7 February 2018
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

Withdrawal assessment report for Zydax (EMEA/V/C/004375/0000)

Common name: glucuronoxylan sulfate sodium (pentosan polysulfate sodium)

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Introduction

The applicant Parnell Technologies (UK) Limited submitted on 26 February 2016 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Zydax, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004 (optional scope).

The active substance of Zydax is glucuronoxylan sulfate sodium (GXS), a semisynthetic polysaccharide with a sulfated linear xylan backbone. The compound is a member of the pentosan polysulfate sodium (PPS) family. PPS has anti-inflammatory and antiphlogistic properties and acts by modification of the intraarticular proteoglycans.

The eligibility to the centralised procedure was agreed upon by the CVMP in June 2011 (and re-confirmed in January 2016) as the Committee considered that Zydax contains a new active substance, glucuronoxylan sulfate sodium (GXS), which was not authorised as a veterinary medicinal product in the Union on the date of entry into force of Regulation (EC) No 726/2004. This decision was based on the justification provided by the applicant that there are structural differences, as well as a different mode of action resulting in a different safety and efficacy profile compared to the glycan ester compound pentosan polysulfate sodium (PPS), which is already authorised as a veterinary medicinal product in the EU. However, on the basis of the data provided and the assessment by the CVMP, the Committee later considered that there are no significant chemical differences between the two substances, and that no data have been provided confirming that GXS exerts a different mode of action to PPS.

Zydax is a solution for subcutaneous injection, which is presented in a glass vial (20 ml), containing 100 mg/ml glucuronoxylan sulfate sodium. The applicant applied for the following indication: "For the treatment of lameness, pain and mobility impairment of osteoarthritis (non-infectious arthrosis) and related musculoskeletal disorders by therapeutic activity on the underlying pathological processes (disease modifying osteoarthritis drug) in dogs."

The applicant is registered as an SME pursuant to the definition set out in Commission Recommendation 2003/361/EC.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC – full application.

On 7 February 2018, Parnell withdrew the application at day 200 of the procedure. In its letter notifying the Agency of the withdrawal of application, the applicant stated that the reason for the withdrawal are commercial reasons, as no further studies would be conducted which would be necessary for completion of the marketing authorisation.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (version May 2017), which fulfils the requirements of Directive 2001/82/EC. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

Complete manufacture of the dosage form, including secondary packaging, takes place outside the EEA. The site has a manufacturing authorisation issued by the competent authority and a valid GMP certificate has been provided.

Batch release was within the EU at a site which holds a manufacturing authorisation issued by the relevant competent authority.

A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU batch release site. The QP declaration is based on an on-site audit by the manufacturing site responsible for batch release which has taken into consideration the GMP certificate provided for the active substance manufacturing site, which was issued by the competent authority following an inspection.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was considered in line with legal requirements.

The GMP status of both the active substance and finished product manufacturing sites has been satisfactorily established and are generally in line with legal requirements. Some of the information provided regarding the site for batch release into the EU remains to be resolved.

Part 2 - Quality

Composition

The finished product is presented as a solution for injection containing 100 mg/ml glucuronoxylan sulfate sodium (GXS) as the active substance and several excipients.

The product is presented in a multi-dose clear glass vial closed with a rubber stopper.

Containers

The primary packaging is a clear glass vial containing 20 ml solution with a rubber stopper and aluminium cap (with plastic flip-off top) in a cardboard carton. The materials comply with the relevant European Pharmacopoeia (Ph. Eur.) and EU requirements. The choice of the container-closure system has been validated by stability data and is adequate for the intended use of the product.

The product is presented in an outer cardboard box containing one vial of 20 ml solution for injection.

Development pharmaceutics

Appropriate data for pharmaceutical development were submitted. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation.

The use of clear glass vials and siliconised stoppers has been justified. The suitability of the container-closure system for Zydax is supported by stability studies of the finished product stored in both the upright and inverted positions.

Method of manufacture

The manufacturing process consists of dissolution of the active substance and the excipients in the solvent followed by a sterilising filtration. The dry heat sterilised glass vials are aseptically filled, stoppered and crimped. In-process controls for each step are described and are considered adequate. The process is considered a non-standard manufacturing process. The use of aseptic manufacturing and sterile filtration has been justified taking into account the thermal instability of the active substance and its aqueous solutions.

The manufacturing process has been validated. From the data provided in the dossier, it can be concluded that the manufacturing process is well controlled and yields a veterinary medicinal product of adequate and consistent quality. The applicant provided a commitment that they would complete the validation of the manufacturing process with two further production scale batches.

Control of starting materials

Active substance

The active substance of Zydax, glucuronoxylan sulfate sodium (GXS), is not described in the European Pharmacopoeia. The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

GXS is a semi-synthetic polysaccharide with a linear xylan backbone which was developed as a non-steroid anti-inflammatory and anti-rheumatic agent for use in veterinary medicine. It has a structure similar to pentosan polysulfate sodium (PPS). Like PPS, GXS is synthesised from a natural source (xylan obtained from beech wood); therefore, its molecular formula and molecular weight can only be expressed in terms of ranges. The applicant initially claimed that it is a new chemical entity, and considered GXS to be in a distinct subset of the broadly defined PPS family, because it differs from PPS by having more fully sulfated oligosaccharides and a more homogeneous molecular weight. However, a significant chemical difference between GXS and PPS was not demonstrated. PPS with a sulfur content of more than 18%, and a sodium sulfate content below 1%, combined with a similar tight relative average molecular weight of 4000–6000 Da is available. Thus, a side-by-side comparison of PPS and two batches of GXS did not justify the classification of GXS being a new active substance. Based on all the data presented, the CVMP considered that GXS would not represent a new active substance as GXS and PPS were not considered to have significantly different chemical and/or biological properties.

The chemical name of GXS is (1-2)-4-O-methyl-α-D-glucurono-poly(1-4)-β-D-xylan sodium sulphate. GXS is a white to off-white hygroscopic powder, which has a solubility of 50% at 25 °C in water. Polymorphism has not been observed; GXS is an amorphous material.

The synthesis and purification of GXS has been described sufficiently. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was

considered satisfactory. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Evidence of structure has been confirmed as well as on prior knowledge about the structure of the starting material, xylan from beech wood. The use of xylan as the active substance starting material is justified.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

The active substance specification includes tests for appearance, clarity and colour of solution, absorbance, identity, pH, assay, impurities, total sulphur, residual solvents, water content, heavy metals, metals, free sulfate and microbial impurities.

Related substances, residual solvents, other organic impurities, elemental impurities, other inorganic impurities and low-molecular-weight impurities are discussed.

There are no differences in the specifications from the ASMF holder and the finished product manufacturer.

The analytical methods used by the active substance and the finished product manufacturer have been sufficiently adequately described and non-compendial methods appropriately validated in accordance with VICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Further information on the primary packaging materials and updated active substance specifications (release and shelf life) were still outstanding and would have had to be provided, including amending the active substance specification to include the determination of heavy metals (Ph. Eur. 2.4.8).

Batch analysis data for three batches of the active substance have been provided from the active substance manufacturer as well as from the finished product manufacturer. The results are within the specifications and consistent from batch to batch.

Stability data on three batches of active substance from the proposed manufacturer stored in packaging which offers less protection from moisture than the intended commercial package have been provided. Data from 24 months storage under long-term, intermediate and accelerated storage conditions are available. Results from stress tests including thermal stress and a photostability study are used to justify the proposed storage conditions.

The parameters tested are the same as in the active substance specification. The analytical methods used were the same as for the active substance specification and were stability indicating.

The stability results justify the proposed retest period of 6 months. The proposed storage conditions are 2 °C to 8 °C in moisture protective packaging.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, however an outstanding issue remained regarding their bioburden limits and inclusion of a limit for such in their specifications. There are no novel excipients used in the finished product formulation.

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

The product does not contain any materials derived from human or animal origin. None of the starting materials used for the active substance or the finished product are risk materials as defined in the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01-Rev.3). The product is therefore out of the scope of the relevant Ph. Eur. monograph and the Note for guidance.

Control tests on the finished product

The specifications proposed at release and at the end of shelf life are mostly appropriate to control the quality of the finished product.

In general, the analytical methods used have been adequately described and appropriately validated in accordance with the VICH guidelines. Two issues are still not fully resolved in relation to the proposed specification and analytical methods.

Batch analysis results are provided for two pilot batches and one industrial scale batch confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

Stability data were provided from a total of 3 batches of the finished product, two pilot batches and one industrial scale batch. The samples were stored under long term conditions for 24 months at 2°C – 8°C and 25 ºC/60% RH, and for up to 12 months under accelerated conditions at 40 ºC/75% RH, according to the VICH guideline GL4. The batches of Zydax are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. The samples were stored in both the upright and inverted positions.

In addition to long term and accelerated stability studies, the influence of freezing conditions and freeze-thaw cycles on the stability of the finished product have also been investigated.

One batch was exposed to light as defined in the VICH guideline GL5 on photostability testing of new veterinary drug substances and medicinal products. The results showed that the product is not sensitive to light.

Based on the available stability data, the proposed shelf life of 2 years, when stored in the refrigerator (2 °C – 8 °C), is acceptable.

The in-use stability of the product was examined in accordance with the CVMP Note for Guidance: In-use stability testing of veterinary medicinal products (EMEA/CVMP/424/01–final). The proposed in-use shelf life of 28 days is considered acceptable. The applicant has committed to confirm the in-use shelf life by in-use stability testing one batch of finished product approaching the end of its shelf life when available.

Overall conclusions on quality

Information on the development, manufacture and control of the active substance and the finished product has been presented. The results of tests carried out could have indicated consistency and uniformity of important product quality characteristics, which could have led to the conclusion that the

product should have a satisfactory and uniform performance in clinical use, provided that remaining outstanding issues had been satisfactorily resolved.

The information on the active substance is provided according to the ASMF procedure and is in general satisfactory. However, some specifications need to be reconsidered and updated release/shelf life specifications would still need to be provided prior to a marketing authorisation being granted.

An issue on the bioburden limits of the excipients remained to be resolved.

The finished product specification includes the relevant quality attributes. However, updated release/shelf life specifications still remain to be provided in order to fully address some outstanding concerns. Most of the control methods are described and appropriately validated. Two issues are still not fully resolved in relation to the analytical methods for clarity and colour of solution and identity test for sodium metabisulfite.

The product does not contain any materials derived from human or animal origin.

Stability studies on the finished product are performed under VICH conditions. The shelf life of 24 months at 2 °C – 8 °C is justified. The claimed in-use shelf life of 28 days has been justified, although confirmation of its applicability to product at the end of its shelf life would ultimately have been needed to be provided.

The following information would have been recommended (to be provided post-authorisation):

1. Completion of the validation of the manufacturing process with data from two further production scale batches.
2. The applicant should review and aim to decrease in the limit for water in the shelf life specification for the active substance GXS when stability results in the proposed packaging material are available.
3. Confirmation of the in-use shelf life of the product with data from in-use stability testing of one batch of finished product approaching the end of its shelf life.

In general, the dossier takes into account current rules and guidelines. However, several outstanding quality issues remained that would have needed to be resolved prior to a marketing authorisation being granted, including some remaining concerns on the applicant's part of the ASMF.

Part 3 – Safety

The active substance of Zydax is glucuronoxylan sulfate sodium (GXS), a semisynthetic polysaccharide with a sulfated linear xylan backbone. The compound is a member of the pentosan polysulfate sodium (PPS) family.

A range of *in vitro* and *in vivo* toxicity studies using either glucuronoxylan sulfate sodium (GXS) as active substance (alone or in the final formulation) or pentosan polysulfate sodium (PPS) have been provided. Since no significant chemical or biological differences have been demonstrated between GXS and PPS, it was accepted that data from PPS could be extrapolated to support the safety of the application.

Pharmacodynamics

GXS is a semisynthetic polysaccharide and a member of the PPS family, which has anti-inflammatory and antiphlogistic properties and acts by modifications to the intraarticular proteoglycans (see Part 4).

Pharmacokinetics

See Part 4.

Toxicological studies

The GXS final formulation used in the toxicity studies was a laboratory-scale batch of a higher strength, Zydax 250 mg/ml solution for injection. Zydax 250 mg/ml was selected for use in the toxicity studies as it provides for a worst-case when compared with the proposed Zydax 100 mg/ml strength, given that the active ingredient is included at a concentration of 250 mg GXS/ml, i.e. 2.5 times that of Zydax 100 mg/ml. Zydax 250 mg/ml additionally contains a higher concentration of the buffering salts.

Single dose toxicity

Acute toxicity studies of Zydax 250 mg/ml were carried out in Sprague Dawley rats by dermal route. The study was compliant with GLP and OECD guideline for acute toxicity test (No 402). After dermal exposure, the acute toxicity of GXS was low as no apparent toxicity was observed at up to 500 mg/kg bw.

When GXS was administered subcutaneously by once daily injection for three consecutive days in mice, a dose of 180 mg/kg bw was associated with significant morbidity.

Repeat dose toxicity

In repeat dose studies in mice and rats conducted by oral route with PPS administered 5 days per week for 14 weeks, a minimal decrease of erythrocytes and increased leukocyte and platelet count were observed that may have been secondarily related to the inflammatory lesions observed in various tissues. Histiocytic cellular infiltration and chronic active inflammation of the rectum were observed in both species with ulcers seen in rats. Vacuolated histiocytes were seen in various tissues, which were identified as lysosomal structures that exhibited a variety of contents. In rats, NOEL for rectal lesions was 63 mg/kg bw/day in males; a NOEL was not determined for females because rectal lesions were observed in all dosed groups of females. In mice, the NOEL was determined to be 63 and 125 mg/kg bw/day in males and females, respectively.

No repeat-dose toxicity studies in laboratory animals were conducted with GXS, which is acceptable since these are not requested if data in the target species are available.

Tolerance in the target species of animal

See Part 4.

Reproductive toxicity

Study of the effect on reproduction

The potential reproductive toxicity of PPS was evaluated in Sprague-Dawley rats using the Reproductive Assessment by Continuous Breeding protocol (U.S. National toxicology program, 1997). A reproductive toxicity study conducted by oral route demonstrated that there was no effect of PPS on any of the reproductive endpoints in either generation at dose levels up to 1000 mg/kg bw/day.

Study of developmental toxicity

No studies of developmental toxicity have been provided.

According to the product monograph for a human medicinal product containing PPS as active substance, no teratogenic effects were observed in rats, when PPS was administered intramuscular or intraperitoneal at doses up to five-fold of the recommended human oral dose. In mice and rabbits, no teratogenicity was seen, when PPS was subcutaneously given at twofold and fourfold of the recommended oral human dose, respectively. No adverse effects on peri- and postnatal development in the offspring of rats exposed to parenteral PPS was observed.

Genotoxicity

The genetic toxicology potential of GXS was evaluated in a standard test battery in accordance with VICH guideline GL23.

In the Ames test, GXS was negative for induction of reverse mutations in the five tested strains of *Salmonella typhimurium* in the presence and absence of metabolic activation.

GXS induced no statistically significant increase in chromosomal aberrations in the Chinese Hamster Ovary cell line (CHO-KI) at doses up to 5.0 mg/ml in presence of a rat liver metabolic activation system. Treatment was also not associated with cytotoxicity in this mutagenicity test.

In an *in vivo* micronucleus test, the proportion of micronucleated polychromatic erythrocytes (MNPCEs) among the total polychromatic erythrocytes (PCEs) cells was not increased in mice treated on three consecutive days with subcutaneous doses of 18, 57, and 180 mg GXS/kg bw/day.

Based on the above studies, it is concluded that GXS is not genotoxic.

Carcinogenicity

No carcinogenicity data have been provided. This is considered acceptable due to the lack of genotoxic potential, the lack of structural alerts, and the lack of findings relevant to neoplastic lesions in the target animal safety study. However, the World Health Organisation International Agency for Research on Cancer (IARC) evaluated PPS and concluded (IARC Monograph for PPS (2015), Vol. 108) that there was sufficient evidence for the carcinogenicity of PPS in experimental animals (mice), and classified PPS as possibly carcinogenic to humans (Group 2B). It is noted that the genotoxicity studies conducted with both PPS and GXS were negative and PPS was not carcinogenic in the species rat. Therefore, the positive findings in the mouse study are considered of minor relevance, and it can be assumed that PPS/GXS at the proposed therapeutic dose is not carcinogenic.

Studies of other effects

Dermal irritation potential of Zydax 250 mg/ml was evaluated in an *in vivo* study in New Zealand White rabbits. The substance was found to be non-irritant.

Eye irritation potential of Zydax 250 mg/ml was evaluated in rabbits. The substance was found to be slightly eye-irritant.

In a local lymph node assay in mice, Zydax 250 mg/ml tested at concentrations up to 50% in propylene glycol did not show any skin sensitisation potential.

Excipients

No special information on the excipients was given. This is acceptable, since all excipients are well-known and widely used in veterinary medicinal products. Furthermore, their acute dermal toxic potential and the potential to induce eye/ dermal irritation and skin sensitisation were included in the studies performed with Zydax 250 mg/ml.

User safety

The applicant has presented a user safety risk assessment (URA), which has been conducted in accordance with the CVMP Guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1).

The anticipated users are skilled veterinary professionals (veterinarian or trained veterinary staff). Other users, including children, are not expected to be exposed to the product and were therefore not specifically addressed in the user risk assessment. The main potential routes of accidental contact with the product are those of dermal and/or parenteral exposure as a single acute event. Acute toxicity studies with the product have shown that there is no potential of dermal irritation or skin sensitisation. Nevertheless, due to the presence of some of the excipients in the product, which are known to be a sensitizer in humans already at lower concentrations, the following warning phrase should be included in the SPC: “People with known hypersensitivity to the active substance or any of the excipients should avoid contact with the veterinary medicinal product”.

Systemic effects after dermal contact are not expected, and dermal acute toxicity is considered to be low according to the data submitted. The product’s potential to be irritating to the eye is reflected in suitable warning phrases.

GXS/PPS did not show adverse effects on reproduction in rats and no teratogenic effects or adverse effects in peri- and post-natal development of the offspring in rats, mice and rabbits.

Since there are no toxicological NOELs derived for GXS, the applicant compared the estimated dermal and parenteral exposure of 0.05 and 0.1 ml/person, respectively (i.e. 0.08 and 0.17 mg/kg bw, respectively) with the 1x intended dose GXS/kg bodyweight derived from the target animal safety (TAS) study, which is generally supported. However, this dose is considered not a NOEL, but a LOEL due to its anticoagulation effect. Consequently, an additional uncertainty factor of 2 should be applied for the risk characterisation, and the margins of exposure (MOE) are therefore lower than those proposed by the applicant (i.e. 18 for dermal and 9 for subcutaneous exposure, respectively). Although these MOEs are far away from 100, the risk can be accepted, since it is minimized by suitable warning phrases. In addition, the product is a prescription-only medicine and will be administered by veterinary surgeons or veterinary staff, who are proficient in the safe handling, use and disposal of the product.

No data on toxicity of excipients have been provided in the URA. However, the lack of the data is considered acceptable, since the excipients are well-known and some toxicity studies were performed with the product (acute dermal toxicity study and studies on eye/ dermal and skin sensitisation).

As a result of the user safety assessment the following advice to users/warnings for the user are considered appropriate:

- Care should be taken to avoid accidental self-injection. In case of self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

- The product can cause skin and eye irritation. Handle this product with care to avoid exposure. In the case of contact with skin, wash with soap and water. In case of accidental eye exposure, flush the eyes with plenty of water. If irritation persists seek medical advice.
- People with known hypersensitivity to the active substance or any of excipients should avoid contact with the veterinary medicinal product. If you develop symptoms following accidental exposure, such as a skin rash, you should seek medical advice and show the package leaflet or the label to the physician. Swelling of the face, lips or eyes or difficulty in breathing are more serious symptoms and require urgent medical attention.
- Wash hands after use.

Based on the above risk assessment the CVMP concluded that the product does not pose an unacceptable risk to the user. However, user safety warnings in the SPC are currently not considered sufficient and further information needs to be added.

Environmental risk assessment

A Phase I environmental risk assessment was provided in line with VICH Phase I guideline (CVMP/VICH/592/98-FINAL) and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005).

The environmental risk assessment can stop in Phase I, and no Phase II assessment is required because the product is for the individual treatment of non-food animals (dogs) only.

Zydax is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

Data from the provided dermal acute toxicity study show that no deaths and no apparent toxicity could be observed following a dermal dose of 500 mg GXS/kg bw (2 ml/kg Zydax 250 mg/ml), indicating low dermal toxicity. When GXS was administered subcutaneously by once daily injection in mice, a dose of 180 mg/kg bw was associated with significant morbidity.

Studies investigating repeat-dose toxicity of PPS showed NOELs for rectal lesions of 63 mg/kg bw/day in male rates; and 63 and 125 mg/kg bw/day in male and female mice, respectively. No repeat-dose toxicity studies in laboratory animals were conducted with GXS, which is acceptable since these are not requested if data in the target species are available.

No developmental toxicity study with GXS was conducted. In the absence of such studies the use of the product is contraindicated for pregnant and lactating animals.

GXS is not genotoxic. Carcinogenicity studies with GXS have not been performed and are not requested. However, the World Health Organisation International Agency for Research on Cancer (IARC) classified PPS as possibly carcinogenic to humans (Group 2B). It is noted that the genotoxicity studies conducted with both PPS and GXS were negative and PPS was not carcinogenic in the species rat. Therefore, the positive findings in the mouse study are considered of minor relevance, and it can be assumed that at proposed therapeutic dose and the dose that the user may be exposed to PPS/GXS is not carcinogenic.

In rabbits, GXS (Zydax 250 mg/ml dermal) was found to be non-irritant to skin and slightly eye-irritant.

In a local lymph node assay in mice, GXS (Zydax 250 mg/ml) tested at concentrations up to 50% did not show any skin sensitisation potential.

The data presented are considered adequate to characterise the toxicity profile of the active substance.

A user safety assessment in line with the relevant guidance document has been presented. Based on that assessment, the potential health risk of the product to all users (veterinarian and veterinary staff) is considered low and acceptable. However, user safety warnings in the SPC are currently not considered as sufficient and further information needs to be added.

An appropriate environmental risk assessment was provided. The product is not expected to pose a risk for the environment when used according to the SPC.

Part 4 – Efficacy

Glucuronoxylan sulfate sodium (GXS) is a member of the pentosan polysulfate sodium (PPS) family. The compound is a semi-synthetic polysaccharide with a sulfated linear xylan backbone. A significant chemical difference between GXS and PPS has not been demonstrated (see quality part). The applicant initially claimed relevant differences of biological effects between GXS and PPS but these could not be verified by data. Consequently, as there were no significant differences between GXS and PPS, the CVMP agreed that extrapolations of agreed pharmacological properties from PPS to GXS could be accepted in support of the dossier.

Pharmacodynamics

The pharmacodynamics of PPS has been reviewed, based on published papers. A range of pharmacological activities have been demonstrated for PPS that are relevant to metabolic pathways implicated in the pathobiology of osteoarthritis (OA), such as

i. supporting chondrocyte anabolic activities, including biosynthesis of aggrecan and downregulating or inhibiting proteinases responsible for matrix catabolism,

ii. reducing synovial inflammation, complement activity, and release of pro-inflammatory mediators,

iii. cytoprotection of synoviocytes and normalisation of their ability to synthesize high-molecular-weight hyaluronan, and

iv. improving blood flow in synovium and subchondral bone by stimulating release of tissue plasminogen activator, superoxide dismutase, and lipase from capillary endothelium.

Two *in vitro* studies were conducted to investigate pharmacological activities of GXS. However, the first test system was not sufficiently validated and therefore the results were not robust enough to allow for firm conclusions. In the second study, GXS did not significantly affect the relevant activity in a canine co-culture model of osteoarthritis, except for a certain influence on proteoglycan content that was observed for GXS at higher doses.

Because a significant difference between GXS and PPS has not been demonstrated, similar pharmacodynamic properties must be assumed for GXS and PPS. Thus, the SPC would still have to be amended and general information on pharmacodynamic properties of PPS added prior to a marketing authorisation being granted.

In two published papers, secondary pharmacodynamic effects of PPS such as increase of the capillary blood flow and profound effects on blood coagulation, fibrinolytic, and lipid/cholesterol systems were

described. In addition, the target animal safety study conducted with GXS in dogs showed that the most striking secondary pharmacodynamics effects found for GXS were increased plasma activated partial thromboplastin time (aPTT) values.

To demonstrate potential drug interactions, a study in dogs investigating the safety of GXS when administered in conjunction with the NSAID carprofen was provided. The study was uncontrolled and of explorative character only and thus did not allow for firm conclusions on adverse reactions/interactions. However, a transient increase in aPTT was noted, which was attributed to GXS (rather than to carprofen).

Pharmacokinetics

A GCP-compliant pharmacokinetic study was provided to investigate the pharmacokinetics of GXS in dogs following a single subcutaneous dose of 1 x the recommended treatment dose (RTD), 3 x RTD, and 5 x RTD. In addition, the plasma activated partial thromboplastin time (aPTT) as an alternate indicator of dose proportionality was examined. However, due to major shortcomings, the study was only considered supportive; nevertheless, dose proportionality of GXS was demonstrated for the parameter C_{max}, and a dose-dependent effect was found for aPTT, which could lead to a safety concern at higher GXS doses.

No information was provided for PPS kinetics in the target species dog. However, information on pharmacokinetics of PPS was provided for different species based on published articles, showing that bioavailability of PPS when used by the oral route was lower compared to the subcutaneous route.

In response to questions by the CVMP, a GLP compliant, randomized, parallel designed pharmacokinetic study was provided to determine the plasma pharmacokinetics of total radioactivity following a single subcutaneous dose of [^{3}H]GXS at three dose levels of GXS to Beagle dogs. In this study, shortcomings with regard to the detection method and the study design were observed.

In conclusion, no adequate product-related pharmacokinetic data for GXS were provided that could be included in the SPC, or used for dose finding purposes, and this remains an outstanding issue.

Dose justification

The proposed dose of Zydax was extrapolated from the approved dosage of a PPS containing product (Cartrophen Vet; Biopharm Australia) authorised in the UK (and Australia and New Zealand) for the treatment of lameness and pain of degenerative joint disease/osteoarthrosis in dogs. Considering that no significant chemical or biological difference has been demonstrated between GXS and PPS, this approach could, in principle, be accepted.

However, the applicant initially also claimed that there are "differences of biological effects between GXS and PPS". Whilst such differences have not been specified and supported by appropriate data, slight differences in the active substance specifications between GXS and PPS might potentially impact on the biological activity. Thus, dose equivalency between GXS and PPS could not be assumed and, therefore, more robust data were deemed necessary to support dose justification.

In response to questions by the CVMP, the applicant submitted a new bioequivalence study intended to demonstrate that extrapolation of data from PPS to GXS is possible to further support the dose equivalence between GXS and PPS. A GLP compliant bioequivalence study was submitted to determine the plasma pharmacokinetics of total radioactivity following a single subcutaneous dose of [^{3}H]PPS or [^{3}H]GXS and to compare the extent of bioequivalence of [^{3}H]PPS and [^{3}H]GXS in Beagle dogs. However, due to methodological and statistical shortcomings in the study design, the study could not

be interpreted. The CVMP noted the shortcomings in the study, but also considered that a bioequivalence study would not be a suitable way to clarify specific differences in biological effects.

However, the applicant did not pursue their claim any longer that GXS and PPS would have significantly different biological effects. In the agreed absence of significant differences in the chemical and biological properties of GXS and PPS, the CVMP therefore agreed, in principle, to the applicant's approach to extrapolate a proposal for a dose for Zydax from a dose already authorised for other PPS-containing veterinary medicinal products for dogs. However, the proposed dose for Zydax would need to be confirmed by clinical studies; but appropriate studies (dose confirmation/field studies) have not been provided.

Dose determination / finding studies

No dose determination study has been provided for Zydax.

Target animal tolerance

One target animal safety study according to the relevant guideline VICH 43 was provided. Additionally, some target animal safety information could be gained from the pharmacokinetics study and a small interaction study with the NSAID carprofen, as well as from literature references on PPS. In addition, one pivotal and one pilot clinical efficacy study were provided to investigate target animal safety of the product in the field.

The pivotal GLP-compliant target animal safety study was performed according to the relevant guideline VICH 43. Zydax was administered as a single subcutaneous injection at 0, 1, 3, and 5x the recommended therapeutic dose (RTD) for a period of 26 weeks (6 months), once weekly, to 32 healthy young Beagle dogs randomly allocated to four treatment groups of 4 males/4 females each. Dogs were housed in single pens; but daily socialization per treatment group was provided.

Zydax was clinically well-tolerated in doses of up to 5x RTD. Clinical adverse events, e.g. vomitus and diarrhoea were rare and usually mild and occurred in all groups. The occurrence of alopecia and erythema was slightly increased in treated dogs compared to the placebo group, but these reactions were usually mild, resolved before the end of the study and in most cases attributed to the long period of housing under laboratory conditions. Gross and histopathology data did not reveal any changes attributable to Zydax.

However, following treatment with Zydax, plasma activated partial thromboplastin time (aPTT) increased in a dose-dependent manner. With respect to aPTT, no margin of safety could be derived with regard to subgroups of dogs with an increased risk of bleeding (see below). Increased aPTT is a sign of a considerable decrease in one or several blood coagulation factors of the so-called intrinsic and the common system.

Increased aPTT was also noted in the pharmacokinetic study and in the pivotal field study (in the PK study also in a dose-dependent manner). In literature provided by the applicant, similar effects were reported in dogs and other species following treatment with PPS. Also, in an analysis of adverse reactions reported following the use of PPS in dogs, severe haemorrhages, including fatal events, occurred in dogs. It is acknowledged that these events could not reliably be linked to the use of PPS, but a treatment relation appears at least possible.

In the target animal safety study, secondary bleeding from the injection site and injection site swelling could also be indicative for this anticoagulative effect. However, none of the studies revealed clinical adverse events related to an anticoagulative effect of Zydax. A possible explanation is that an

increased bleeding tendency for a limited period of time might not lead to any haemorrhage in young, healthy dogs, which were enroled in the target animals safety study. In the clinical field study, subtle effects may have been overlooked and/or the number of dogs treated may still have been too small to include sensitive subgroups at risk.

Although no spontaneous haemorrhagic events were noted in any of the preclinical and clinical studies provided, the administration of Zydax bears the risk of haemorrhagic events in a sensitive subgroup of patients, in particular in dogs with underlying conditions which may start bleeding, e.g. gastrointestinal ulcers, highly vascularized abdominal tumours, teleangiectasis. This also includes dogs at risk of traumatic events (e.g. by contact to other dogs, or a high level of activity).

Furthermore, pain on injection, which was noted as a dose-dependent (volume-independent) reaction in the target animal safety study, an increase in lymphocyte counts apparent in the target animal safety study and lameness and stiffness, which occur in a notably higher frequency in treated compared to control dogs, are not yet adequately addressed in the product literature.

In the pilot and the pivotal field efficacy study, Zydax was relatively well tolerated in dogs. However, in addition to mild pain reactions and mild swellings following s.c. injection of the test product, adverse effects known from PPS (such as vomitus, inappetence, anorexia and lethargy) were observed more frequently in dogs from the test group than in control dogs. The frequency and seriousness of these effects should be included in the product literature.

Clinical field trials

The efficacy of Zydax in canine osteoarthritis in comparison to placebo has been examined in three multi-centre, prospective, randomized, masked field studies in several veterinary clinics in the USA and Australia.

In a pilot field efficacy study, Zydax was examined in canine osteoarthritis (OA) in comparison to placebo in a large number of dogs in 9 veterinary clinics in USA using a multi-centre, prospective, randomized, masked, superiority design. Male and female dogs were enrolled, mostly neutered, 11 months - 20 years old, with a history, clinical signs and radiographic evidence of OA, and Pain Severity Scores (PSS) and Pain Interference Scores (PIS). However, the study was discontinued early, following an interim analysis in 75 dogs as the placebo success rate was found to be unexpectedly high. Zydax was generally well tolerated in dogs in this study (see “target animal tolerance”). The study author agreed that the efficacy of Zydax in canine osteoarthritis had not been demonstrated in this pilot study, possibly because of the incorrect use of the questionnaire by the dog owners.

In a GCP-compliant field efficacy study, Zydax has been examined in canine osteoarthritis (OA) in comparison to placebo in 29 veterinary clinics in USA and Australia using a multi-centre, prospective, randomized, masked, superiority design. The study enrolled male and female dogs, non-pregnant, non-lactating, mostly neutered, 1-16 years old, with a history, clinical signs and radiographic evidence of OA. The dogs were treated with Zydax or with placebo.

The primary endpoints were the frequency of lameness assessed by veterinarians (1), and the treatment success based on the animal owner's AIS assessment (2). Secondary endpoints were (1) a descriptive analysis of the owner assessment of total pain severity scores (PSS) and activity impairment scores (AIS) at multiple time points, and (2) a descriptive analysis of scored outcomes of the veterinary pain assessment by frequency at each time point for each treatment.

Statistical analysis: Following an interim analysis planned solely for sample size re-estimation the applicant changed the success definition and the statistical method. Such procedures are considered

not compliant with the statistics guideline and, thus, invalidate the study as a pivotal one.

Efficacy: Apart from obvious deficits in the general statistical design (see above), the primary efficacy variable “treatment success” (AIS assessment by the dog owner) did not show any significant improvement.

In response to questions raised by the CVMP, the applicant provided a second GCP-compliant field efficacy study. In this study Zydax has been examined in canine osteoarthritis (OA) in comparison to placebo in 32 veterinary clinics in USA and Australia using a multi-center, prospective, randomized, masked, superiority design. The study enrolled male and female dogs, non-pregnant, non-lactating, mostly neutered, 1-18 years old, with a history, clinical signs and radiographic evidence of OA. The dogs were treated with Zydax or with placebo. As discussed following, this field study had major shortcomings which preclude any valid conclusions on efficacy and safety of the test product.

The primary endpoint was the treatment success using Activity Impairment Score (AIS) which was assessed solely by the dog owners. No veterinary lameness assessment was performed and this remains an outstanding requirement for registration. Based on owners' assessment, treatment success rates for the primary efficacy parameter were considered by the applicant as statistically significant. However, this conclusion was not shared by the CVMP. The study protocol states that an interim analysis was planned. The plan to perform interim analyses necessitates an adjustment for type I error inflation. Thus, the study was considered inadequate for registration purposes.

Zydax was well tolerated and no treatment-related serious adverse effects were observed (please see section “target animal tolerance” above).

Conclusion

Overall, the efficacy of Zydax in the claimed indications has not been demonstrated (Outstanding issue).

Overall conclusion on efficacy

Pharmacodynamics:

Glucuronoxylan sulfate sodium (GXS) is a member of the pentosan polysulfate sodium (PPS) family. The compound is a semisynthetic polysaccharide with a sulfated linear xylan backbone. A significant chemical difference between GXS and PPS has not been demonstrated (see quality part), therefore general pharmacodynamic properties of PPS can be extrapolated to GXS. Relevant differences of biological effects between GXS and PPS were initially also claimed by the applicant, but later in the procedure not further pursued.

For PPS, a range of pharmacological activities relevant to metabolic pathways implicated in the pathobiology of osteoarthritis (OA) have been demonstrated, and thus, PPS has been described as a disease modifying osteoarthritis drug (DMOAD).

For GXS, only two *in vitro* studies with limited significance were conducted to investigate pharmacological activities. Results of these studies are not robust enough to justify sufficiently the inclusion of specific pharmacodynamic effects of GXS as proposed by the applicant. Merely, a beneficial effect of GXS on the tissue proteoglycan content in concentrations above 1 µg/ml in an *in vitro* canine co-culture model of osteoarthritis has been demonstrated.

Similar pharmacodynamic properties are assumed for GXS and PPS and general information on pharmacodynamic properties of PPS should be added in the SPC accordingly.

Secondary pharmacodynamic effects described for PPS are increase of the capillary blood flow and profound effects on blood coagulation, fibrinolytic, and lipid/cholesterol systems. In a target animal safety study and in a study on potential drug interactions, a transient increase in plasma activated partial thromboplastin time (aPTT) was the most striking secondary pharmacodynamic effect observed for GXS. In addition, in a pharmacokinetic study, a dose dependent effect of GXS was shown for aPTT.

Pharmacokinetics:

Only sparse information on the pharmacokinetic profile of PPS is available from literature. A pharmacokinetic study conducted to evaluate the pharmacokinetics and dose proportionality of GXS showed major shortcomings regarding the validity of the analytical method used for GXS determinations. Thus, PK values could not be reliably determined. With regard to the bioavailability of GXS, a relation to the dose can therefore not be ascertained. Thus, and although the study was not provided to justify the dose regimen of Zydax, resulting data are not supportive to establish an effective dose regimen. However, a dose-dependent effect was found for aPTT, which could lead to a safety concern at higher GXS doses.

A further pharmacokinetic study was provided to determine the plasma pharmacokinetics of total radioactivity following administration to Beagle dogs. However, absolute values determined for T_{max}, C_{max}, AUC and half-lives were not reliable due to shortcomings with regard to the detection method and the study design.

In conclusion, no adequate product-related pharmacokinetic data for GXS were provided that could be included in the SPC and this remains an outstanding issue.

Dose determination/justification:

No dose determination and dose confirmation studies for GXS have been provided.
The proposed dose was derived by extrapolation from the approved dose of a PPS containing product for use in dogs. In the absence of significant differences in the chemical and biological properties of GXS and PPS, the CVMP, in principle, agreed to this approach; however, the proposed dose for Zydax would need to be confirmed by clinical data, but appropriate studies (dose confirmation/field studies) have not been provided.

Tolerance:

In a target animal safety study, Zydax was clinically well tolerated at doses up to 5x the recommended dose when given weekly for 26 consecutive weeks. Clinical adverse events, e.g. alopecia/erythema, vomitus and diarrhoea were incidental and usually mild and transient. Gross and histopathology data did not reveal any changes attributable to Zydax.

Zydax proved to exert a distinct anticoagulant effect as indicated by an increase in aPTT in a dose-dependent manner; with respect to this parameter no margin of safety can be derived. In consequence, although no spontaneous haemorrhagic events were noted in any of the studies provided, it is possible that the administration of Zydax bears the risk of haemorrhagic events in a sensitive subgroup of patients including dogs with underlying conditions which may start bleeding, e.g. gastrointestinal ulcers, highly vascularized abdominal tumours, teleangiectasis. This also includes dogs at risk of traumatic events (e.g. by contact to other dogs, or a high level of activity). The anticoagulant effect of Zydax is a major concern, and current information in the SPC including contraindications, precautionary warnings, etc needs further amendment.

In the field efficacy studies, Zydax was generally well tolerated in dogs. Adverse effects recorded included injection site reactions, anorexia, lethargy, diarrhoea and vocalization. In addition, a range of

musculoskeletal events such as lameness and muscle stiffness were observed in 11.2% of the treated dogs. Information on these adverse effects in the product literature needs to be completed (outstanding issue).

Efficacy:

The results from three clinical field trials (a pilot study and two field trials) do not support the claimed indication “for the treatment of lameness, pain and mobility impairment of osteoarthritis (non-infectious arthrosis) and related musculoskeletal disorders” in dogs at the proposed dose.

Part 5 – Benefit-risk assessment

Introduction

Zydax is a solution for subcutaneous injection for dogs, containing as the active substance 100 mg/ml glucuronoxylan sulfate sodium. The product is presented in one pack size, a clear, multi-dose 20 ml glass vial.

The active substance, glucuronoxylan sulfate sodium (GXS), is a semisynthetic polysaccharide belonging to the pentosan polysulfate sodium (PPS) family. PPS has anti-inflammatory and antiphlogistic properties and acts by modifying the underlying mechanism of osteoarthritis. Based on the data presented, there is no significant chemical difference between GXS and PPS, although the applicant initially considered that there are "relevant differences of biological effects between GXS and PPS".

The applicant applied for the following indication: “For the treatment of lameness, pain and mobility impairment of osteoarthritis (non-infectious arthrosis) and related musculoskeletal disorders by therapeutic activity on the underlying pathological processes (disease modifying osteoarthritis drug) in dogs.”

The application was submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC – full application.

Benefit assessment

Direct therapeutic benefit

The benefit of Zydax would have been its effect in the treatment of lameness, pain and mobility impairment of osteoarthritis (non-infectious arthrosis) and related musculoskeletal disorders in dogs.

The proposed dose was extrapolated from an authorised veterinary medicinal product for dogs containing PPS as active substance; however, the efficacy of this dose for Zydax is not demonstrated by adequate further data.

The clinical efficacy of Zydax in the proposed indication, which was investigated in three field studies, has not been satisfactorily demonstrated.

One pilot field study failed to show efficacy, while one clinical field study did not show any effect in regard to the primary endpoints (efficacy assessment by dog owner and veterinarian). Another clinical field study showed major shortcomings in the study design with regard to the assessment of the primary parameter, and was not considered adequate to support the efficacy.

The CVMP, therefore, considers that, at present, the data provided are inadequate to support an acceptable level of efficacy for the proposed indication at the proposed dose.

Additional benefits

None.

Risk assessment

Quality:

Although the formulation and manufacture of Zydax is well described and the proposed specifications would ensure that product of consistent quality will be produced, the assessment of quality of the product remains incomplete as there are some remaining outstanding issues, which would need to be satisfactorily resolved prior to a marketing authorisation being granted, including some remaining concerns on the applicant's part of the ASMF.

Safety:

Risk for the target animal:

Zydax affects the coagulation parameter aPTT and carries a potentially increased risk for haemorrhagic events in subgroups at risk. In addition, in the pivotal efficacy study, Zydax induced lameness and muscle stiffness in treated dogs at a notably higher rate than in controls. Administration of Zydax also resulted in mild swelling and erythema at the injection sites. In the absence of developmental toxicity studies, the use of the product is contraindicated for pregnant and lactating animals.

Several sections in the product information will still need amendments to address specific aspects in regard to the target animal safety.

Risk for the user:

The CVMP concluded that user safety for this product could be acceptable when the product is used according to the SPC recommendations, which would still need to be amended.

Risk for the environment:

Zydax is not expected to pose a risk to the environment when used according to the SPC recommendations.

Risk management or mitigation measures

User safety risks have been identified, mainly concerning the risks associated with accidental exposure. These risks are currently not adequately addressed in the SPC, and further information needs to be added to ensure safe use of the product.

Risk mitigation measures included in the SPC are currently not considered to be sufficient, and further information needs to be added to inform on the potential risks of this product relevant to the target animal, and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

In the presence of outstanding major and other concerns, no conclusions can be taken on the benefit-risk balance.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) considers that the application for Zydax is not approvable at the present time since "major objections" (and other concerns) were identified which preclude a recommendation for marketing authorisation. No conclusions can currently be taken on the benefit-risk balance of the application.