

Drug review/P030004

1. Do you believe that the amount of DMSO being used is equivalent to therapeutic drug concentrations? Please support your opinion based upon known dosages of DMSO currently, clinically used.
2. Do you believe that the preclinical evaluations adequately characterize the device with respect to safety concerns for DMSO in the targeted intravascular space? If not, why not, and what additional studies do you believe the sponsor should conduct?
3. Do you believe that the amount of DMSO used in the embolization procedure could have systemic toxic effects that would not have been observed in the studies that were conducted? If so, please identify the toxic, non-intended effects you believe DMSO could have and why they would not have been observed in the studies already conducted. What studies, if any, would you suggest that the sponsor conduct to evaluate for systemic effects?
4. With regard to product labeling, what Warnings, Precautions, statements, etc..., do you believe should be provided to users of the product specifically regarding the DMSO component?

The only approved use of DMSO in human is for interstitial cystitis as a 50% solution (RIMSO⁷). The concentration and duration of exposure to DMSO for this indication is quite different from the arteriovenous malformation (AVM) indication in that a lower concentration of DMSO is used for a short period and the solution is withdrawn. Therefore, systemic exposure appears to be low.

In contrast, in the AVM condition, undiluted DMSO is delivered directly into vascular space for a short period. Therefore, previous clinical experiences do not provide much useful and relevant information for safety assessment. The proposed maximum single exposure to DMSO in an AVM patient is 131 mg/kg, which is well below the lowest toxic intravenous dose of 600 mg/kg (NTP). The concentration of DMSO from which this dose was derived was not reported, but the possibility of vasospasm and damage to the vascular wall and blood elements is known to increase with increasing concentration and rate of delivery of DMSO solution.

Because undiluted solutions of DMSO are being used in a novel delivery mode, the safety of the concentration and mode of delivery needs to be established empirically. The sponsor has provided results from a non-clinical study with DMSO in the swine rete mirabile model indicating that a single delivery of undiluted DMSO at a rate of less than 0.3 mL/min caused minimal vasospasm and no permanent vascular damage. Although the protocol mentioned repeated indication, no results were provided.

The safety of ONYX⁷ was tested in the swine rete mirabile model. In this study, animals were treated with single administration of EMBOLYXJ and were followed

for 3, 6, and 12 month. No vasospasm, neurological deterioration, or behavioral changes were observed. However, hyperplasia, inflammatory reaction, foreign body giant cells and disruption of elastica without evidence of hemorrhage or angiogenesis were observed. Some of the histopathological changes were still present at 3, 6 and 12 months after administration.

Although the result of these studies provide adequate information for determination of the safety of single administration of DMSO in this mode, it does not provide any information on the safety of multiple administration.

It is indicated that in some cases of AVM, there might be a need for multiple treatments. In such cases, the safety of multiple doses of DMSO could not be determined from non-clinical findings because only single treatment was tested in animals. Also, the clinical experience with multiple exposure is limited (a total of 16 patients with 3 or more treatments).

Considering that some of the effects observed in animals following a single treatment were still present after 12 months, there may be a need for assessment of the safety of multiple doses of DMSO in animals models. The extent of systemic exposure could also be evaluated in this study by collecting blood at various intervals and determining pharmacokinetic/toxicokinetic parameters of DMSO and its metabolites. The latter will provide valuable information for assessing the safety of systemic exposure to DMSO through this route.

For labeling, similar information to that found in the RIMSO⁷ label should be included in addition to the safety information from the studies on the multiple exposure