CPAG Summary Report for Clinical Panel – URN1709
Clinical evidence review of vonicog alfa for the treatment and prevention of bleeding in adults with von Willebrand disease

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	
2.	Progression free survival	
3.	Mobility	
4.	Self-care	
5.	Usual activities	
6.	Pain	
7.	Anxiety / Depression	
8.	Replacement of more toxic treatment	
9.	Dependency on care giver / supporting independence	
10.	Safety	This outcome looked at how many adverse events were thought to be caused by vonicog alfa, and how many occurred during treatment with vonicog alfa. There were 2 main studies for this outcome. Gill et al. (2015) looked at the efficacy of vonicog alfa to prevent bleeding episodes (n=37). Peyvandi et al. (2018) looked at efficacy of vonicog alfa for treating and preventing bleeding during surgery (n=15). Gill et al. (2015) reported that 6.4% (8/125) of adverse events were thought to be related to vonicog alfa. This included 2 serious adverse events in 1 participant which were chest discomfort and increased heart rate and required hospitalisation for observation. Peyvandi et al. (2018) reported 12 adverse events in 6 participants during treatment with vonicog alfa. This included a deep vein thrombosis. This was asymptomatic and detected on screening which is not routine practice in the UK.

		However it was recorded as serious and thought to be possibly related to vonicog alfa. Results suggest that adverse events are mostly mild or moderate. Results should be interpreted with caution because they are based on non-comparative studies. This means that the studies did not compare the treatment with any other standard treatment. Therefore this study does not provide evidence that vonicog alfa is any better or worse than other treatments for this outcome. The results are limited to people with severe types of VWD, however the licensed indications do not differentiate between severe and less severe types of VWD suggesting that people with different severities of VWD can be treated with vonicog alfa. Some patients received recombinant factor 8 and other treatments such as tranexamic acid which may influence the adverse events experienced.
11.	Delivery of intervention	

Other health outcome measures determined by the evidence review		
No	Outcome measure	Summary from evidence review
1.	Extent of control of the bleeding episode	This outcome considered how well, on average, vonicog alfa controlled bleeding for individual study participants. It was defined as the number of participants with a mean haemostatic efficacy rating score of < 2.5. The rating score was measured using a 4-point scale based on the actual number of infusions administered compared with the estimated (by the treating doctor) number of infusions needed to control the bleed. A score of 1 indicated excellent control and a score of 4 indicated no control of the bleeding episode. A score of < 2.5 indicated excellent or good control of the bleeding episode and was defined as treatment success. Gill et al. (2015) (n=22 participants) reported that all bleeds were treated successfully, with an overall treatment success rate on a study participant level of 100% (Clopper-Pearson exact 90% CI: 87.3 to 100.0%). Please also see outcome 3 for information on control of bleeding episodes (n=192 bleeding episodes) for the 22 participants.

		The result suggests that all participants had excellent or good control of their bleeding episode with vonicog alfa. The probability that the true value is contained within the range of 87.3% to 100% is 90%. This result should be interpreted with caution because it is based on a small and non-comparative study. Therefore this study does not provide evidence that vonicog alfa is any better or worse than other treatments for this outcome. Also, this outcome was subjectively assessed by the treating doctor using a pre-defined scale rather than by using a validated tool, which may introduce bias. The results are limited to people with severe types of VWD, however the licensed indications do not differentiate between severe and less severe types of VWD suggesting that people with different severities of VWD can be treated with vonicog alfa. These limitations described are often common and considered acceptable in studies investigating treatment in people with bleeding conditions. The main reasons for the limitations include: the treating conditions of interest were episodic and recruitment was limited to severe types of VWD in the study; it would be impractical and unethical to blind participants who are bleeding and treating them with placebo; and subjective assessments are commonly used for assessing treatment efficacy in this population.
2.	Overall investigator-assessed haemostatic efficacy during/after surgery	This outcome looked at how well vonicog alfa controlled bleeding 24 hours after the last infusion (which may have been before or during surgery, or at completion of the study) in people with VWD **undergoing surgery**. This was assessed by using a 4-point rating scale (excellent, good, moderate or none) based on bleeding control relative to a person who does not have VWD undergoing the same surgery . A score of 1 indicated 'excellent' control of bleed, where control with vonicog alfa (with/without recombinant factor 8) was as good as or better than expected for the type of procedure performed in a person without VWD, and a score of 4 indicated no control of bleeding. Peyvandi et al. (2018) (n=15) reported an overall haemostatic efficacy rating of excellent or good in 100% of the participants who had surgery (Clopper-Pearson exact 90% CI: 81.9 to 100.0%). The result suggests that all participants who had surgery had control of bleeding as good or better than that expected, or probably as good as that expected, relative

		to a person who does not have VWD undergoing the same surgery, The probability that the true value is contained within the range of 81.9% to 100% is 90%. See outcome number 1 for information on the reliability of results.
3.	Number of treated bleeding episodes with an efficacy rating of excellent or good	This outcome looked at how many bleeding episodes treated with vonicog alfa were rated as having excellent or good control of the bleed. This was assessed by the treating doctor using a 4-point scale of excellent, good, moderate, or none. Gill et al. (2015) (n=22) reported that all 192 bleeding episodes were rated as either excellent or good (100% [Clopper-Pearson exact 95% CI: 98.1 to 100.0%]). The result suggests that all the bleeding episodes had either an excellent or good control with vonicog alfa. The probability that the true value is contained within the range of 98.1% to 100% is 95%. See outcome number 1 for information on the reliability of results
4.	Number of infusions and units of vonicog alfa/ recombinant factor 8 (rFVIII) and/or vonicog alfa per bleeding episode	This outcome looked at how many infusions and units of vonicog alfa were required to stop a bleeding episode. Vonicog alfa was given with recombinant factor 8 at the first infusion to maintain baseline plasma factor 8 activity, and was subsequently given without recombinant factor 8 as long as therapeutic plasma factor 8 activity levels were maintained. Minimised numbers of treatment infusions/units can reduce treatment burden for patients. Gill et al. (2015) (n=22) reported that 81.8% of the bleeding episodes were stopped by 1 infusion (median 1, range 1 to 4 infusions) of vonicog alfa. Out of the 192 bleeding episodes, 10 bleeding episodes in 3 participants were treated with the first infusion of vonicog alfa without recombinant factor 8 and the efficacy was rated as excellent for all these bleeds. The median dose of vonicog alfa needed to stop a bleed was 46.6 IU/kg (range 23.8 to 139.6 IU/kg) and for recombinant factor 8 was 33.6 IU/kg (range 16.6 to 129.3 IU/kg). The results suggest that most of the bleeds were stopped with 1 infusion of vonicog alfa. The greatest number of infusions needed to stop a bleed was 4. The dose of vonicog alfa needed to control a bleeding episode was a minimum of 23.8 IU/kg and a maximum of 139.6 IU/kg when given with recombinant factor 8.

		Please note the limitations are those applicable to those described for outcome 1, other than the point on subjectivity. In full, this result should be interpreted with caution because it is based on a small and non-comparative study. Therefore this study does not provide evidence that vonicog alfa is any better or worse than other treatments for this outcome. The results are limited to people with severe types of VWD, however the licensed indications do not differentiate between severe and less severe types of VWD suggesting that people with different severities of VWD can be treated with vonicog alfa. These limitations described are often common and considered acceptable in studies investigating treatment in people with bleeding conditions. The main reasons for the limitations include: the treating conditions of interest were episodic and recruitment was limited to severe types of VWD in the study; and it would be impractical and unethical to blind participants who are bleeding and treating them with placebo.