European Medicines Agency
Veterinary Medicines and Inspections

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WITHDRAWAL ASSESSMENT REPORT

FOR

ZUBRIN – ORAL SUSPENSION

International Non-proprietary Name: Tepoxalin

Procedure No.: EMEA/V/C/057/X/027

Extension (new pharmaceutical form)

Withdrawal at Day 120

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1. SUMMARY OF THE DOSSIER

On 4 September 2007, S-P Veterinary submitted to the EMEA an application for the extension of a marketing authorisation for Zubrin for a new pharmaceutical form (Zubrin 100 mg/ml oral suspension for dogs).

The proposed form was presented in glass bottles and was indicated for use in dogs for the reduction of inflammation and relief of pain caused by acute and chronic musculoskeletal disorders. The route of administration was oral use. At present the product is authorised for dogs in three strengths (50, 100 and 200 mg) as oral lyophilisates in the same indications.

Since this application concerns the extension to an already authorised veterinary medicinal product, cross-reference was made to relevant sections of dossier(s) already submitted and assessed by the CVMP an previous occasions.

The CVMP on the basis of quality, safety and efficacy data submitted, considered that the application was not approvable at Day 120 since major objections had been identified, which precluded a recommendation for marketing authorisation. The concerns were in relation to the efficacy and safety of Zubrin oral suspension at the suggested dose level.

On 3 October 2008, S-P Veterinary withdrew the application at Day 120 of the procedure.

2. QUALITY ASSESSMENT

Cross-reference was made to the quality data previously submitted for Zubrin oral lyophilisates for dogs. Additional data have been provided in relation to this extension application for an oral solution.

Composition

The product contains tepoxalin (100 mg/ml) as active ingredient and standard preservatives (methyl parahydroxybenzoate and propyl parahydroxybenzoate), suspending (microcrystalline cellulose, carmellose sodium, xanthan gum), sweetening (sorbitol solution) and wetting agents (Polysorbate 80), as well Propylene glycol as dissolution aid and Water for injections as diluent. Most ingredients in the suspension are described in Ph.Eur., except for a mixture of two ingredients for which further clarification was requested.

Container

The suspension is packaged in glass bottles in the package sizes, 20 ml, 40 ml and 100 ml. The caps are tamper-evident and child resistant and consist of polypropylene with a liner. A press-in-bottle-adaptor and a syringe are supplied with each bottle. However, more information on dose accuracy of the syringes is required. The packaging materials are in accordance with relevant EU requirements.
The packaging material is satisfactorily described and controlled except for the child resistant cap for which more data were requested.

Development Pharmaceutics

The objective of the pharmaceutical development programme for the oral suspension was to develop an aqueous oral suspension dosage form designed to be dosed upon shaking. The development work has been thoroughly described and the manufacturing process is a standard process. Validation data from pilot scale batches would be needed before marketing and also additional information regarding the in-process controls.

Method of manufacture

The manufacturing process is a standard process that has been well described. Considering the non-critical process it is acceptable that process validation is performed prior to marketing. The submitted process validation plan is in accordance with the EC Guideline CPMP/QWP/848/96 Note for Guidance on Process Validation. Production scale validation data will be provided after approval but before marketing. A question was raised about the in-process controls.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The starting materials of animal origin used in the production of the final product comply with the current regulatory texts related to the TSE Note for Guidance (EMEA/410/01-Rev.2) and Commission Directive 1999/104/EEC.

Control tests on the finished product

The description of the methods used for the control of the finished product and the specifications were provided. The specifications for release and shelf-life of drug product were not acceptable by the Committee and a number of additional data were requested, in particular on dissolution since poor dissolution could influence the bioequivalence. The analytical methods for control of drug product were satisfactorily described and validated, except for the method for description of the oral suspension.

Stability

The stability data were in general considered satisfactory and showed that Zubrin oral suspension is stable during storage and very little degradation is seen. A shelf-life of 2 years with no special storage precautions was considered acceptable. The in-use stability study showed that the suspension was stable for at least 28 days after first opening at ambient storage conditions.

3. SAFETY ASSESSMENT

For most safety documentation, cross-reference was made to the safety data previously submitted for Zubrin oral lyophilisates for dogs; however, additional studies were submitted to support the user safety documentation.

User safety

In support of this application, five new GLP-compliant studies were provided to support the user safety assessment, investigating the oral and dermal toxicity in rats, the skin and eye irritant potential in rabbits and the skin sensitisation potential in the mouse.

Zubrin oral solution was considered to be of low acute dermal toxicity with LD_{50} values above 2100 mg/kg bodyweight, and was not considered to be a skin or eye irritant, or having skin sensitising potential.

A new user safety assessment was provided, concluding that there were no foreseeable risks. However, the CVMP concluded that the user safety assessment would need to be revised taking into account additional exposure scenarios before a final conclusion on user safety could be reached. Additional information was considered necessary with regard to (chronic) dermal absorption and accidental oral ingestion by a child.

Environmental risk assessment

A Phase I environmental risk assessment was provided. The CVMP considered that this extension was intended for use in individual non-food producing animals (dogs) and that the environmental exposure would be limited. A Phase II Assessment was therefore not required.

A risk of environmental impact following the intended use of Zubrin oral suspension for dogs was considered unlikely.

4. EFFICACY ASSESSMENT

Cross-reference was made to the efficacy data previously submitted for Zubrin oral lyophilisates for dogs, however, additional studies were submitted to support pharmacokinetics, target animal safety and clinical efficacy of the proposed extension.

Pharmacokinetics

Three new studies were submitted investigating bioequivalence between the new oral suspension and the already authorised lyophilisate tablets (1), pharmacokinetics following single and multiple dosing (2) and the impact of food on the efficacy of the product (3). In all studies the parent drug and the active metabolite tepoxalin pyrazole acid were measured. Tepoxalin is a dual cyclooxygenase/5-lipoxygenase inhibitor, while the metabolite is an inhibitor of cyclo-oxygenase only. The composition used in the pharmacokinetic studies and the clinical studies was the same as the marketing formulation.

The quality of the documentation was not considered adequate. For example, the bioanalytical methods had not been documented and validated in accordance with accepted standards. Furthermore, two of the three studies were non-GLP. In all studies there was a very large variability between animals. The plasma concentrations versus time curves exhibited in many cases double peaks, in particular for the metabolite, and the curves commonly followed an irregular pattern. The underlying reasons for those shapes were not sufficiently explained.

Bioequivalence could not be demonstrated between the oral suspension and the oral lyophilisate. The point estimate for AUC indicated that the oral suspension might have a lower bioavailability compared with the lyophilisate when administered in fed dogs. However, no final conclusions could be drawn from this study. The mean ratio between the formulations for AUC (90% CI) was 0.68 (0.40 - 1.16) and 0.93 (0.55 – 1.57) for the parent drug and the metabolite, respectively. Similar values were obtained for maximum concentrations. The inter-animal variability was similar for the two formulations. Bioavailability was indicated to increase in fed dogs although an adequate quantitative assessment was not performed. Following repeated once daily dosing, no accumulation was observed for the parent drug, as expected. However, for the metabolite, there was an accumulation, which had not been observed in previous studies. In addition, the exposure of the parent drug and the metabolite, in particular, was significantly higher in this study compared with the other submitted studies and previous studies. Further clarification was required on the discrepancy.

The conclusion on pharmacokinetics was that the large inter-individual variability in exposure evident for the lyophilisate was also found for the suspension. Thus, the CVMP expressed concern that the risk for adverse reactions and lack of efficacy due to exposures outside the therapeutic window was high and dose/exposure accuracy low also for the suspension. Furthermore, the new repeat dose study indicated a different systemic drug exposure of the metabolite.

Target animal tolerance

A new GLP-compliant target animal safety study was provided investigating the tolerance of tepoxalin (oral suspension) at 1x, 3x and 5x the suggested dose (10mg/kg BW) during 6 month exposure in purpose-bred mongrel dogs (2005).

Dogs (4-8 month old) were placed in one of four dose-groups; placebo, 1x (10 mg/kg bodyweight), 3x (30 mg/kg) or 5x (50 mg/kg) the proposed dose. The dogs received the medicinal product once daily during 182 days.

Two dogs in the 5x dose groups died at Day 37 and it is unclear whether these events were treatment dependent. Abnormal faeces were sporadically noted in some dogs in the 3x and 5x groups. A dose dependent minor decrease in red blood cell parameters was noted, and bleeding time was increased in all Zubrin treatment groups. In single animals from the 3x and 5x dose groups, necropsy revealed minor mucosal bleedings and ulcers in the stomach. Histopathology confirmed the occurrence of mucosal insults in one or two dogs from each of the three Zubrin treated groups. Minor signs of chronic inflammation of the pancreas were also noted in some dogs from the 1x and 3x dose group.

The CVMP noted that these results may not be fully relevant for the target population of the final product which is more likely to be used in older dogs that are less tolerant to this type of compound as the young dogs included in this study. As could be expected for this type of compound (NSAID), the study demonstrated the occurrence of treatment-related gastrointestinal disturbances consisting of abnormal faeces and mild to moderate stomach reactions. Such events mainly affected dogs at 3x and 5x the recommended dose, although minor changes were also noted in some dogs at the recommended dose level. The observed hematological changes are likely connected to these effects. Changes to the pancreas were a novel observation for this compound which should be further commented. Furthermore, the causality for the fatalities in the 5x dose group should be further explored.

Field studies

Since bioequivalence between the new formulation (oral solution) and the previously approved lyophilisate could not be demonstrated, two GCP-compliant new field studies were submitted to support efficacy and safety for the oral solution.

One was a new multi-centre GCP-compliant field study, performed in 2005-2006 in the USA investigating the efficacy and tolerance of Zubrin oral suspension in the control of pain and inflammation associated with osteoarthritis in the dog. The study included a large number of dogs (average age 9 years) suffering of osteoarthritis. Dogs were treated either with Zubrin oral suspension (10 mg/kg BW, once daily for 14 days) together with food or with a positive control containing meloxicam (0.2 mg/kg BW Day 0, then 0.1 mg/kg BW for 13 days, once daily).

The second study was a multi-centre, masked clinical field study investigating the efficacy and safety of tepoxalin oral suspension in cases of chronic osteo-articular disorders in dogs in Germany and France (2004-2005). The study included a large number of dogs (average age 9 years) suffering of pain/inflammation from osteoarthritis of different locations. Dogs were treated either with Zubrin oral suspension (10 mg/kg BW, once daily for 56 days) or with a positive control containing meloxicam (0.2 mg/kg BW Day 0, then 0.1 mg/kg BW for 56 days, once daily).

In both studies, treatment improvement was seen in both groups (Zubrin and meloxicam). Non-inferiority was tested by use of several different endpoints related to locomotory function. Confidence interval calculations indicate non-inferiority for Zubrin towards meloxicam.

The CVMP noted that both studies included a large number of the target population (i.e. mainly older dogs suffering chronic osteoarthritis) and the studies in general appeared appropriate with regards to selection of study population, inclusion and exclusion criteria and blinding. However, it appeared that in both field studies, only Per Protocol (PP) analyses were presented (and not the intended to treat population (ITT) and different approaches were used regarding the selection of primary efficacy

endpoints and the definition of treatment success. Furthermore, the non-inferiority margin was not justified, and it seems as different non-inferiority limits were pre-determined in the two studies. The CVMP also noted that for an extension application, the most obvious choice would have been to compare Zubrin oral suspension with the approved Zubrin lyophilisate and the applicant was asked to justify the decision to use another product as comparator.

With regard to tolerance, only in one of the studies the safety profile seemed comparable for the two products whereas in the long-term study Zubrin seemed inferior to meloxicam.

Overall conclusion on efficacy

In the original dossier concerning the lyophilisate (tablet), high pharmacokinetic variability was noted and this was presumed to be formulation dependent to a large extent. Thus, improvement in this respect would have been expected for the oral suspension, but variability seemed to remain and consequently bioequivalence between the two formulations was not demonstrated. In this situation for an extension application, a study on potential therapeutic equivalence between the lyophilisate and the oral suspension would have been expected. Instead the applicant aimed at demonstrating sufficient efficacy and safety for the oral suspension, by tolerance testing in the target species and by comparing clinical performance to another NSAID.

The pharmacokinetic data indicated a possibly lower bioavailability for the oral suspension as compared to the lyophilisate and likely as a consequence of this, clinical efficacy appeared inferior for Zubrin oral suspension as compared to meloxicam. The non-inferiority analysis presented indicated for several relevant endpoints that the performance of Zubrin was inferior to meloxicam. Furthermore, the incidence of adverse reactions appears to be higher for Zubrin.

Additional questions regarding study design and statistical evaluation of the results from the clinical studies would need to be addressed and furthermore, the high exposure for the active metabolite tepoxalin pyrazole acid after repeated administration as indicated by a pharmacokinetic study should be commented on before a conclusion on efficacy and safety at the proposed dose can be drawn.

5. BENEFIT-RISK ASSESSMENT

Benefit

The potential benefit of Zubrin oral suspension is reduction of pain and inflammation in dogs with musculoskeletal disorders in a formulation that would allow exact dosing. However, the data presented in the current application did not provide support for a conclusion on these proposed effects.

Risk

The safety data indicate a similar or worse safety profile for Zubrin oral suspension as compared to meloxicam. In addition to the previously known impact on the gastrointestinal tract and the pancreas, unexpected mortality cases occurred in animals treated with Zubrin oral suspension, which may indicate a different safety profile for this formulation as compared to the previously approved lyophilisate. The very high inter-individual variability in pharmacokinetics increases the risk for adverse reactions Zubrin oral suspension.

Benefit-risk balance

The data presented regarding pharmacokinetics, efficacy and tolerance indicate that the potential benefits of this product do not outbalance the potential risks and thus the benefit/risk balance appears negative. However, deficiencies in the data presented, as detailed in the List of Questions preclude a final conclusion on this issue.

6. OVERALL CONCLUSIONS

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP at Day 120 of the procedure considered that the extension application for Zubrin oral suspension was not approvable since major objections had been identified, which precluded a recommendation for marketing authorisation. The details of these major objections were provided in a List of Questions. (Major objections are critical points requiring resolution before recommendation for a marketing authorisation.)