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Modeling of Daily Administration of N8-GP (ESPEROCT®) vs Standard Half-life FVIII for Patients With Hemophilia A Participating in Sports Activities

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Abstract

Objective: Daily administrations of FVIII products are considered useful for providing high FVIII coverage for active patients with hemophilia A. This analysis was performed to determine the daily dose levels required of N8-GP (turoctocog alfa pegol, ESPEROCT ®) vs standard half-life (SHL) FVIII (N8, turoctocog alfa, Novoeight ®) to normalize risk of activity-related bleeding for patients with hemophilia participating in daily sports activities (practices, games) of varying risk profiles. Methods: Patients with hemophilia engaging in physical activity have associated increased bleeding risk with sports that have increased potential for contact injuries as classified by Broderick et al (JAMA. 2012): Class 1 - no contact (eg, swimming); Class 2 - contact might occur (eg, basketball); and Class 3 - inevitable contact (eg, American football). To normalize the risk of bleeding, nominal targets of FVIII activity levels for at least 2 h/d based on Broderick et al were chosen: above 30% (Class 1), above 50% (Class 2), and above 70% (Class 3). Pharmacokinetic (PK) simulations were performed using a one-compartment model with first-order elimination. FVIII PK profiles were simulated for the extended half-life (EHL) N8-GP based on the pathfinder 1 PK trial showing 60% prolonged half-life compared with prior SHL FVIII. For PK simulations of an SHL, N8 was used due to 104^0F stability with PK based on the guardian clinical trial program. Summary: Daily doses to sustain at least 2 h/d of 30%/50%/70% activity were estimated for N8-GP (9, 15, and 21 IU/kg) and N8 (14, 23, and 33 IU/kg). Steady-state PK profile simulations of once-daily administration are shown in the Figure . Broderick Class 1 (>30%) Broderick Class 2 (>50%) Broderick Class 3 (>70%) N8-GP Daily (weekly), IU/kg 9 (63) 15 (105) 21 (147) Peak/trough activity 32%/13% 54%/21% 76%/29% Difference from 50 IU/kg Q4D -28% 21% 69% N8 Daily (weekly), IU/kg 14 (98) 23 (171) 33 (231) Peak/Trough activity 36%/6% 59%/10% 87%/14% Difference from 25 IU/kg QD 13% 97% 166% N8-GP vs N8 Utilization, IU/kg -36% -39% -36% Conclusion: Experience with routine prophylaxis with EHL/SHL FVIIIs towards guideline recommended >1% activity does not readily translate to HCP understanding of the PK with high daily or much higher every-other-day administration required to minimize risk for the active patient. With a 1.6x (60%) prolongation in half-life for adolescents/adults, this model shows daily N8-GP to be a more efficient strategy compared with daily SHL FVIII (N8) to cover the active patient; N8-GP achieves higher trough levels with a smaller increase in overall factor consumption compared with standard prophylaxis with SHL FVIII.