneth over, Seminars in Thrombosis and Hemostasis 34(8):747–761. https://www.thieme-connect.com/products/ejournals/pdf/10.1055/s-0029-1145257.pdf 130 Shibata M, Shima M, Misu H, Okimoto Y, Giddings JC and Yoshioka A (2003). Management of haemophilia B inhibitor patients with anaphylactic reactions to FIX concentrates, Haemophilia 9(3):269–271. http://onlinelibrary.wiley.com/doi/10.1046/j.1365-2516.2003.00772.x/abstract **6.2 Inhibitors** 6.2.1 In haemophilia, 'inhibitors' refer to immunoglobulin G (IgG) antibodies that neutralise clotting factors. 6.2.2 In the current era, in which clotting factor concentrates have been subjected to appropriate viral inactivation, inhibitors to FVIII or FIX are considered to be the most severe treatment-related complication in haemophilia. 6.2.9 Inhibitors are much less frequently encountered in haemophilia B, occurring in less than 5% of affected individuals.[222] Management of bleeding 6.2.21 Choice of treatment product should be based on titre of inhibitor, records of clinical response to product, and site and nature of bleed.[224; 227] 6.2.25 Alternative agents include bypassing agents such as rFVIIa and PCC, including APCC. 6.2.26 The efficacy of two doses of rFVIIa and one dose of APCC for management of joint bleeding has been shown to be essentially equivalent.[228] 6.2.27 Some patients respond better to one agent than the other, highlighting the need to individualise therapy.[228-229] Allergic reactions in patients with haemophilia B 6.2.31 Up to 50% of haemophilia B patients with inhibitors may have severe allergic reactions, including anaphylaxis, to FIX administration. Such reactions can be the first symptom of inhibitor development. 6.2.32 Newly diagnosed haemophilia B patients, particularly those with a family history or with genetic defects predisposed to inhibitor development, should be treated in a clinic or hospital setting capable of treating severe allergic reactions during the initial 10–20 treatments with FIX concentrates. Reactions can occur later, but may be less severe.[118; 230] Referenzen

118 Recht M, Pollmann H, Tagliaferri A, Musso R, Janco R and Neuman WR (2011). A retrospective study to describe the incidence of moderate to severe allergic reactions to factor IX in subjects with haemophilia B, *Haemophilia* 17(3):494–499. http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2516.2011.02436.x/abstract

222 Bolton-Maggs PHB and Pasi KJ (2003). Haemophilias A and B, Lancet 361(9371):1801–1809. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(03)13405-8/abstract

224 Hay CRM, Brown S, Collins PW, Keeling DM and Liesner R (2006). The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors' Organisation, *British Journal of Haematology* 133(6):591–605. http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2006.06087.x/full

227 Teitel J, Berntorp E, Collins P, D'Oiron R, Ewenstein B, Gomperts E, et al. (2007). A systematic approach to controlling problem bleeds in patients with severe congenital haemophilia A and high-titre inhibitors, Haemophilia 13(3):256–263. http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2516.2007.01449.x/abstract

228 Astermark J, Donfield SM, DiMichele DM, Gringeri A, Gilbert SA, Waters J, et al. (2007). A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA NovoSeven Comparative (FENOC) Study, *Blood* 109(2):546–551. http://www.bloodjournal.org/content/bloodjournal/109/2/546.full.pdf

229 Chitlur M, Warrier I, Rajpurkar M and Lusher JM (2009). Inhibitors in factor IX deficiency a report of the ISTH-SSC international FIX inhibitor registry (1997-2006), *Haemophilia* 15(5):1027–1031. http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2516.2009.02039.x/abstract

230 Coppola A, Di Minno MND and Santagostino E (2010). Optimizing management of immune tolerance induction in patients with severe haemophilia A and inhibitors: towards evidence-based approaches, *British Journal of Haematology* 150(5):515–528. http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2010.08263.x/full

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am **24.04.2017**

#	Suchfrage
#1	MeSH descriptor: [Hemophilia B] explode all trees
#2	(Haemophil*:ti,ab,kw or hemophil*:ti,ab,kw) and b:ti,ab,kw
#3	Haemophil*:ti or hemophil*:ti
#4	factor:ti,ab,kw and IX:ti,ab,kw and deficien*:ti,ab,kw
#5	Christmas:ti,ab,kw and disease*:ti,ab,kw
#6	(Plasma Thromboplastin Component Deficien*):ti,ab,kw
#7	#1 or #2 or #3 or #4 or #5 or #6
#8	#7 Publication Year from 2012 to 2017, in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 24.04.2017

#	Suchfrage
#1	Hemophilia B[MesH]
#2	(haemophil*[Title/Abstract] OR hemophil* [Title/Abstract]) AND b[Title/Abstract]
#3	Haemophil*[Title] OR hemophil*[Title]
#4	factor[Title/Abstract] AND IX[Title/Abstract] AND deficien*[Title/Abstract]
#5	Christmas[Title/Abstract] AND disease*[Title/Abstract]
#6	Plasma Thromboplastin Component Deficien*[Title/Abstract]
#7	#1 or #2 or #3 or #4 or #5 or #6
#8	(#7) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
#9	(#8) AND ("2012/04/01"[PDAT] : "2017/04/30"[PDAT])
#10	(#9) NOT "The Cochrane database of systematic reviews"[Journal]

Leitlinien in Medline (PubMed) am 24.04.2017

#	Suchfrage
#1	Hemophilia B[MesH]
#2	(haemophil*[Title/Abstract] OR hemophil* [Title/Abstract]) AND b[Title/Abstract]
#3	Haemophil*[Title] OR hemophil*[Title]
#4	factor[Title/Abstract] AND IX[Title/Abstract] AND deficien*[Title/Abstract]
#5	Christmas[Title/Abstract] AND disease*[Title/Abstract]
#6	Plasma Thromboplastin Component Deficien*[Title/Abstract]

#	**Suchfrage**
#7	#1 or #2 or #3 or #4 or #5 or #6
#8	(#7) AND (Guideline[Publication Type] OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type] OR Consensus Development Conference, NIH[Publication Type] OR guideline*[Title] OR recommendation*[Title])
#9	(#8) AND ("2012/04/01"[PDAT] : "2017/04/30"[PDAT])
#10	(#9) NOT ((comment[Publication Type]) OR letter[Publication Type])

Literatur:

1. **Australian Haemophilia Centre Directors' Organisation.** Guidelines for the management of haemophilia in Australia [online]. Melbourne (AUS): Australian Haemophilia Centre Directors' Organisation; 2016. [Zugriff: 27.04.2017]. URL: https://www.blood.gov.au/system/files/HaemophiliaGuidelines-interactive-updated-260317v2.pdf.

2. **Coppola A, Franchini M, Makris M, Santagostino E, Di Minno G, Mannucci PM.** Thrombotic adverse events to coagulation factor concentrates for treatment of patients with haemophilia and von Willebrand disease: a systematic review of prospective studies. Haemophilia 2012;18(3):e173-187.

3. **Coppola A, Windyga J, Tufano A, Yeung C, Di Minno MND.** Treatment for preventing bleeding in people with haemophilia or other congenital bleeding disorders undergoing surgery. Cochrane Database of Systematic Reviews [online]. 2015(2):Cd009961. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009961.pub2/abstract.

4. **Franchini M, Makris M, Santagostino E, Coppola A, Mannucci PM.** Non-thrombotic-, non-inhibitor-associated adverse reactions to coagulation factor concentrates for treatment of patients with hemophilia and von Willebrand's disease: a systematic review of prospective studies. Haemophilia 2012;18(3):e164-172.

5. **Gemeinsamer Bundesausschuss (G-BA).** Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Albutrepenonacog alfa vom 1. Dezember 2016 [online]. Berlin (GER): G-BA; 2016. [Zugriff: 28.04.2017]. URL: https://www.g-ba.de/downloads/39-261-2776/2016-12-01_AM-RL-XII_Albutrepenonacog_D-227_BAnz.pdf.

6. **Gemeinsamer Bundesausschuss (G-BA).** Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Eftrenonacog alfa vom 15. Dezember 2016 [online]. Berlin (GER): G-BA; 2016. [Zugriff: 28.04.2017]. URL: https://www.g-ba.de/downloads/39-261-2804/2016-12-15_AM-RL-XII_Eftrenonacog-alfa_D-233_BAnz.pdf.

7. **Golestani M, Eshghi P, Rasekh HR, Cheraghali AM, Salamzadeh J, Imani A.** Comparison of bypassing agents in bleeding reduction in treatment of bleeding episodes in patients with haemophilia and inhibitors. Iran Red Crescent Med J 2014;16(12):e24551.

8. **Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG).** Therapie von Hämophilie-Patienten; Rapid Report; Auftrag A13-07 [online]. 28.05.2015. Köln (GER): IQWiG; 2015. [Zugriff: 27.04.2017]. (IQWiG-Berichte; Band 305). URL: https://www.iqwig.de/download/A13-07_Rapid-Report_Therapie-von-Haemophilie-Patienten.pdf.

9. **Matino D, Makris M, Dwan K, D'Amico R, Iorio A.** Recombinant factor VIIa concentrate versus plasma-derived concentrates for treating acute bleeding episodes in people with haemophilia and inhibitors. Cochrane Database of Systematic Reviews [online]. 2015(12):Cd004449. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004449.pub4/abstract.

10. **Oladapo AO, Epstein JD, Williams E, Ito D, Gringeri A, Valentino LA.** Health-related quality of life assessment in haemophilia patients on prophylaxis therapy: a

systematic review of results from prospective clinical trials. Haemophilia 2015;21(5):e344-358.