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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Publication** | **Factor VIII Product** | **Study design Study  period Follow up (FU)** |  | **Definition FVIII level haemophilia A** | **Number recruited PUP/MTP + Severity** | **Inhibitor test Bethesda assay, + Nijmegen modification, other** | **Frequency of testing** | **Parameters according to ClinGL fulfilled?** | | | | |
| **Study location (number of sites)** | **>= 50 PUPs (no MTPs)** | **>= 50 ED FU** | **Severity <1%** | **Bethesda (or later than ca. 1995: Nijmegen Modification)** | **Inhibitor testing frequency (** |
| **(Addiego et al. 1993)** | pdFVIII Cryo-precipitate FFP | retrospective, uncontrolled, 1975-1985  FU: 5 years or 30 exposure days | USA (7) | severe: < 1 % | 89 PUP | Bethesda assay | at least annually | y | n | y | y | n |
| **(Auerswald et al. 2012)** | Advate | prospective, uncontrolled 2004-2009 FU: 3 years or 75 EDs | USA (13), France (4) Germany (2), Austria (1), Canada (1), Italy (1), Spain (1), UK (1), | severe: < 1%,  moderately severe:1–2% | 18 PUP/ 37 MTP, 53 severe, 1 moderate, 1 mild | Bethesda test Nijmegen assay | ≤10, 20,or 30 EDs | n | y | y | y | y |
| **(Auerswald et al. 2015)** | Advate | prospective, historically controlled 2011-2012 FU: 50 EDs | Germany (4), Russia (3), USA (2), Poland (2), Austria (1), Bulgaria (1), Canada (1), Czech Republic (1), Lithuania (1), Netherlands (1), Serbia (1), Spain (1) | severe: < 1 % | 11 PUP/ 8 MTP | Nijmegen modified Bethesda assay | at infusion number 3, 6, 10, 15, 20, 30, 40 and 50 | n | y | y | y | y |
| **(Batorova et al. 2016)** | pdFVIII rFVIII | prospective, uncontrolled 1997-2015 FU: up to 50 and 150 EDs | Slovakia | severe: < 1 % | 59 PUP: pdFVIII: 50  rFVIII: 9 | Both standard Bethesda method and Nijmegen modification | every 4 to 5 exposure days (EDs) during the first 20 EDs, then every 10 and 20 EDs up to 50 and 150 EDs | y | y | y | y | y |
| **(Biasi et al. 1994)** | pdFVIII | prospective, uncontrolled 1975-1992 FU: no FU in ED defined | Italy | severe and moderate: < 1 % to =< 5% | 64 PUPs, 48 severe, 16 moderate | Bethesda assay | repeatedly when clinically indicated or at least annually | y | n | y | y | n |
| **(Blatny et al. 2015)** | pdFVIII rFVIII | retrospective, uncontrolled, 2003-2013 FU: at least 100 EDs | Czech Republic | no definition provided | 86 PUP rFVIII: 45 (22 severe, 11 moderate, 12 mild) pdFVIII: 41(20 severe, 5 moderate, 16 mild) | Nijmegen modified Bethesda assay | every 5 exposure days (EDs) during the first 20 EDs, then every 10 EDs up to 50 Eds and then 6 monthly | y | y | unknown | y | y |
| **(Bray et al. 1994** **(Bray 1992; Gruppo R. et al. 1998; Rothschild et al. 2000; Goodeve et al. 2000)** | Recombinate | prospective, uncontrolled 1990-1997 FU: minimum of 24 months or 50 rAHF ED | USA (26), Denmark (2), France (2), Italy (1), Germany (1) | severe: < 1 %,  moderate: ≤ 2% | 69 PUP, 2 MTP, 55 severe , 14 moderate | Bethesda | every 3 month | y | y | y | y | n |
| **(Calvez et al. 2014; Calvez et al. 2018)** | Recombinate/Bioclate, Kogenate/Helixate, Refacto, Kogenate FS/Helixate NexGen, Advate, ReFacto AF/Xyntha, Factane | retrospective, uncontrolled 1993-2014 ( -2016) FU: the first 75 EDs | France | severe: < 1 % | 490 PUP | Bethesda method or the Nijmegen modified assay | results show: On average, these assays were performed every 6.3 EDs during the first 25 EDs and every 9.9 EDs during the overall follow-up period | y | y | y | y | y |
| **(Chalmers et al. 2007)** | pdFVIII rFVIII | retrospective, uncontrolled 1987-2003 FU: >50 EDs | UK | severe: < 1 % | 348 PUP | Bethesda assay | Monitoring for inhibitory antibodies was performed on a regular basis at least every 3–6 months | y | y | y | y | n |
| **(Collins et al. 2014)** | Advate Kogenate Bayer/Helixate ReFacto Refacto AF Recombinate | retrospective, uncontrolled 2000-2011 FU: 75 EDs | UK | severe: <1% | 407PUP  Advate:172  Kogenate Bayer/Helixate: 128 ReFacto: 52  Refacto AF: 44  Recombinate: 11 | "measured locally using standard Bethesda or Nijmegen assays" | not reported | y | y | y | y | unknown |
| **(Courter and Bedrosian 2001)(Lusher et al. 2003)**  **(Lusher and Roth 2005; Philipp CS et al. 2001; Pollmann et al. 2007; Pollmann H 2001; Smith et al. 2005; Feingold JM et al. 2004; Lusher JM et al. 1999)** | Refacto | prospective, uncontrolled 1994-2005 FU: 50ED or up to 5 years | Germany  (3), Spain (6), Austria (3), Holland (2), UK (7), France (7), Italy (3), Sweden (1),  Denmark (2), Switzerland (1), Hungary (1), South  Africa (1), Turkey (1), Belgium (1), USA (10) | severe: <2% | 101 PUP | Bethesda assay | not specified | y | y | n | y | unknown |
| **(ElAlfy et al. 2000)** | Cryoprecipitate | prospective, uncontrolled 1996 -1999  FU: 3 years | Egypt | severe: < 1 % | 25 PUP | Bethesda | twice a year | n | unknown | y | y | n |
| **(Fischer et al. 2015)** | Advate,   Helixate NexGen,  Kogenate Bayer, Recombinate, Refacto,Refacto AF, PD products | retrospective, uncontrolled  (EUHASS) 2008 - 2012 FU: >50EDs | EU (26) | no definition provided | 297 PUP all severe | No information | not specified | y | y | unknown | unknown | unknown |
| **(Goudemand et al. 2006; Rothschild et al. 1998; Goudemand J et al. 2003; Bray et al. 1994)** | Recombinate pdFVIII-LFB Kogenate | retrospective,  uncontrolled 1986-2002  FU: median observation time 108 ED | France (23) | severe: <1 % | 148 PUP all severe | Bethesda | not specified | y | n | y | y | unknown |
| **(Gouw et al. 2007a)**  **(; Gouw et al. 2007b; Gouw SC et al. 2010; Mauser-Bunschoten et al. 2007; Mauser-Bunschoten et al. 2001; van der Bom et al. 2003)** | PdFVIII: 135, RdFVIII: 181, | retrospective, uncontrolled  (CANAL) 1990-2000 FU: up to 50 ED or until inhibitor development | EU (13), Canada (1) | severe: <2% | 316 | Bethesda | not specified | y | y | n | y | unknown |
| **(Gouw et al. 2013a)**  **(Gouw et al. 2013b; Gouw S et al. 2010; Gouw S et al. 2012; Gouw SC et al. 2011; van den Berg et al. 2016)** | 1 pdFVIII 2 Recombinate 3 Kogenate FS 4 ReFacto 5 Advate | prospective, uncontrolled  (RODIN)  2000-2010 FU: 75 ED | 29 centers in Europe, Israel and Canada | severe: <1 % | 574 PUP | Bethesda | not specified | y | y | y | n | unknown |
| **(Gringeri et al. 2006)** | Emoclot | retrospective,  uncontrolled 1987–2003 FU: at least 20 EDs | Italy (13) | severe: <1% moderate: 1–5% | 31 PUP (12 severe, 17 moderate)68 MTP (57 severe, 11 moderate) | Bethesda | every 5–10 EDs | n | n | y | y | y |
| **(Gringeri A et al. 2000)** | BDDrFVIII Refacto | Retrospective, uncontrolled 1999-2000 FU: median 20 EDs | Italy (32) | severe: <2%,  non-severe: ≥2% | 17 PUP: 15 PUP severe, 2 PUP non-severe | Bethesda | not specified | n | n | n | y | unknown |
| **(Guérois et al. 1995)** | highly purified pdFVIII | prospective, uncontrolled 1988-1993 FU: median 26 | France (13) | severe: <1% | 56 PUP | 1991-1993: Bethesda, <1991 = APTT (n=10) | every 3 to 6 month but at least once a year | y | n | y | n | n |
| **(Kurnik K et al. 2009)**  **(Halimeh et al. 2013; Kurnik et al. 2010)** | pdFVIII rFVIII | Prospective, uncontrolled, 1982-2007  FU: 200 ED | Germany (5) | severe/no definition provided | 150 PUPs | Bethesda assay or Nijmegen modification | at least monthly to 3 monthly | y | y | n | y | n |
| **(Klukowska et al. 2018)**  **(Klukowska A et al. 2014; Klukowska A et al. 2010; Klukowska A et al. 2011; Klukowska A et al. 2013; Klukowska et al. 2011; Jansen M et al. 2013a, 2013b; Jansen M et al. 2013c)** | Octanate | prospective, uncontrolled 2000-2018 FU: 100 EDs | Poland, Czech Republic, Russia | severe: < 1 %  moderate < 2 % | 51 PUP recruited 45 PUP: severe 4 PUP: moderate (excluded) 2 PUP :<20 Eds (excluded) | Bethesda assay with Nijmegen modification | every 3-4 exposure days (ED 1-20), every 10 EDs (ED 21-100),  . | y | y | n | y | y |
| **(Kreuz et al. 2005)**  **(Kreuz et al. 2001; Giangrande 2002)** | Kogenate FS | Prospective, uncontrolled,  1997-2001  FU: median 114 EDs | US (13), Germany (4), Spain (3), France (3), UK (3), Sweden (2), Denmark (2), Portugal (1), Israel (1) | severe: < 2 % | 37 PUP, 24 MTP: 49 severe, 12 moderate | Bethesda assay with Nijmegen modification | every 3rd-4th ED until the 20th ED, then after every 10th ED until the 50th ED | n | n | n | y | y |
| **(Kreuz et al. 2002)****( Ehrenforth S et al. 1992)** | pdFVIII rFVIII | prospective, uncontrolled 1976-1999 FU: pdFVIII: median 290 ED; rFVIII: median 59 | Germany | severe: <1% moderate: 1 to 5% | 72 PUP Pd FVIII: 51, rFVIII: 21,  Severe: 46, moderate: 26 | Bethesda method | every 3rd to 5th ED during the first 20 ED, every 10th ED until the 200th ED | y | n | y | y | y |
| **(Lusher and Salzman 1990; Lusher 1991)** | Monoclate Hemofil | prospective, uncontrolled, 1986-1989, FU: surveillance at 6-month intervals | US (10), UK (2), Netherlands (1), Israel (1) | no definition provided | Monoclate 38 (19 PUP, 19 MTP), Hemofil: 51 (48 PUP, 3 MTP), Severity not clear | Bethesda | at baseline , then every six month | y | unknown | unknown | y | unknown |
| **(Lusher et al. 2004; Lusher et al. 1993)** | Kogenate | prospective, uncontrolled 1988 –1997 FU: up to 75 ED | USA (15), Canada (1), Germany (4), Italy (3), Spain (3), Sweden (2) | severe: <2 | 100 PUP, 2 MTP,  65 severe, 16 moderate, 21 mild | Bethesda (without Nijmegen) | before study entry, then every three month | y | y | n | y | n |
| **(Maak B. et al. 2012)** | Haemoctin SDH | prospective, uncontrolled 1998-ongoing FU: mean observation period of 53 months | Germany (12) | Severe: <2 | 6 PUP | no information | at baseline, then at least once a year | n | unknown | n | unknown | n |
| **(Mancuso et al. 2012)** | pdFVIII  rFVIII | retrospective, uncontrolled 1922 - 2009 FU: 150 EDs or detection of inhibitors | Italy (3) | severe: <1% moderate: 1%–4% | 377 analysed: 279 PUP and 98 MTP, 318 severe | Bethesda assay ; Nijmegen modification | frequency not specified | y | y | y | y | unknown |
| **(Matysiak et al. 2011)** | Optivate | prospective, uncontrolled period not clear FU: 26 weeks of treatment | Poland (5) | severe: <1% | 1 PUP | other + Bethesda/Nijmegen assay | every three month | n | unknown | y | y | n |
| **(Musso et al. 2008)** | Kogenate | prospective, uncontrolled 2002-2005 FU: up to 24 months, mean (± SD) of 187 (121)  EDs | Austria (2), Belgium (2), Denmark (1), France (24), Greece (2), Italy (6), The Netherlands (6), Spain (4), Sweden (3), Switzerland (2) | Severe: <2% | 13 PUPs | Bethesda | frequency not specified | n | n | n | n | unknown |
| **(Oldenburg et al. 2010; Luu et al. 2007; Pollmann et al. 2013)** | Advate | prospective, uncontrolled 2004-2012 FU: 12 months following study entry | US, Austria, Belgium, Denmark, France, Gemrany, Greece, The Netherlands, Spain, Sweden, Switzerland, UK | severe: <1% moderately severe: 1% -≤2%  moderate: 2% - ≤5%   mild:>5% | 11 severe to moderate PUP  1 mild PUP (Those with 0–3 ED were considered PUPs) | Bethesda | frequency not specified | n | unknown | y | n | unknown |
| **(Peerlinck et al. 1993)** | Cryoprecipitate | retrospective, uncontrolled 1971-1990  FU: <100 ED | NL (1) | severe: <1% | 72 PUP (67 treated) severe: 48  moderate: 10  mild: 14 | other and Bethesda assay | frequency not specified | y | y | y | y | unknown |
| **(Peyvandi et al. 2016)** | rFVIII (Advate, Kogenate FS, Recombinate, ReFacto AF); pdFVIII (Alphanate, Emoclot, Factane, Fanhdi) | prospective, controlled 2010- 2014 FU: 50 consecutive EDs or 3 years | Italy, India, Iran, US, Mexico, Brazil, Chile, Argentina, South Africa, Spain, Saudi-Arabia, Austria, Turkey, Netherlands | severe: <1% | 251 PUP: pdFVIII: 125 rFVIII: 126 | Bethesda assay with the Nijmegen modification local and central laboratory | every 3 to 4 exposure days during the first 20 infusions, then every 10 exposure days or every 3 months | y | y | y | y | y |
| **(Schwartz et al. 1990)** | Kogenate | prospective, uncontrolled 1988 – 1990 FU: not specified | US, EU, Japan | severe: <1% moderate: 1%-5% mild: > 5% | 20 PUP (severe), 1 MTP (moderate) | Bethesda | approx. every 12 weeks | n | unknown | y | y | n |
| **(Strauss et al. 2011)**  **(Halimeh et al. 2013)** | Refacto/Refacto AF; Kogenate FS/Helixate NG, full length second generation rFVIII or B domain deleted products, pdFVIII concentrates | retrospective 1984-1995 prospective 1996-2008, uncontrolled FU: at least 75 EDs | Israel | severe: <1% | 292 PUP:  pdFVIII: 249 rFVIII: 43 | Bethesda method | 1984-1996: once a year,>1996: at least every 6 month | y | y | y | y | n |
| **(Vepsäläinen et al. 2016)** | Recombinate, Kogenate/Helixate, Refacto, Advate, ReFacto AF, Amofil, Haemate, Cryoprecipitate | retrospective, uncontrolled 1994 - 2013 FU: at least 75 EDs | Finland (5) | severe: <1% | 62 PUP:  rFVIII: 39 pdFVIII: 23 | Bethesda assay | every 6 month or upon clinical suspicion | y | y | y | n | n |
| **(Vézina et al. 2014)** | Advate, Kogenate FS or Helixate, Wilate, RefactoAF/ Xyntha | retrospective, uncontrolled 2005-2010 FU: at minimum 20 ED | Canada (26) | severe: <1% | 99 PUP | Bethesda assay or Nijmegen modification | frequency not specified | y | n | y | y | unknown |
| **(Yee et al. 1997)** | pdFVIII | prospective, uncontrolled 1985-1995 FU: median of 200 ED | UK (2) | severe: <2% | 37 PUP | Bethesda assay or other | every three month, every four months, biannually or annually | n | n | n | y | n |
| **(Yoshioka et al. 2006)** | Kogenate | prospective, uncontrolled 1993-1999 FU: 11 to 80 months | Japan (33) | severe: <1% moderate: 1%-5% mild: > 5% | 43 PUP: 31 severe 9 moderate 3 mild | Bethesda assay | at inclusion and 3, 6, 9, 12, 18 and 24 months after inclusion | n | n | y | y | n |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  | 28 | 23 | 26 | 34 | 11 |
|  |  |  |  |  |  |  |  | 21 | |  | |  |
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