Australian Government

Australian Pesticides and Veterinary Medicines Authority

# Public Release Summary

On the evaluation of the new active constituent paracetamol in the product Pracetam 400 mg/ml Oral Solution for Pigs

APVMA product number 86212

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**Comments and enquiries regarding copyright:**

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This publication is available from the APVMA website.

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# PREFACE

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is the Australian Government regulator responsible for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia. Before approving an active constituent and/or registering a product, the APVMA must be satisfied that the statutory criteria, including the safety, efficacy, trade and labelling criteria, have been met. The information and technical data required by the APVMA to assess the statutory criteria of new chemical products, and the methods of assessment, must be consistent with accepted scientific principles and processes. Details are outlined on the APVMA website.

The APVMA has a policy of encouraging transparency in its activities and seeking community involvement in decision making. Part of that process is the publication of public release summaries for products containing new active constituents. This Public Release Summary is intended as a brief overview of the assessment that has been conducted by the APVMA and of the specialist advice received from advisory agencies, including other Australian Government agencies and State departments of primary industries. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience to encourage public comment.

## About this document

This Public Release Summary indicates that the APVMA is considering an application for registration of a veterinary chemical. It provides a summary of the APVMA's assessment, which may include details of:

- the toxicology of both the active constituent and product
- the residues and trade assessment
- occupational exposure aspects
- environmental fate, toxicity, potential exposure and hazard
- efficacy and target animal safety.

Comment is sought from interested stakeholders on the information contained within this document.

## Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of Pracetam 400 mg/ml Oral Solution for Pigs and approval of active constituent paracetamol should be granted. Submissions should relate only to matters that the APVMA is required, by legislation, to take into account in deciding whether to grant the application. These matters include aspects of public health, occupational health and safety, chemistry and manufacture, residues in food, environmental safety, trade, and efficacy and target animal safety. Submissions should state the grounds on which they are based. Comments received that address issues outside the relevant matters cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on **24 February 2020** and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

Relevant comments will be taken into account by the APVMA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

When making a submission please include:

- contact name
- company or group name (if relevant)
- email or postal address (if available)
- the date you made the submission.

All personal information, and confidential information judged by the APVMA to be confidential commercial information (CCI)[1] contained in submissions will be treated confidentially. Unless requested by the submitter, the APVMA may release a submission, with any CCI redacted, to the applicant for comment.

Written submissions on the APVMA's proposal to grant the application for registration that relate to the grounds for registration should be addressed in writing to:

Case Management and Administration Unit

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Sydney NSW 2001

**Phone:** +61 2 6770 2300

**Email:** enquiries@apvma.gov.au

## Further information

Further information can be obtained via the contact details provided above.

Copies of technical evaluation reports covering chemistry, efficacy and safety, toxicology, occupational health and safety aspects, residues in food and environmental aspects are available from the APVMA on request.

Further information on public release summaries can be found on the APVMA website.

[1] A full definition of "confidential commercial information" is contained in the Agvet Code.

# 1 INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of Pracetam 400 mg/ml Oral Solution for Pigs, and approval of the new active constituent, paracetamol.

## 1.1 Applicant

Ceva Animal Health Pty Ltd.

## 1.2 Purpose of application

Ceva Animal Health Pty Ltd has applied to the APVMA for registration of the new product Pracetam 400 mg/ml Oral Solution for Pigs, containing 400 g/L, as an oral liquid formulation of the new active constituent paracetamol.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of the product Pracetam 400 mg/ml Oral Solution for Pigs, and approval of the new active constituent paracetamol.

## 1.3 Proposed claims and use pattern

Pracetam 400 mg/ml Oral Solution for Pigs will be added to drinking water at a dose of 30 mg of paracetamol per kg body weight and per day, for five days, for the symptomatic treatment of fever in pigs. A decrease of hyperthermia will be expected 12–24 hours after onset of treatment depending on the medicated water intake.

## 1.4 Mode of action

Paracetamol mechanism of action involves a number of central mechanisms and a combination of pathways. The antipyretic effect produced by paracetamol is due to reduction of the specific oxidase form of the cyclooxygenases (COX) enzymes, preventing it from forming pro inflammatory chemicals which induce fever. On the other hand, several pathways are involved in analgesic effect of paracetamol. Mechanisms which are involved are mainly endogenous cannabinoid system, serotonergic pathway and inhibition of pro inflammatory compounds via effect on prostaglandin synthesis.

## 1.5 Overseas registrations

The product is currently registered in a number of other countries including the European Union and Canada, as Pracetam at different concentrations from 20 per cent to 40 per cent.

# 2 CHEMISTRY AND MANUFACTURE

## 2.1 Active constituent

The active constituent paracetamol has not previously been approved for veterinary use in Australia, however it has an extensive history of use in human pharmaceuticals as an analgesic and antipyretic. Paracetamol is an odourless, white, crystalline powder with a bitter taste. It is sparingly soluble in water, freely soluble in ethanol, methanol, acetone, dimethylformamide, and ethyl acetate and very slightly soluble in methylene chloride. The melting point of paracetamol is 168°C–172°C and the density is 1.293 g/cm$^3$ at 21°C.

The active constituent paracetamol is manufactured overseas. Details of the chemical name, structure, and physicochemical properties of paracetamol are listed below (Tables 1–2).

**Table 1: Nomenclature and structural formula of the active constituent paracetamol**

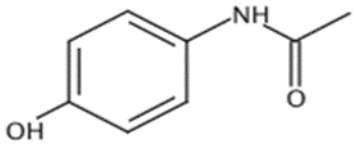
| | |
|---|---|
| **Common name (AUSTRALIAN APPROVED NAME—AAN):** | Paracetamol |
| **IUPAC name:** | N-(4-hydroxyphenyl)acetamide |
| **CAS registry number:** | 103–90–2 |
| **Molecular formula:** | $C_8H_9NO_2$ |
| **Molecular weight:** | 151.2 g/mol |
| **Structural formula:** |  |

Table 2: Key physicochemical properties of the active constituent paracetamol

| | |
|---|---|
| **Physical form:** | White crystalline powder |
| **Colour:** | White |
| **Odour:** | Odourless |
| **Melting point:** | 168–172°C |
| **Specific gravity/density/bulk density** | 1.293 g/cm$^3$ at 21°C |
| **Stability:** | Stable under normal temperatures and pressures, stable on storage for at least two years under normal conditions. |
| **Safety properties:** | Paracetamol is non-volatile (vapour pressure = 6.29 × 10-5 mm at 25°C) and non-inflammable (auto ignition temperature 540°C). It is incompatible with strong oxidising agents. |
| **Solubility in water:** | Sparingly soluble |
| **Organic solvent solubility:** | Freely soluble in ethanol, methanol, dimethylformamide, acetone and ethyl acetate.<br>Very slightly soluble in methylene chloride |
| **Dissociation constant ($PK_a$):** | 9.38 |
| **PH:** | 5.5–6.5 for a saturated aqueous solution. |
| **Octanol/water partition coefficient (Log $K_{ow}$/$K_{OW}$):** | 0.46 |
| **Vapour pressure:** | 6.29 × $10^{-5}$ mm Hg at 25°C |

## 2.2 Formulated product

The product Pracetam 400 mg/ml Oral Solution for Pigs will be manufactured overseas. It is a viscous dark blue coloured clear liquid, which is readily miscible with water. Tables 3 and 4 outline some key aspects of the formulation and physicochemical properties of the product.

**Table 3: Key aspects of the formulation of the product Pracetam**

| | |
|---|---|
| **Distinguishing name:** | Pracetam 400 mg/ml Oral Solution for Pigs |
| **Formulation type:** | Solution for oral administration (via drinking water) |
| **Active constituent concentration:** | Paracetamol 400 g/L |

**Table 4: Physicochemical properties of the product Pracetam**

| | |
|---|---|
| **Physical form:** | Viscous dark blue coloured clear liquid |
| **PH:** | 4.0–7.0 (5% v/v dilution in water) |
| **Specific gravity/density:** | 1.10–1.30 |
| **Safety properties:** | Non-flammable, non-volatile, non-corrosive and non-reactive liquid. |
| **Storage stability:** | Nominated shelf life at 30°C (Room Temperature) |

## 2.3 Recommendations

The APVMA Chemistry section has evaluated the chemistry of the active constituent paracetamol and associated product Pracetam 400 mg/ml Oral Solution for Pigs, including the physicochemical properties, identification, manufacturing process, quality control procedures, stability, batch analysis results and analytical methods, and found them to be acceptable. The available storage stability data indicate that the formulated product is expected to remain stable for the nominated shelf life when stored below 30°C (room temperature).

Based on a review of the chemistry and manufacturing details, the registration of Pracetam 400 mg/ml Oral Solution for Pigs, and approval of the active constituent paracetamol, are supported from a chemistry perspective.

# 3 TOXICOLOGICAL ASSESSMENT

The APVMA has considered the toxicological profile and likely exposure associated with the use of formulated product Pracetam 400 mg/ml Oral Solution for Pigs and the active constituent paracetamol. The APVMA has concluded that the human health risk posed by the active and the product is acceptable according to the criteria stipulated in Section 5A of the *Agricultural and Veterinary Chemicals Code Act (1994)*.

There are no objections on human health grounds to the approval of the new active ingredient, paracetamol.

There are no objections on human health grounds to the registration of Pracetam 400 mg/ml Oral Solution for Pigs containing 400 g/L paracetamol and 340 g/L dimethyl sulfoxide.

## 3.1 Evaluation of toxicology

### Chemical class and mode of activity

Paracetamol is a mild analgesic and antipyretic non-steroidal anti-inflammatory.

### Pharmacokinetics

Paracetamol is rapidly and relatively uniformly distributed in the tissues. Binding to plasma proteins is considered to be minimal. Paracetamol reaches peak plasma levels in 30 to 120 minutes and has a half-life of one to three hours in both humans and experimental animals. Paracetamol is extensively metabolised and only two to five per cent of the therapeutic dose is excreted unchanged in the urine. The most important site for biotransformation of orally administered paracetamol in humans and animals is the liver, where the major metabolites are glucuronide (approximately 60 per cent) and sulphate conjugates (approximately 35 per cent). At therapeutic doses in humans, only a limited amount, three to10 per cent, of paracetamol is converted by CYP enzymes, (specifically CYP2E1 and CYP3A4), to the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). In overdose, toxicity is probably due to depletion of hepatic glutathione and N-acetyl-p-benzoquinone imine reacting with sulphydryl groups in hepatic proteins.

No laboratory species provides an ideal animal model for human metabolism, but the hamster was closest with respect to metabolites formed and susceptibility to acute toxic effects. Rat metabolism is very different from humans and other species. The major urinary metabolite is the sulphate, rather than the glucuronide and is reported to be more resistant to liver necrosis than hamsters or mice. Rats converted only three to four per cent of non-toxic doses to the mercapturic acid (an index of the toxic N-acetyl-p-benzoquinoneimine intermediate), compared with 13 to 15 per cent in mice and hamsters. It is, therefore, probable that the mouse is the best toxicological animal model.

In humans, the kidney and gut are two other important sites for paracetamol. Paracetamol causes acute renal tubular necrosis by a similar mechanism as seen in the liver. In the intestine, the glucuronide conjugate can be hydrolysed to the parent compound which thereby can go through enterohepatic circulation. Urinary excretion is the predominant pathway of elimination for all paracetamol metabolites. However, excretion in the bile is also of importance for the glucuronide and glutathione conjugates.

## Acute toxicity (active constituent)

Excessive single oral doses of paracetamol cause hepatotoxicity and nephrotoxicity in laboratory animals. Oral $LD_{50}$ values range from 338 to 900 mg/kg bw in the mouse and more than 2000 mg/kg bw in adult rats, rabbits and guinea pigs. Lethal oral doses in the dog and cat are around 500 mg/kg bw and more than 50 mg/kg bw, respectively. In the latter two species methaemoglobinaemia is the predominant adverse effect, generally not seen in other species but reported in overdosed children.

## Acute toxicity (product)

No acute toxicity data on the formulated product Pracetam 400 mg/ml Oral Solution for Pigs was available. The formulation toxicity was estimated based on a consideration of its individual constituents. It was considered that Pracetam 400 mg/ml Oral Solution for Pigs was of moderate oral toxicity and low dermal toxicity. It was considered to be a slight skin and eye irritant.

## Repeat-dose toxicity

Dietary doses of up to 1000 mg/kg bw are well tolerated for up to 14 days in the mouse, while in the rat decreased bodyweight gain is observed at doses higher than 800 mg/kg bw/day. Signs of liver toxicity were seen after dietary exposure for 13 weeks in both mice and rats from 3200 mg/kg bw/day, with renal toxicity seen in male rats at 1600 mg/kg bw/day.

## Chronic toxicity and carcinogenicity

In two year studies in rats and mice, there was no evidence of carcinogenicity in male rats, or male or female mice at doses up to 6000 ppm in the diet. There was equivocal evidence of carcinogenicity in female rats based on an increased incidence of mononuclear cell leukaemia without effects on mortality.

## Reproductive and developmental toxicity

Paracetamol is in pregnancy category A (ie has been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed).

## Genotoxicity

Paracetamol is not mutagenic either in bacteria or in mammalian cells. Paracetamol has been shown to increase the frequency of chromosomal damage in mammalian cell lines, isolated human lymphocytes and experimental animals. This might imply that paracetamol is in fact genotoxic; however, the results are inconclusive. The International Agency for Research on Cancer has evaluated the carcinogenicity of paracetamol and have concluded with the following: There is inadequate evidence in humans and experimental animals to show a carcinogenicity potential. Paracetamol is not classifiable as to its carcinogenicity to humans (Group 3).

### Mode of action (toxicology)

The mode of action of paracetamol is thought to involve the inhibition of an enzyme (cyclooxygenase) in the brain and at the site of pain. This enzyme normally produces the compounds (prostaglandins) involved in inflammation and repair after injury. Thus, the inhibition of this enzyme activity results in a reduction of pain intensity and fever.

### Reports related to human toxicity

Paracetamol is widely used in human therapeutics, and has been available as a human therapeutic agent for over 50 years. Accidental and intentional misuse in humans is associated with liver toxicity, with an acute toxic dose in humans being approximately 200 mg/kg bw.

## 3.2 Health-based guidance values and poisons scheduling

### Poisons Standard

The Poisons Standard has been amended to include paracetamol for the treatment of animals in Schedule 4 of the Standard for the Uniform Scheduling of Medicines and Poisons. In addition, a new listing has been created in Part 2 of the Poisons Standard to include the requirement for child resistant closures for paracetamol included in Schedule 4, when packed and labelled for the treatment of animals.

### Health-based guidance values

#### *Acceptable Daily Intake (ADI)*

Based on the pharmacological (antipyretic) lowest observed effect level (LOEL) of 5 mg/kg bw in human infants, an ADI of 0.05 mg/kg bw/d for paracetamol can be calculated by applying a uncertainty factor of 100 to the LOEL. An uncertainty factor of 100 (10- x 10 fold) was considered justified when the usual 10 fold uncertainty factor for variability in human sensitivity is combined with 10 fold for the use of an ‘effect’ dose rather than a no observed effect level. An effect dose (5 mg/kg bw) in children is also very close to the therapeutic dose in adults (~7 mg/kg bw; assuming 70 kg bw). A toxicological ADI could not be established because the NOAEL for an adverse effect in laboratory animals, ie thyroid hyperplasia in a two year chronic mouse study (90 mg/kg bw/d) occurred at much higher doses. It has been shown that these adverse effects are due to the reactive intermediates that are formed at very high doses at which the glucuronidation capacity of the liver is overwhelmed.

#### *Acute Reference Dose (ARfD)*

Since the ADI is based on an antipyretic effect in humans following a single dose of paracetamol, the same LOEL and uncertainty factor are appropriate for establishing an ARfD. Thus, an ARfD for paracetamol can be established at 0.05 mg/kg bw.

## 3.3 Recommendations

There are no objections on human health grounds to the approval of the new active ingredient, paracetamol.

There are no objections on human health grounds to the registration of Pracetam 400 mg/ml Oral Solution for Pigs containing 400 g/L paracetamol and 340 g/L dimethyl sulfoxide.

# 4 RESIDUES ASSESSMENT

Target animal metabolism data and residue trial data as well as analytical methodology was evaluated in support of the proposed use in pigs.

## 4.1 Metabolism and residue definition

The distribution of radioactivity following oral administration of 14C-paracetemol was studied in pigs and the highest concentration was observed in the liver followed by kidney and then fat/skin. Generally, residue levels quickly disappeared from organs and tissues, with results for most treated animals not showing any quantifiable levels 24 hours following treatment.

In the paracetamol depletion study provided, residues were reported for paracetamol only as its metabolites p-aminophenol and N-acetyl-p-benzoquinoneimine could not be quantified due to their transitory nature.

Based on the available metabolism and residues data, the recommended residues definition (marker residue) is parent “Paracetamol”. This is considered appropriate for enforcement and consumer safety purposes.

## 4.2 Analytical methods and storage stability

The analytical method comprised of homogenisation of plasma or tissue samples followed by liquid/liquid extraction of paracetamol with ethyl acetate. After evaporation of organic phase to dryness the residue was resuspended in water prior to analysis by reverse phase HPLC, using a C18 column and detection by UV absorbance. Paracetamol concentrations in plasma, muscle, liver, kidney and skin/fat were determined using a validated HPLC method. The LOD and LOQ for each matrix was 0.05 mg/kg and 0.1 mg/kg respectively.

In the storage stability study that was provided, the maximum storage duration was three months and it corresponded to the maximum duration of frozen storage in the available residue studies for pigs. The results obtained during this study indicate that the test item remained stable during the three months of conservation at -20$^{o}$C.

## 4.3 Residues in pig tissues

The proposed dose regime for Pracetam 400 mg/ml Oral Solution for Pigs containing paracetamol involves treatment at a dose level of 30 mg paracetamol/kg bw/per day for a maximum of five days administered in the drinking water (oral administration).

In a critical GLP residue depletion, 10 week old pigs were orally administered 30 mg paracetamol/ kg bw per day over five consecutive days through drinking water (1x the proposed maximum dosage regime). The pigs were sacrificed (n=3 per time point) at three, five and seven days after treatment. Paracetamol residues were below the validated LOQ of 0.1 mg/kg in each sample of pig muscle, liver, kidney and fat/skin at each time-point including the first sampling time of three days after cessation of treatment.

As the critical residues depletion study that addressed the proposed dosage regime found residues in the four edible tissues to be below the LOQ of 0.1 mg/kg at three days after cessation of treatment, it is recommended that paracetamol MRLs for pig fat/skin, pig kidney, pig liver and pig muscle be established at *0.1 mg/kg for the proposed use in combination with a three day meat withholding period.

## 4.4 Dietary risk assessment

The chronic dietary exposure to paracetamol is estimated by the National Estimated Daily Intake (NEDI) calculation encompassing all registered/temporary uses of the chemical and the mean daily dietary consumption data derived primarily from the 2011–12 National Nutritional and Physical Activity Survey. The NEDI calculation is made in accordance with WHO Guidelines and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for paracetamol is equivalent to < one per cent of the ADI. It is concluded that the chronic dietary exposure to paracetamol is acceptable.

The acute dietary exposure is estimated by the National Estimated Short Term Intake (NESTI) calculation. The NESTI calculations are made in accordance with the deterministic method used by the JMPR with 97.5th percentile food consumption data derived primarily from the 2011–12 National Nutritional and Physical Activity Survey. NESTI calculations are conservative estimates of short-term exposure (24 hour period) to chemical residues in food. The highest acute dietary intake was estimated at < two per cent of the ARfD. It is concluded that the acute dietary exposure of paracetamol is acceptable.

## 4.5 Recommendations

The following amendments are required to be made to the APVMA MRL Standard.

**Table 5: Amendments to the APVMA MRL Standard**

| Amendments to Table 1 | | |
|---|---|---|
| **Compound** | **Food** | **MRL (mg/kg)** |
| ADD: | | |
| Paracetamol | | |
| | Pig fat/skin | *0.1 |
| MO 1284 | Pig kidney | *0.1 |
| MO 1285 | Pig liver | *0.1 |
| | Pig muscle | *0.1 |
| **Amendments to Table 3** | | |
| **Compound** | **Residue** | |
| ADD: | | |
| Paracetamol | Paracetamol | |

# 5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

## 5.1 Commodities exported and main destinations

Pig meat and offal are considered to be major export commodities. Significant markets for pig meat an offal are considered Japan, Singapore and countries that may accept Codex MRLs and it is noted that Singapore accepts Codex MRLs. In 2017–18, 35 kiloton of Australian pig meat valued at AUD 136 million was exported.

## 5.2 Overseas registrations and MRLs

MRLs for paracetamol have not been established overseas. The use of paracetamol in pigs is approved in Europe where the Committee for Veterinary Medicinal Products (CVMP) concluded that there was no need to establish an MRL for oral use paracetamol in pigs[2].

## 5.3 Potential risk to trade

The proposed use involves treatment of a pigs which are a major export species however, based on the available data, paracetamol residues above the validated LOQ of 0.1 mg/kg are not expected to arise in pig meat or offal after observing a three day withdrawal period. It is therefore concluded that an Export Slaughter Interval (ESI) of three days (equal to the recommended meat withholding period) should prevent an undue risk to international trade.

[2] EMEA/MRL/551/99-Final February 1999: ema.europa.eu/en/documents/mrl-report/paracetamol-summary-report-committee-veterinary-medicinal-products_en.pdf

# 6 WORK HEALTH AND SAFETY ASSESSMENT

## 6.1 Health hazards

No acute toxicity data on the formulated product Pracetam 400 mg/ml Oral Solution for Pigs was available. The formulation toxicity was estimated based on a consideration of its individual constituents. It was considered that Pracetam 400 mg/ml Oral Solution for Pigs was of moderate oral toxicity and low dermal toxicity. It was considered to be a slight skin and eye irritant. Data from human use suggests that liver toxicity is a critical end point.

## 6.2 Occupational exposure

### Exposure during use

The liquid concentrate product will be added to drinking water to treat weaned piglets and pigs. Limited exposure is anticipated, as the use requires mixing the formulated product with water. Adequate protection to minimise exposure has been estimated from a consideration of the product's toxicological hazard profile. Exposure is therefore minimised, based on the use of gloves during preparation of the product for use.

### Exposure during re-entry or rehandling

Post-application exposure to residues of Pracetam 400 mg/ml Oral Solution for Pigs is expected to be much lower than the exposure to the product during mixing, the risk from re-handling was considered to be minimal. Therefore, a re-handling statement is not required.

## 6.3 Public exposure

The product is intended for professional use only and is not intended for use by the general public.

## 6.4 Recommendations

The following first aid instructions, safety directions and precautionary (warning) statements are recommended for the product label.

### First aid instructions

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131 126; New Zealand; New Zealand 0800 764 766. If swallowed, do NOT induce vomiting.

### Safety directions

Poisonous if swallowed. Avoid contact with eyes and skin. When preparing product for use wear disposable gloves. Wash hands after use.

## Precautionary (warning) statements

Do not mix with other medication except on veterinarian’s advice.

# 7 ENVIRONMENTAL ASSESSMENT

## 7.1 Fate and behaviour in the environment

Paracetamol is extensively metabolised in the animal's body after oral administration. However, the metabolites formed are mainly conjugates and it was demonstrated in pig slurry that reversion to paracetamol cannot be excluded after excretion. Therefore, the environmental assessment assumed that 100 per cent of the applied dose may be excreted unchanged from the target animals.

Degradation of 14C-paracetemol was tested on three different soils where it was applied within a slurry. Paracetamol was very short lived in all soils with $DT_{50}$ and $DT_{90}$ values both below one day. No metabolite exceeding five per cent of the applied amount was observed in the soils. The metabolism of paracetamol was attributed to biological degradation with the resulting metabolites were rapidly bound to the soil matrix.

Several studies also considered the degradation of paracetamol in pig slurry which showed low mineralisation. The major of residues were bound to the soil matrix within 10 days of application.

In a standard batch equilibrium study investigating adsorption and desorption characteristics of paracetamol in two soils (silt loam and sandy loam), the KF values were 0.23 and 0.60 L/kg and the $K_{Foc}$ values were 18 and 24 L/kg, respectively. Therefore, paracetamol is expected to have very high mobility and low adsorption in both soils.

## 7.2 Effects and associated risks to non-target species

Intensively reared animals such are pigs are housed indoors throughout the production cycle so treatment with paracetamol is carried out in the housing. The environmental assessment assumed that the total dose was excreted in the stable and incorporated in the manure. Paracetamol would then reach the environment when the manure from the stable is spread onto land. Terrestrial species would be exposed to the resulting soil residues and aquatic species could be exposed by runoff from manured lands.

### Terrestrial vertebrates

Paracetamol has low toxicity to soil macro-organisms ($LC_{50}$ >1000 mg ac/kg dry soil, *Eisenia fetida*) and non-target terrestrial plants ($EC_{50}$ 168 mg ac/kg dry soil, three species tested). Paracetamol also did not have any adverse impact on soil processes such as nitrogen mineralisation at exaggerated soil concentrations (NOEC 25 mg ac/kg dry soil). Following long-term exposure, reduced reproduction of earthworms was observed at 133 mg ac/kg dry soil (NOEC 95 mg ac/kg dry soil).

Following VICH phase II guidance[3] and assuming the whole herd was treated, the maximum predicted soil concentrations were 1.3 mg ac/kg dry soil for weaners, 0.88 mg ac/kg dry soil for fattening pigs, and 0.31 mg ac/kg dry soil for sows with litter.

The maximum predicted soil concentrations were considerably lower than concentrations at which no adverse effects in non-target terrestrial species were observed. In addition, based on the octanol-water partition coefficient (log $K_{ow}$) of 0.5 for paracetamol, bioaccumulation in earthworms is not expected. Therefore, secondary dietary exposure of birds and mammals is not of concern. Considering all available information, risks to terrestrial species from the use of Pracetam 400 mg/ml Oral Solution for Pigs are considered to be acceptable.

### Aquatic species

Paracetamol was not toxic to fish ($LC_{50}$ >100 mg ac/L, *Brachidanio rerio*) or algae ($E_rC_{50}$ >100 mg ac/L, *Desmodesmus subspicatus*), but it is considered to be moderately toxic to aquatic invertebrates ($EC_{50}$ 2.5 mg ac/L, Daphnia magna). Following long-term exposure, no adverse effects were observed in Daphnia magna at the highest test concentration (NOEC 0.25 mg ac/L).

Based on the maximum predicted soil concentrations and VICH phase II guidance, the maximum predicted surface water concentrations as a result of runoff were 0.24 mg ac/L for weaners, 0.17 mg ac/L for fattening pigs, and 0.06 mg ac/L for sows with litter.

The maximum predicted surface water concentrations were lower than regulatory acceptable concentrations and therefore, risks to aquatic species from the use of Pracetam 400 mg/ml Oral Solution for Pigs are considered to be acceptable.

## 7.3 Recommendations

In considering the environmental safety of the use of Pracetam 400 mg/ml Oral Solution for Pigs, the APVMA had regard to the toxicity of the active constituent and its residues, including metabolites and degradation products, in relation to relevant organisms and ecosystems. Based on the outcome of the risk assessment, the APVMA was satisfied under s 14 of the *Agricultural and Veterinary Chemicals Code Act 1994* that the use of the product meets the safety criteria with respect to s5A(1)(c), and the label meets the labelling criteria under s 5D(1).

[3] CVMP (Committee for Medicinal Products for Veterinary Use), 2008, Revised guideline on environmental impact assessment for veterinary medicinal products in support of the VICH Guidelines GL6 and GL38, EMEA/CVMP/ERA/418282/2005-Rev.1

# 8 EFFICACY AND SAFETY ASSESSMENT

## 8.1 Proposed product use pattern

Pracetam 400 mg/ml Oral Solution for Pigs, is a proposed new veterinary oral liquid product containing 400 g/L paracetamol for the symptomatic treatment of fever in pigs.

The proposed product contains the active ingredient paracetamol. Paracetamol (synonym: acetaminophen) is an antipyretic and analgesic substance of the para-aminophenol group of the non-steroidal anti-inflammatory drugs. Paracetamol, although approved for use in humans for many years in Australia, is not registered with the APVMA for use in animals.

Pracetam 400 mg/ml Oral Solution for Pigs, will be added to drinking water at a dose of 30 mg of paracetamol per kg body weight per day, equivalent to 0.75 mL of PRACETAM Solution per 10 kg body weight per day for five days. The main indications are for treatment of signs associated with fever due to infectious diseases, such as respiratory disease, or as a result of vaccination. A decrease of hyperthermia is expected 12–24 hours after onset of treatment depending on the medicated water intake.

## 8.2 Efficacy and target animal safety

### Efficacy

The efficacy data submitted and assessed included overseas trial data, scientific literature and scientific justifications. The studies included preliminary trials (two) to develop hyperthermia model, pharmacokinetic studies, pharmacodynamics scientific literature, bioequivalence studies (comparing the proposed product and the European registered PRACETAM 20 per cent), dose determination studies, a dose confirmation study and two clinical field studies.

The pharmacokinetics of paracetamol have been well established, and show that metabolism is rapid, and that excretion is mainly via the urine. The proposed dosage form of via drinking water gives good bioavailability and appropriate excretion profiles. A dose of 30 mg/kg BW/day was considered following dose determination and confirmation studies including assessment of published scientific articles.

Two field trials were performed across several different European countries to confirm the efficacy of the proposed product. In the first field study, a total of 61 pigs were treated and matched with 61 control pigs recruited across the four farms in a double blinded parallel study. The change in rectal temperature and the total clinical score from day one to day six was statistically significant in favour of the paracetamol-treated group. There was no significant difference in average daily weight gain and no general reactions were reported. The administration of paracetamol in drinking water at a dose rate of 30 mg/kg/d was effective at reducing rectal temperature and other clinical signs in pigs suffering hyperthermia as a result of a viral in fattening pigs.

In a second study, 62 pigs (approx. 35 days old) with an acute respiratory disease were randomly allocated into two treatment groups. Half the pigs received the paracetamol in their drinking water for five days at a dose rate of 30 mg/kg/day. The other half received an oral placebo by the same route. Rectal temperature

and clinical scores were recorded for each group. The findings demonstrated that clinical signs of hyperthermia were relieved on day three in the treated group.

The applicant provided a scientific justification that data generated in Europe could be applied to the Australian industry for the purposes of APVMA registration, given the similarities between the two industries. In addition, the applicant has also reviewed the GCP and VICH guidance to determine if there were any data gaps to be satisfied that the overseas trial data is acceptable for use in Australian pigs.

No specific palatability studies were conducted, however, the amount of water consumed during the safety and efficacy studies presented show that the addition of the product to drinking water, did not affect the amount of water consumed by the target species. It may be concluded that the product does not affect the palatability of drinking water.

Based on the results submitted, a proposed dose of 30 mg of paracetamol per kg body weight per day given for five days in drinking is supported.

## Animal safety

A number of studies were carried out to determine the margin of safety of the proposed product. In one study, paracetamol was orally administered in drinking water to three groups of six pigs over five consecutive days on the basis of a 1x, 2x and 5x the therapeutic dose of 30 mg/kg/day with a fourth non treated group of six as a control. There was no observation of clinical signs, no effect on rectal temperature, no modification of body weight, no effect on feed or water consumption and no modification of blood biochemistry parameters. The results showed that there was good tolerance for paracetamol, if added to drinking water in clinically healthy fattening pigs.

Another safety study demonstrated high gastric and haematological tolerance with no obvious effects of paracetamol observed even at a dose rate of more than 11x the recommended therapeutic dose. 24 pigs divided in four groups were repeatedly given Pracetam 10% Premix for Pigs at various dose rates (five times and 10 times dose for five days, five times dose for 10 days). The doses given were equivalent to Pracetam 400 mg/ml Oral Solution for Pigs proposed dose. Only occasional soft faeces were observed in the treated groups.

In a study of 80 breeding sows, no effects were found on any reproductive parameters after the administration of paracetamol to sows at different stages of pregnancy at three times the therapeutic dose and to sows just prior to artificial insemination. No effects of the treatment were found on reproduction when administered throughout pregnancy (first, second or third stages of pregnancy), during lactation or at the moment of insemination.

Based on the evidence and literature provided by the applicant for registration as a new veterinary product, the contraindications, precautions, side effects and other label statements made relating to target animal safety are considered appropriate.

## 8.3 Recommendations

The APVMA has evaluated the efficacy and target animal safety data of the proposed product Pracetam 400 mg/ml Oral Solution for Pigs, and found it to be acceptable. Based on a review of the data submitted, Pracetam 400 mg/ml Oral Solution for Pigs would be effective and would not be likely to have an unintended effect that is harmful to the target species when used as directed.

# 9 LABELLING REQUIREMENTS

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| Company Name: | CEVA ANIMAL HEALTH PTY LTD |
| Product Name: | Pracetam 400 mg/mL Oral Solution for Pigs |
| APVMA Approval No: | 86212/115018 |
| Date: | 28 JAN 2020 |

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| Label Name: | Pracetam 400 mg/mL Oral Solution for Pigs |

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| Signal Headings: | PRESCRIPTION ANIMAL REMEDY<br>KEEP OUT OF REACH OF CHILDREN<br>FOR ANIMAL TREATMENT ONLY<br>READ SAFETY DIRECTIONS BEFORE OPENING OR USING |

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| Constituent Statements: | Active constituent: Paracetamol 400 g/L<br>Also contains: Dimethyl sulfoxide 340 g/L |

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| Claims: | For the symptomatic treatment of fever in pigs. |

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| Net Contents: | 500 mL, 1L, 2.5L, 5L |

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| Directions for Use: | |

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| Restraints: | |

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| Contraindications: | Do not use in animals with known hypersensitivity to paracetamol and to any other ingredients of the product.<br>Do not use in animals with severe hepatic or renal impairment.<br>Do not use in animals suffering from dehydration or hypovolaemia. |

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| Precautions: | Animals with reduced water intake and/or disturbed general condition should not be treated with this product.<br><br>In case of combined viral and bacterial aetiology of the disease, an appropriate anti-infective therapy should be given concomitantly.<br><br>Concurrent administration of nephrotoxic drugs should be avoided.<br><br>DO NOT MIX with other medications without the advice of a veterinarian |

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| Side Effects: | In rare cases, transient soft faeces can occur and can persist up to 8 days after the withdrawal of administration. It does not have any effect on general condition of animals and resolves without any specific treatment. |

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| Dosage and Administration: | Use contents of container within 3 months of first opening. Drinking water should be replaced every 24 hours with a fresh dose.<br><br>Use 30 mg of paracetamol per kg body weight and per day, for 5 days, orally, administered in the drinking water, equivalent to 0.75 ml of Pracetam Solution per 10 kg body weight per day for 5 days.<br><br>The intake of medicated drinking water depends on the clinical condition of the animals. In order to obtain a correct dosage, the concentration in the drinking water must be adjusted accordingly.<br><br>Recommendation for dissolution: The product is easily dissolved in ambient temperature water (20°C to 25°C).<br>When using the product through a water proportioner, adjust the proportioner from 5% to 3%. Do not set proportioners under 3%.<br><br>Freshly prepare solution every 24 hours. No other source of drinking water should be available during the medication period. |

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| General Directions: | PRACETAM 400 mg/mL Oral Solution for Pigs, is added to drinking water in order to treat the symptoms of fever due to infectious diseases, such as respiratory disease, or as a result of vaccination.<br>A decrease of hyperthermia is expected 12-24 hours after onset of treatment depending on the medicated water intake.<br><br>Studies in laboratory animals have not detected any teratogenic nor foetotoxic effects at therapeutic doses. The administration of the product up to three times the recommended dose, during pregnancy or lactation, did not result in adverse effects,so the product may be administered during pregnancy and lactation.<br><br>Pharmacodynamic properties<br>Paracetamol or acetaminophen or N-acetyl-p-aminophenol is a paraminophenol derivative with analgesic and antipyretic properties.<br><br>Pharmacokinetic properties<br>Absorption: Paracetamol is rapidly and almost completely absorbed after oral administration (bioavailability of about 90% after administration in the drinking water). Peak concentrations are reached in a little less than 2 hours after ingestion.<br><br>Metabolism: Paracetamol is mainly metabolised in the liver. The two major metabolic pathways are conjugation to glucuronate and conjugation to sulphate. The latter route is rapidly saturable at dosages higher than therapeutic doses. A minor pathway, catalysed by cytochrome P450 (CYP), leads to the formation of the intermediary reagent, N-acetyl-benzoquinoneimine which, under normal conditions of use, is rapidly detoxified by reduced glutathione and removed in urine after conjugation with cystein and mercapturic acid. On the contrary, after massive intoxication, the quantity of this toxic metabolite is increased.<br><br>Elimination: Paracetamol is mainly eliminated in the urine. In the pig, 63% of the ingested dose is eliminated by the kidneys in 24 hours mainly conjugated to glucuronate and suphate. Less than 5% is eliminated in unchanged form. The elimination half-life is approximately 5 hours. |

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| Withholding Periods: | MEAT: REMOVE ALL MEDICATED WATER Three (3) days before slaughter for human consumption. |

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| Trade Advice: | EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than three days before slaughter for export. |

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| Safety Directions: | Poisonous if swallowed. Avoid contact with eyes and skin. When preparing product for use wear disposable gloves. Wash hands after use. |

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| First Aid Instructions: | If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126. If swallowed, do NOT induce vomiting. |

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| First Aid Warnings: | |

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| Additional User Safety: | |

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| Environmental Statements: | ENVIRONMENTAL PROTECTION<br>DO NOT contaminate wetlands or watercourses with this product or used containers. |

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| Disposal: | For 500mL and 1L containers: Dispose of container by wrapping with paper and putting in garbage.<br><br>For 2.5L and 5L containers: Triple-rinse container into the medicated water. Do not dispose of undiluted chemicals on-site. If recycling, replace cap and return clean container to recycler or designated collection point. If not recycling, break, crush, or puncture container and deliver to an approved waste management facility. If an approved waste management facility is not available, bury the broken, crushed or punctured containers 500 mm below the surface in a disposal pit specifically marked and set up for this purpose clear of waterways, vegetation and tree roots, in compliance with relevant local, state or territory government regulations. Do not burn empty containers or product. |

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| Storage: | Store below 30°C (Room Temperature). Close lid tightly after use. Protect from light. |

# ABBREVIATIONS

| | |
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| ACCS/ACMS | Advisory Committee for Chemicals Scheduling/Advisory Committee for Medicines Scheduling |
| ac | active constituent |
| ADI | Acceptable Daily Intake (for humans) |
| AHMAC | Australian Health Ministers Advisory Council |
| ai | active ingredient |
| ARfD | Acute Reference Dose |
| bw | bodyweight |
| d | day |
| DAT | Days After Treatment |
| $DT_{50}$ | Time taken for 50% of the concentration to dissipate |
| EA | Environment Australia |
| $E_bC_{50}$ | concentration at which the biomass of 50% of the test population is impacted |
| $EC_{50}$ | concentration at which 50% of the test population are immobilised |
| EEC | Estimated Environmental Concentration |
| $E_rC_{50}$ | concentration at which the rate of growth of 50% of the test population is impacted |
| ESI | Export Slaughter Interval |
| EUP | End Use Product |
| $F_0$ | original parent generation |
| g | gram |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GVP | Good Veterinary Practice |
| h | hour |
| Hct | Haematocrit |
| Hb | Haemoglobin |
| HPLC | High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography |

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|---|---|
| id | intradermal |
| im | intramuscular |
| ip | intraperitoneal |
| IPM | Integrated Pest Management |
| iv | intravenous |
| in vitro | outside the living body and in an artificial environment |
| in vivo | inside the living body of an animal |
| kg | kilogram |
| $K_{OC}$ | Organic carbon partitioning coefficient |
| KFoc | organic-carbon normalized Freundlich distribution coefficient. |
| L | Litre |
| $LC_{50}$ | concentration that kills 50% of the test population of organisms |
| $LD_{50}$ | dosage of chemical that kills 50% of the test population of organisms |
| LOD | Limit of Detection—level at which residues can be detected |
| Log $K_{OW}$ | Log to base 10 of octanol water partitioning co-efficient, synonym $P_{OW}$ |
| LOQ | Limit of Quantitation—level at which residues can be quantified |
| mg | milligram |
| mL | millilitre |
| MRL | Maximum Residue Limit |
| MSDS | Material Safety Data Sheet |
| NEDI | National Estimated Daily Intake |
| NESTI | National Estimated Short Term Intake |
| ng | nanogram |
| NHMRC | National Health and Medical Research Council |
| NOEC/NOEL | No Observable Effect Concentration Level |
| NOAEL | No Observed Adverse Effect Level |
| OC | Organic Carbon |

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|---|---|
| OM | Organic Matter |
| po | oral |
| ppb | parts per billion |
| PPE | Personal Protective Equipment |
| ppm | parts per million |
| Q-value | Quotient-value |
| RBC | Red Blood Cell Count |
| REI | Re-Entry Interval |
| s | second |
| sc | subcutaneous |
| SC | Suspension Concentrate |
| SUSMP | Standard for the Uniform Scheduling of Medicines and Poisons |
| TGA | Therapeutic Goods Administration |
| TGAC | Technical grade active constituent |
| µg | microgram |
| vmd | volume median diameter |
| WG | Water Dispersible Granule |
| WHP | Withholding Period |

# GLOSSARY

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| Active constituent | The substance that is primarily responsible for the effect produced by a chemical product |
| Acute | Having rapid onset and of short duration |
| Carcinogenicity | The ability to cause cancer |
| Chronic | Of long duration |
| Codex MRL | Internationally published standard maximum residue limit |
| Desorption | Removal of a material from or through a surface |
| Efficacy | Production of the desired effect |
| Formulation | A combination of both active and inactive constituents to form the end use product |
| Genotoxicity | The ability to damage genetic material |
| Hydrophobic | Repels water |
| Metabolism | The chemical processes that maintain living organisms |
| Subcutaneous | Under the skin |
| Toxicokinetics | The study of the movement of toxins through the body |
| Toxicology | The study of the nature and effects of poisons |

# REFERENCES

APVMA 2015, *Data Guidelines,* Australian Pesticides and Veterinary Medicines Authority, Canberra, available at apvma.gov.au/registrations-and-permits/data-guidelines.

CVMP (Committee for Medicinal Products for Veterinary Use), 2008, *Revised guideline on environmental impact assessment for veterinary medicinal products in support of the VICH Guidelines GL6 and GL38, EMEA/CVMP/ERA/418282/2005-Rev.1.*

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