



MAY 16 2007

Nancy Thompson-Brown  
Senior Regulatory Compliance Specialist  
Schering-Plough Animal Health Corporation  
1095 Morris Avenue  
Union, NJ 07083-1982

**RE: NADA 141-193 Zubrin® Tablets**  
**Direct to Consumer Promotional Piece (SPAH-ZB-77)**

Dear Ms. Thompson-Brown,

The Center for Veterinary Medicine's Division of Surveillance (CVM DOS) reviewed your March 17, 2006, Drug Experience Report (DER) submission concerning Zubrin (tepoxalin) Tablets, NADA 141-193. This submission includes a brochure entitled "*Why should Zubrin® be your first NSAID choice?*" (SPAH-ZB-77). This brochure is false or misleading because it makes unsubstantiated safety claims and minimizes the risks associated with Zubrin®.

CVM DOS has also reviewed your December 21, 2006, DER submission. This submission includes three newspaper wraps (e.g., SPAH-ZB-127C), and the Clinician's Update (SPAH-ZB-74). These items are apparently intended to be disseminated at the 2007 North American Veterinary Conference (NAVC). These items are also false or misleading because they make unsubstantiated safety claims and minimize the risks associated with Zubrin®.

CVM's DOS has also reviewed a series of mailers sent to veterinarians (e.g., SPAH-ZB-86) that also are false or misleading because they make unsubstantiated safety claims and minimize the risks associated with Zubrin®.

For these reasons Zubrin® is misbranded under section 502(a) and (n) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 USC 352(a) and (n)]. These violations concern us from a veterinary health perspective because they suggest that Zubrin is safer than has been demonstrated.

### **Background**

Zubrin® (tepoxalin) is a non-steroidal anti-inflammatory drug (NSAID) indicated for the control of pain and inflammation associated with osteoarthritis in dogs. The FDA-approved labeling for Zubrin® contains the important risk information in the sections entitled Warnings, Precautions, and Adverse Reactions. As noted in the approved label for Zubrin®, dogs should be clinically monitored using appropriate laboratory tests before and during treatment with all NSAIDs

including Zubrin®, and pet owners should be advised to observe for signs of potential drug toxicity. Furthermore, as a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal, hepatic and renal toxicity, and concomitant treatment with any other NSAIDs or corticosteroid drugs should be avoided while dogs are being treated with Zubrin®. The safety of Zubrin® when administered to breeding, pregnant, lactating dogs, or puppies less than 6 months of age, and when given concomitantly with other protein bound drugs has not been conclusively studied.

### Unsubstantiated Safety Claims

The brochure, SPAH-ZB-77, states that "*Core studies in rats have shown that tepoxalin given before gastric ulcer-generating doses of indomethacin was able to prevent the formation of ulcers.*" This suggests that the studies have shown that tepoxalin would be able to prevent the formation of ulcers not only in rats but also in dogs. This suggestion is reinforced by the fact that the statement appears underneath the larger, bolded heading "Unprecedented GI Ulceration Safety Profile" and that the cover page of the brochure says "Unprecedented Gastric Ulceration Safety Profile." Kirchner T, et al., 1997, which is cited as support, involves laboratory animals. While it also describes additional studies, those are all *in vitro* studies. The claims are therefore misleading because they present a favorable conclusion from nonclinical studies for which clinical significance has not been demonstrated in a way that suggests the conclusion has clinical significance (see 21 C.F.R. 202.1(e)(6)(vii)).

The promotional materials make the following additional claims regarding the gastro-intestinal safety of Zubrin:

- "*Tepoxalin is the only NSAID shown not to induce ulcers in dogs when given as high as 30 times the daily recommended dose, every day, for 28 days*" (brochure, SPAH-ZB-77)
- "*Would you feel safe giving a dog 30 times the recommended dose of any NSAID – every day for 28 days? . . . We did.*" (newspaper wrap, SPAH-ZB-127C, and mailer, SPAH-ZB-86)
- "*In a target animal safety study, dogs dosed with tepoxalin . . . at 30 times the recommended daily dose everyday, for 28 days showed: NO Gastro Intestinal Ulcers*" (newspaper wrap, SPAH-ZB-127C, and mailer, SPAH-ZB-86)
- "*Exceptional gastrointestinal safety profile (even at 30X recommended dose for 28 days)*" (Clinician's Update, SPAH-ZB-74)

These claims are misleading because they imply that Zubrin is safe, at least with respect to gastrointestinal safety, at 30 times the approved dose for 28 days when this has not been demonstrated by substantial evidence of effectiveness. The claims are supported by a citation to "Data on file." CVM has reviewed this data, which is a report entitled "Four-Week Oral Toxicity Study of RWJ-20485-000 (Tepoxalin) in Dogs with a Four Week Recovery Period." A four-week study is not adequate to demonstrate safe use for a four-week period. Safety studies are typically three times the duration of the intended administration of the product. Moreover, other field studies strongly suggest that there are safety concerns associated with use of Zubrin in dogs, specifically gastric irritation and ulceration. These include a 26-week study with 13-week

interim necropsy and a 1-year oral toxicity study, both of which are part of the Freedom of Information Act (FOI) Summary for Zubrin.

These claims are also misleading because they imply that Zubrin is safer, with respect to ulcers, than other NSAIDs when this has not been demonstrated by substantial evidence of effectiveness. To substantiate a comparative claim, it should be supported by well-controlled, head-to-head comparative studies, which the Four-Week Oral Toxicity Study is not.

Not only is the claim about 30 times the dose for 28 days misleading, it also sends a dangerous message to veterinarians by suggesting that overdose (>1 times dose) with tepoxalin is safe. Veterinary patients could be injured by being given an unapproved overdose.

The promotional materials make the following claims regarding the hepatic and renal safety of Zubrin:

- *"Minimal Impact on Kidney and Liver"* (brochure, SPAH-ZB-77)
- *"Tepoxalin provides a wide margin of renal tolerance, proven in safety studies and years of field use"* (brochure, SPAH-ZB-77)
- *"With less than 1% of tepoxalin excreted through the kidneys, dogs with renal impairment are not at greater risk of drug accumulation"* (brochure, SPAH-ZB-77)
- *"Dogs given tepoxalin showed no clinically significant changes in liver enzymes or kidney parameters (in a one year safety study)"* (brochure, SPAH-ZB-77)
- *"NO Significant Increase in Liver Enzymes or Kidney Parameters"* (Clinician's Update, SPAH-ZB-74)

These claims are misleading because they imply that Zubrin is safer than has been demonstrated by substantial evidence of effectiveness. The claims in the brochure are supported by a citation to "Data on file." CVM has reviewed this data, which is a study by Fusellier et al., 2005. The study was performed to investigate renal function in clinically normal dogs receiving tepoxalin, with and without an angiotensin-converting enzyme inhibitor (ACE inhibitor). The study concluded that tepoxalin did not alter renal function in healthy female Beagle dogs receiving ACE inhibitors. The study used only healthy female Beagle dogs, so it is not adequate to demonstrate safety in the general dog population. Moreover, while the Fusellier study is used to support the statement that "dogs with renal impairment are not at greater risk of drug accumulation," it was not conducted in renally-impaired dogs and the study stated that it "gives preliminary results that need to be confirmed" and that "the effects of tepoxalin on renal function should be investigated in dogs of various breeds- older, client-owned dogs with heart and/or renal failure being chronically treated with an ACEI." In addition, the number of animals for this study, ten, is too low to draw statistically significant conclusions regarding hepatic and renal safety.

### **Minimizing Risk Information**

Improper use of Zubrin® or administration of excessive doses may result in injury or death of treated dogs. We note that statements that communicate favorable information about the product are generally presented using large, bolded headers and with a significant amount of white space

around them. The risk information, however, is presented in a smaller, more difficult to read font and, for the brochure, only on the eighth page. It does not, in that case, satisfy the requirement for a "true statement" of information required under section 502(n) of the Act [21 USC 352(n)] and 21 CFR 202.1(e)(5).

### **Conclusion and Requested Action**

These promotional items make unsubstantiated safety claims and minimize the risks associated with Zubrin® in violation of the Act [21 USC 352(a) and (n)].

The Center for Veterinary Medicine requests that Schering-Plough Animal Health immediately cease the dissemination of the Zubrin® promotional items described above, and any other materials that may contain similar unsubstantiated promotional claims. Please submit a written response within 30 days of receipt of this letter describing whether you intend to comply with this request, and listing all violative promotional materials for Zubrin® the same as or similar to those described above, and explaining your plan for discontinuing use of such materials.

Please direct your response to me at the Food and Drug Administration, Division of Surveillance, HFV-216, 7519 Standish Place, Rockville, MD 20855. We remind you that only written communications are official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to see that your promotional materials for Zubrin®, as well as other Schering-Plough Animal Health products, comply with the requirements of the Act and the FDA implementing regulations.

Sincerely yours,  
Christopher Melluso, DVM  
Team Leader (acting), Post-approval  
Regulatory Review Team, HFV-216  
Division of Surveillance  
Center for Veterinary Medicine