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IG- associated thrombotic adverse events – Pharmacovigilance

Risk Mitigation Strategies to Address Potential Procoagulant Activity in Immune Globulin Products

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Background

IVIG Octagam

- **Signal: July-August 2010**
  - 8 cases of TEE associated with one batch (B010C844A) in Germany revealed an 80fold higher rate of of TEE compared to the product information
- **Regulatory Actions: September 2010**
  - Suspension of MA and recall of all batches IVIG Octagam 5 % by PEI 15.9.2010
  - Initiation of Article 107 procedure according to Directive 2001/83 EC by PEI
  - CHMP Opinion 22.9.2010
  - Commission decision 4.10.2010: Suspension of IVIG Octagam 5% and 10 %
  - Art. 31 procedure start: 9/ 2010, positive opinion of CHMP 4/2011 (Commission decision pending)
  - Standing Committee phase started 17 May 2011

Background

ICIG Vivaglobin

- **Signal: March 2011**
  - **In-house research testing by the MAH revealed that several lots contain certain levels of procoagulant activity**
  - **Urgent Safety restriction to change the SPC and the package leaflet**
  - **Dear Healthcare Professional Communication**
  - **Initiation of an Art. 36 procedure according to Directive 2001/84 EC**

Reporting rate of TEEs of selected Human Normal IGs

IG	Reporting rate	
	Period	1 TEE : Kg Ig distributed
IG O	2010	1: 75 - 1 : 150* kg
IG O	2004 – 2010	1 : 458 kg
IG A	2008 - 1/2011	1:8068 kg
IG B	2/2008- 2/2010	1:4158 kg
IG C	2003 - 2008	1:2673 kg
IG D	1/2008 – 1/2009	1:7000 kg
IG E	2004 – 10/2009	1: 4378 kg
IG F (scIG)	2008 - 2010	1 : 433 kg
IG H	2002 - 2008	< 1: 3700 kg

*** Reporting rate increased after regulatory actions**

TEE Reporting Rate

Year	Octagam 5 % 1 TEE/ kg IG distributed	Vivaglobin 1 TEE/ kg IG distributed
2005	1: 1475 kg	0
2006	1: 1200 kg	0
2007	1: 1600 kg	0
2008	1: 531 kg	1: 683 kg
2009	1: 495 kg	1: 340 kg
2010	1: 75 kg	1: 420 kg

IG- associated thrombosis route cause / trigger

- **Drug factors**
  - **Hyperviscosity**
  - ✓ **Coagulation factor contaminants (FXI, FXIa, FXIIa)**
  - **High doses**
  - **Rapid infusion**

- **Patient factors**
  - **Age**
  - **Co-morbidity (immobilization, previous TEE, cardiovascular disease)**
  - **Co-medication**
  - **Underlining disease (autoimmune disease >> primary immunodeficiency)**

Associated TEE risks in reported cases

	Human Normal Immunoglobulins			
Parameters	Sandoglobulin	Kiovig	Vivaglobin	Octagam 5 %
Median age of patients (range)	53 (17 - 93)	54 (7 – 81)	52 (12 – 77)	64 (11 – 89)
Risk factor for thrombosis documented in pts. with TEE	16/21 (76%)	22/32 (69 %)	8/19 (42%)	30/116 (26%)
Indication autoimmune disorder	9/21 (43 %)	12/32 (38 %)	n.a.	30/116 (26 %)
Art. TEE, stroke, LE, MI	4/21 (19%)	20/32 (63 %)	9/19 (47%)	100/116 (86%)
Onset of TEE <24 h post administration	12/21 (57%)	7/32 (22%)	4/19 (21%)	62/116 (54%)

Summary

- Detection of increased reporting rates of TEE for two normal human immunoglobulins via spontaneous reporting
- The signal is consistent with levels of procoagulant activity of certain batches
- No such signal for other products
- For IG O patients without risk factors for thrombosis concerned and high number of arterial thrombosis

- Next steps
  - Re-evaluation of data with more precise exposure data
  - Link of batches associated with TEEs of several products with coagulation tests (e.g. TGA)

Thank you for your attention

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