EMA/CVMP/926850/2011
Veterinary Medicines and Product Data Management

Withdrawal assessment report for

Oxapex (EMEA/V/C/002342)

CVMP Assessment report with all confidential information removed.
Withdrawal at day 180

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Introduction

An application for the granting of a community marketing authorisation for Oxapex was submitted to the Agency on 28 September 2010 by New A Innovation Limited B.V. in accordance with Regulation (EC) No. 726/2004. Oxapex contains modified and stabilised haemoglobin and is presented in infusion bags of 100 ml. It was indicated to provide immediate oxygen-carrying support improving the clinical signs of anaemia in dogs for at least 24 hours, independent of the underlying condition. The route of administration is intravenous use. The target species is dogs.

Oxapex was classified as a Minor Use Minor Species (MUMS)/Limited markets product. Reduced data requirements in accordance with CVMP guidelines therefore apply.

Scientific advice was sought by New A Innovation Ltd for Oxapex on 9 December 2009. In March 2010, the CVMP provided Scientific Advice in response to 14 specific questions relating to data requirements for quality, safety and efficacy.

The application was validated on 12 October 2010 and the assessment was carried out by the CVMP in line with its normal timetable. In response to questions, supplementary information was provided by the applicant on 14 October 2011, and oral and written explanations were given by the applicant on 8 March 2012. At Day 180 of the procedure, the CVMP considered on the basis of quality, safety and efficacy data submitted, that the product was not approvable, since major objections had been identified, which precluded a recommendation for marketing authorisation. The concerns were mainly in relation to the efficacy of the product.

On 13 March 2012, New A Innovation Limited B.V. withdrew the application at day 180 of the procedure. In its letter notifying the Agency of the withdrawal of application, the company stated the reason for the withdrawal: CVMP considered that the data provided do not allow the Committee to conclude on a positive benefit-risk balance.

Part 1 - Administrative particulars

The applicant has provided a detailed description of the pharmacovigilance system. Based on the information provided, it is accepted that the applicant has a pharmacovigilance system in place that will allow it to comply with its legal requirements relating to pharmacovigilance.

Manufacturing authorisations and inspection status

The manufacturing authorisation for the manufacturer of the finished product was provided.

Scientific Advice

Scientific advice was sought by New A Innovation Ltd for Oxapex on 9 December 2009. In March 2010, the CVMP provided Scientific Advice in response to questions relating to data requirements for quality, safety and efficacy. CVMP accepted that the advice was in general followed by the applicant.

Part 2 - Quality

Composition

Oxapex is an injectable solution for intravenous infusion of modified and stabilised haemoglobin. All excipients are to European Pharmacopoeia (Ph. Eur.) standard.

Container

The formulated and stabilised haemoglobin solution is filled aseptically into gamma irradiated sterile IV bags (100 ml per bag). The overwrap film is used to provide a gas barrier and light protection for the IV bag. The Polyvinyl alcohol (PVA) components meet Ph. Eur. requirements and are considered suitable packaging for infusion purposes.

Development pharmaceutics

Modified and stabilised haemoglobin is the active ingredient of Oxapex and is controlled according to in-house specifications. The haemoglobin is isolated from red blood cells (RBCs) and purified by diafiltration, centrifugation and ultra-purification techniques. Ringer's acetate solution is added to the stabilised haemoglobin to maintain isotonic and isosmotic properties.

Method of manufacture

Manufacture of the finished product takes place in New A Innovation Ltd, Hong Kong. All tests performed in process are well described and validated.

Control of starting materials

Active substance

The active substance is modified and stabilised haemoglobin and is controlled by suitable standards. The manufacture of the active substance is divided into two stages. Manufacture of the starting material purified haemoglobin solution (PHS) from blood and manufacture of active substance from PHS by New A Innovation Ltd, Hong Kong. A process flow diagram was presented for the active substance manufacturing process.

Routine tests for all excipients are to Ph. Eur. standard and Certificates of Analysis were provided.

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

The PHS which is used as starting material for the preparation of the modified and stabilised haemoglobin active substance is extracted from whole blood. Sufficient controls are included in the PHS production process to allow traceability of the blood used to each PHS batch manufactured.

As the intended target species for Oxapex is dogs (which are not considered to be susceptible to TSE) the risk of TSE infection associated with Oxapex is considered to be negligible.

Control tests during production

In-process control tests and acceptance criteria for each step of the manufacturing process were presented. Validation data of the bioburden tests will be addressed during the production of the post authorisation validation batches. The in-process control checks for step four sterile filling (including overfills) and sealing, includes that the weight and sealing integrity are examined. The applicant has provided data on how the process is controlled microbiologically. The critical process parameters and sampling points of the manufacturing process for sample batches were defined and met required in process criteria.

Results from the data collected from 3 batches were presented. The critical process parameters and sampling points of the manufacturing process for these batches were defined and met required in-process criteria.

Control tests on the finished product

The description of the methods used for the control of the finished product and the specifications for each test are provided.

The tests include checks for:

a. oxygen carrying capacity

b. the isotonic and osmotic properties of the solution and

c. the safety of the product for intravenous infusion.

The dossier included details of the validation of the finished product test methods at the New A Innovation Ltd (Hong Kong) site.

Stability

Stability of PHS intermediate when stored in the recommended storage containers has been demonstrated.

In accordance with recommendations made during Scientific Advice, stability results for the 3 pilot Oxapex batches (tested to 6 months at both real and accelerated conditions are presented.

For these batches, the acceptance limits applied for the stability studies are the same as those applied at batch release for the relevant tests. The results obtained are supportive of the proposed shelf life when stored at less than 25° C.

Overall conclusions on quality

Overall sufficient information was provided regarding the manufacture and process control over Oxapex. Details of the active substance characterisation are provided and are sufficient.

Part 3 – Safety

Oxapex is a solution for infusion intended for administration to dogs in order to provide immediate oxygen-carrying support to improve the clinical signs of anaemia, independent of the underlying condition. The product is an ultra-purified, stabilised haemoglobin solution. The product is administered at a proposed variable dose range.

Safety documentation

Pharmacodynamics

See section 4.

Pharmacokinetics

See section 4.

Toxicological studies

Single dose toxicity

The applicant has conducted three acute toxicity studies in the rat. While the studies were not GLP compliant, it is considered that they were of a satisfactory quality. All three studies provided similar results. In the rat, the test article appears well tolerated at various doses. No mortality or adverse effects were evident clinically. A number of effects on clinicopathological parameters were observed. Typically, effects are transient, resolving within a number of days after the end of treatment. It is possible that the presence of haemoglobin in samples (arising from Oxapex treatment) caused assay interference resulting in a number, or all, of these effects.

Repeat dose toxicity

In order to address the safety of the product following repeat-dose administration, the applicant conducted a pilot repeat-dose toxicity study investigating the toxicity of the product following repeated administration of the test product on three occasions in the target species (dogs). The test article was administered at low dose and at high dose. As this study was not conducted in compliance with GLP requirements, it was considered to be only supportive in nature. Based on the findings of this study, it would appear that repeated treatment with the test product was generally tolerated in dogs with anaemia due to acute blood loss: changes in clinical pathological parameters (clinical chemistry and urinalysis) were observed but tended to revert to baseline levels by the end of the study. This study does not allow for evaluation of immunogenicity due to the short time span.

A GLP-compliant IV infusion study (target animal safety study) investigated the safety of high dose Oxapex. Oxapex was well tolerated. No evidence of significant cardiovascular or respiratory changes was reported. Minor, reversible kidney changes were observed. In this study, there was no evidence of immunogenicity following examination of toxicokinetic and

histological data. However, it cannot be concluded that this study confirms the absence of immunogenic potential as the time interval between repeat treatments (four days) would be insufficient to allow the primary immune response and a subsequent anamnestic response to develop.

In conclusion, it is considered that the potential for a repeat dose to induce an immunological reaction remains unclear.

Tolerance in the target species of animal

See section 4.

Reproductive toxicity

Data on reproductive toxicity have not been provided. This is in accordance with the CVMP guideline on the safety and residue data requirements for veterinary medicinal products intended for minor use or minor species, where data in respect of reproductive toxicity (including teratogenicity) are not required provided that the product is not indicated for use in food-producing target species and that the product is not intended for administration to animals intended for breeding.

Mutagenicity / genotoxicity

The applicant investigated mutagenic potential in two *in vitro* mutagenicity tests, a bacterial reverse mutation test and a mouse lymphoma assay. In both test systems, there was no evidence that the test item has mutagenic potential. However, an *in vivo* study has not been conducted/provided. The absence of an in vivo test was justified on the basis that haemoglobin does not contain any structural alerts suggesting a potential for genotoxicity and the results of available studies (bacterial reverse mutation test and the in-vitro mammalian cell gene mutation test in mouse lymphoma cells did not show evidence of any mutagenic potential. Further, it is noted that bovine haemoglobin is already authorised for use in the target species.

Carcinogenicity

The absence of studies investigating the carcinogenicity of the product can be accepted based on the negative findings of the mutagenicity studies. In addition, it is accepted that the active substance (haemoglobin) has no structural similarity to known carcinogens.

Studies of other effects

The applicant conducted an *in-vitro* GLP compliant laboratory study investigating the effect of haemoglobin on clinical chemistry, haematology and urinalysis. The results of this study suggest that the presence of haemoglobin in samples of canine serum, plasma and urine may result in a statistically significant interference in the assayed levels of a number of biochemical, haematological and urological parameters. It is noted that the interference will vary depending on the dose administered, time since infusion, type of analyser and reagents used.

User safety

The applicant has provided a brief user safety assessment.

It can be accepted that user exposure to the product will be limited to the professional user (i.e. the veterinarian and veterinary staff). The routes of exposure identified by the applicant (parenteral, oral and dermal) are considered to reflect realistic exposure routes. The applicant has suggested that exposure to the product is most likely to occur during the application phase. Given that the product will be restricted to professional users and is intended for administration by intravenous infusion, it is accepted that the potential for user exposure is limited.

No data on local effects (dermal/ocular irritancy) have been provided. Given the nature of the active substance and excipients, together with the presentation/packaging and the intended method of administration (limiting potential for exposure), the absence of local effect studies is accepted.

Also, it is argued that the assessment of a similar product containing haemoglobin currently authorised in the EU concluded that that product had an acceptable user safety profile.

While the user safety assessment conducted by the applicant is limited, the CVMP accept, based on the data presented, that the product is unlikely to pose a risk to the user when used as intended.

Environmental risk assessment

The applicant has conducted an environmental risk assessment as required by Directive 2001/82/EC, as amended. In accordance with question number 3 of the Phase I decision tree included in the VICH guideline (GL6), it can be accepted that the product is not intended for administration to food producing species and the assessment can therefore stop at Phase I.

It can be concluded that use of the product is not expected to present an unacceptable risk for the environment.

Overall conclusions on the safety documentation

The data presented in the safety file are limited. However, given the nature of the active substance, and in the context of a MUMS application, they are generally acceptable.

The product is not expected to present an unacceptable risk to the user.

The product is not expected to present an unacceptable risk for the environment.

Residues documentation

The product is not intended for use in a food producing species and therefore the applicant has not provided any residue documentation.

Part 4 – Efficacy

Oxapex is a solution for infusion intended for administration to dogs in order to provide immediate oxygen-carrying support to improve the clinical signs of anaemia. The product is an ultrapurified, stabilised haemoglobin solution.

Pharmacodynamics

In the pharmacodynamics section, reports of three studies were presented. Due to a limited study sample number the tests could only be considered supportive. Therefore, no definitive evidence is available to show an increase in plasma haemoglobin concentration correlating with an increase in tissue oxygenation as a result of Oxapex.

In the first study, a direct pharmacodynamic effect on tissue oxygenation was demonstrated in rats following administration of a single bolus IV injection of 0.2 g/kg bw Oxapex. The study was conducted in healthy rats and that the effect investigated was an increase in tissue oxygen tension above baseline. This was a limited study in terms of animal numbers. While seven, five and four rats were included in the Oxapex, Oxyglobin and Ringers lactate groups, respectively, there were problems with the blood sampling and anaesthetic procedures such that data from all animals in each group was not included at each time point. Given that there are a number of questions regarding the quality of the study, it will be considered supportive only.

The second study was conducted in the dog. The objective of the study was to assess the safety of Oxapex in order to determine pharmacological actions other than the intended therapeutic effect. Thus, no measurements regarding the intended pharmacodynamic effect have been conducted, e.g. measurement of tissue pO2 or haemoglobin concentration in plasma. In terms of secondary pharmacodymamic effects, the administration of Oxapex at doses of 30-60 ml/kg to healthy dogs results in an increase in central venous pressure, an increase in mean arterial pressure and a decrease in heart rate. The effects noted appeared to be related to the duration of the infusion. Again, this study is limited in terms of animal numbers. The findings of the study are further compromised by the fact that, for individual dogs, values at some time points are missing (in particular, for measurements relating to CVP).

A third study was conducted to investigate the pharmacokinetics and effect on tissue oxygenation in 30 male and female beagle dogs following induction of normovolemic anemia and subsequent administration of 15, 30 or 45 ml/kg bw Oxapex as a single IV infusion at a rate of 10 ml/kg/h. Based on the findings of this study, the applicant concludes that a reduction in muscle tissue oxygen tension seen following induction of anaemia was immediately restored by infusion of Oxapex. Interestingly, this study was designed to compare tissue oxygenation ability of different doses of Oxapex versus a negative control (Ringer's solution) and a positive control (oxyglobin). However, for reasons that are not clear the results of the oxyglobin group are not presented in the final report; therefore, a direct comparison of the functional similarity of both products in the target species is not possible. Because of the decision not to report the findings of the oxyglobin group, and a number of other concerns regarding the conduct of the study, the CVMP is of the opinion that this study is unreliable and cannot be used for assessment. Consequently, there is no direct evidence that an increase in

plasma haemoglobin concentration resulting from Oxapex administration can be correlated with an increase in tissue oxygenation in the target species.

Development of resistance

Not applicable.

Pharmacokinetics

The pharmacokinetic profile of Oxapex was evaluated in a total of six studies performed in rats, in healthy male and female beagle dogs, and in dogs suffering from experimentally induced acute haemorrhagic shock. A GLP standard comparative study was conducted and the study shows that Oxapex is capable of increasing plasma haemoglobin concentration.

Pharmacokinetic properties of treatment were studied in healthy animals and in animals with severe acute anaemia due to blood loss. Kinetics in anaemia due to other causes (such as immune-mediated haemolysis) has not been studied, although there may be differences in the pharmacokinetics of treatment with Oxapex in such cases.

Dose determination / justification

Dose Justification

In the original submission, the justification for the dose was based on three literature references where other products were used. Based on these references, the applicant has considered levels of plasma haemoglobin will be adequate to improve tissue oxygenation, and consequently to improve clinical signs of anaemia. The stated objective of Oxapex is to deliver haemoglobin. With this objective in mind, pharmacokinetic studies were performed in order to determine the dose of Oxapex that will deliver a plasma haemoglobin concentration for several hours.

Fundamental to the argumentation of the applicant is that the haemoglobin in the product proposed for marketing behaves in the same way, in terms of tissue oxygenation, as the haemoglobin used in the studies in the various publications referred to by the applicant. Similarity in this respect has not been demonstrated which implies that the assumptions regarding therapeutic concentrations may not be fully relevant for Oxapex.

Based on available information, the CVMP did not accept that maintaining plasma haemoglobin above a concentration for several hours is proof of efficacy: alone, it is not considered to be sufficient grounds to support the proposed indication.

Dose confirmation

In the first study (clinical study), a number of dogs were subjected to experimental induction of acute hypo-volaemic shock, in order to mimic the effects of acute haemorrhagic shock. In this study, the primary efficacy variable was survival. 53% of dogs in the negative control group died within hours of the induction of shock, while survival rates in all Oxapex treatment groups and the positive control group were high, between 86.7 – 100%. The data suggests an increase in survivability. However, there were no differences in survival at the different dose levels of Oxapex. The absence of a dose response in terms of clinical variables is notable given

that the available data indicate marked differences between Oxapex groups in respect of plasma haemoglobin concentrations. While the findings of the pivotal study appear to indicate that the administration of Oxapex reduces mortality, this study was not able to support the reported outcome.

Although this product was classified as MUMS, and that reduced requirements can be considered to apply, the requirements for determining efficacy for minor use indications are to be determined on a case-by-case basis (CVMP guideline on efficacy and target animal safety data requirements for VMPs intended for minor uses or minor species - EMEA/CVMP/EWP/117899/2004)

Having considered all available efficacy data, the only data that can be used in support of the proposed indication are those generated in a clinical study where 53 % of dogs in the negative control group died within hours of the induction of shock, while survival rates in all Oxapex treatment groups and the positive control group were high, between 86.7 – 100 %. These data suggest a positive effect of treatment. Survival, for between group comparisons, was determined from the start of infusion/'resuscitation'.

Target animal tolerance

In accordance with CVMP guideline on efficacy and target animal safety data requirements for VMPs intended for minor uses or minor species (EMEA/CVMP/EWP/117899/2004) appropriate data to characterise the tolerance of the target species to the test product following administration by the proposed route is required. In the application data from a number of different studies in the target species are presented; however, the quality/reliability of the tolerance data is variable.

Relevant studies include:

Two pilot pharmacokinetic studies in healthy dogs. These are limited studies in terms of animal numbers.

One comparative pharmacokinetic study – 12 animals were administered that test product at the rcommended therapeutic dose (RTD).

One repeat dose toxicity study. Product administered at 1x and 1.5 x RTD (n=2/group).

One dose confirmation study ('haemorrhagic shock' model) where the product administered was at 1x and 1.5x RTD. However, the study is unreliable.

One dose confirmation study ('immune mediated haemolytic anaemia' model) where the product was administered at 0.6x RTD.

In the pivotal study, treatment-related adverse reactions included discolouration of mucous membranes, urine and faeces in all dose groups, with the incidence and severity increasing with higher doses.

Typically, the treatment-related adverse effects observed were mild and transient.

In addition to the adverse effects observed in the pivotal target animal safety study, it is clear that overdosing, or too rapid administration of Oxapex, may lead to circulatory overload with associated clinical signs.

Field trials

No field trials have been presented. It should be noted that in the scientific advice given for Oxapex, the CVMP recommended that clinical field trials to confirm the efficacy of Oxapex should, in principle, be provided. Advice was given that it was open to the applicant to attempt to justify the absence of field studies if dose determination/dose confirmation and target animal safety studies provide sufficiently robust data.

Use of the experimental laboratory studies in support of efficacy, rather than a clinical field study, was justified by the applicant on the basis that:

- Recruiting animals to a field trial for this type of study would be extremely difficult for practical reasons,
- Severe blood loss is life-threatening and the patient requires critical care; therefore, there are ethical reasons for suggesting that a field trial would be unacceptable,
- In a field trial, it would not be possible to have proper baseline (pre-treatment) data,
- In a field trial, there would be problems with data collection.

The applicant argued that an experimental model offers a more ethical route to data provision and a more practical scientific and clinical approach. The CVMP however considered that it should be possible to design a field study that is both ethically acceptable and likely to provide useful clinical data.

Overall conclusion on efficacy

The CVMP concluded that similarity in respect of tissue oxygenation has not been demonstrated with the consequence that the assumptions regarding therapeutic concentrations are not proven to be fully relevant for Oxapex.

Based on available information, the CVMP did not accept that maintaining plasma haemoglobin above a concentration for several hours is proof of efficacy: alone, it is not considered to be sufficient grounds to support the proposed indication.

The only data that can be used in support of the proposed indication are those generated in one specific clinical study. In this clinical study, 53% of dogs in the negative control group died within hours of the induction of shock, while survival rates in all Oxapex treatment groups and the positive control group were high, between 86.7 – 100%. These data suggest a positive effect of treatment. However, in view of the outstanding concerns relating to the interpretation/presentation of pivotal study data, CVMP was not in a position to accept the reported outcome of that study.

Part 5 – Benefit risk assessment

Introduction

The product is an ultra-purified, stabilised haemoglobin solution. Oxapex is presented as a solution for infusion intended for administration to dogs in order to provide immediate oxygen-

carrying support to improve the clinical signs of anaemia, independent of the underlying condition.

The application is submitted in accordance with Article 12(3) of Directive 2001/82 EC, as amended. However, Oxapex is classified as MUMS; therefore, reduced data requirements apply.

Benefit assessment

Direct therapeutic benefit

The CVMP concluded that similarity in respect of tissue oxygenation has not been demonstrated with the consequence that the assumptions regarding therapeutic concentrations are not proven to be fully relevant for Oxapex.

Based on available information, the CVMP did not accept that maintaining plasma haemoglobin above a concentration for several hours is proof of efficacy: alone, it is not considered to be sufficient grounds to support the proposed indication.

The only data that can be used in support of the proposed indication are those generated in one specific clinical study. In this clinical study, 53% of dogs in the negative control group died within hours of the induction of shock, while survival rates in all Oxapex treatment groups and the positive control group were high, between 86.7 – 100%. These data suggest a positive effect of treatment. However, in view of the outstanding concerns relating to the interpretation/presentation of pivotal study data, CVMP was not in a position to accept the reported outcome of that study.

Additional benefits

Oxapex increases the range of available treatment possibilities for a minor indication.

Risk assessment

Available target animal tolerance data indicate that Oxapex administration is associated with the following adverse reactions:

- discoloured urine (red),
- dark faeces,
- vomiting
- discolouration of the skin,
- sneezing,
- histopathological renal changes

Typically, the treatment-related adverse effects observed were mild and transient.

Administration of multiples of the RTD (2x and 3x) are associated with an increased incidence and severity of the adverse reactions that occur at the recommended dose. Furthermore, it is clear that too rapid administration of Oxapex may lead to circulatory overload with associated clinical signs.

Data on reproductive toxicity have not been provided. Accordingly, the product is not indicated for use in food-producing target species and that the product is not intended for administration to animals intended for breeding.

The product is not expected to present an unacceptable risk to the user.

The product is not expected to present an unacceptable risk for the environment.

Evaluation of the benefit risk balance

Given the concerns that remain in respect of the claimed indication and the proposed dosing regimen, it was not possible to conclude on the benefit of the product.

Conclusion

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP considers that the application for Oxapex is not approvable at the present time, since major objections on dosing and efficacy have been identified which preclude a recommendation for marketing authorisation.