ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Ketink 300 mg/ml solution for use in drinking water for cattle and pigs [AT, BG, CY, DE, HU, NL, PL, PT, RO, SI]
Ainil 300 mg/ml solution for use in drinking water for cattle and pigs [EL, IT]
Aristal 300 mg/ml solution for use in drinking water for cattle and pigs [BE]
Ketisio 300 mg/ml solution for use in drinking water for cattle and pigs [ES]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Ketoprofen 300 mg

Excipients:

Qualitative composition of excipients and other constituents
Sodium hydroxide
Glycine
Propylene glycol
Citric acid monohydrate (for pH adjustment)
Purified water

Clear yellowish solution.

3. CLINICAL INFORMATION

3.1 Target species

Cattle (calf) and pigs (for fattening).

3.2 Indications for use for each target species

Treatment for the reduction of pyrexia and dyspnoea associated with respiratory disease in combination with anti-infective therapy, as appropriate.

3.3 Contraindications

Do not use in suckling calves.
Do not use in fasting animals or animals with limited access to feed.
Do not use in animals in which there is the possibility of gastrointestinal alterations, ulceration or bleeding in order to not aggravate their situation.
Do not use in dehydrated, hypovolemic or hypotensive animals due to the potential increased risk of renal toxicity.
Do not use in swine fattened at extensive or semi-extensive production farms with access to soil or foreign objects that may damage the gastric mucosa, or with a high parasite burden, or under a severe stress situation.
Do not use in animals suffering from cardiac, hepatic or renal disease.
Do not use in animals when there is evidence of blood dyscrasia.

Do not use in cases of hypersensitivity to ketoprofen, to acetylsalicylic acid or to any of the excipients.
Do not use other non-steroidal anti-inflammatory drugs (NSAIDs) concurrently or within 24 hours of each other.
See also section 3.7.

3.4 Special warnings

Water intake of treated animals should be monitored to ensure adequate intake. Individual animal medication, preferably by injection with a veterinary medicinal product, which is intended for injection, will be required if daily water intake is insufficient.

3.5 Special precautions for use

Special precautions for safe use in the target species:

As ketoprofen may provoke gastrointestinal ulcerations, the use is not recommended in cases of PMWS (post-weaning multisystemic wasting syndrome) because ulcers are already frequently associated with this pathology.
To reduce the risk of adverse reactions do not exceed the recommended dose or duration of treatment.
When administered to pigs less than 6 weeks old or to elderly pigs it is necessary to adjust the dose accurately as well as to perform a close clinical follow-up.
It is recommended that the daily dose is administered over a period of 24 hours. The total daily dose should not be administered over a shorter period than recommended as this has been shown to result in more severe gastric ulceration. For safety reasons the maximum treatment duration should not exceed 3 days. If side effects occur treatment must be stopped and the advice of a veterinarian should be sought. Treatment must be suspended for the whole group.
Avoid use in dehydrated, hypovolemic or hypotensive animals as there potentially is an increased risk of a renal toxicity.
This veterinary medicinal product does not contain any antimicrobial preservative.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

The veterinary medicinal product may cause hypersensitivity reactions (skin rash, urticaria). People with known hypersensitivity to ketoprofen or any of the excipients should avoid contact with the veterinary medicinal product.
Handle the veterinary medicinal product with care to avoid contact with skin and eyes while adding it to water.
Personal protective equipment consisting of rubber gloves and safety glasses should be worn when handling the veterinary medicinal product.
In case of accidental spillage onto skin, the affected area should be rinsed immediately with water. In case of accidental eye contact, irrigate the eyes thoroughly with clean running water immediately. Seek medical advice if irritation persists.
Contaminated clothing should be removed and any splashes on to the skin should be washed off immediately.
Wash hands after use.
Do not smoke, eat or drink while handling the product.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cattle (calf):

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Gastric ulcer[1], soft stool[2]

[1] Serious adverse event observed under severe stressful situations (transportation, dehydration, fasting, etc)
[2] Transitory, which disappears during or at the end of the treatment

Pigs (for fattening):

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Gastric ulcer[3], soft stool[4]

[3] At the recommended therapeutic dose may cause superficial and deep erosion of the gastrointestinal tract. Observed also in black Iberian pigs resulting in fatality related to being fattened at soil stations with a high parasite burden and the ingestion of foreign bodies. In intensive farming have been related to forced fasting situations prior or during treatment.
[4] Transitory, which disappears during or at the end of the treatment.

If side effects occur treatment must be stopped for the whole group and the advice of a veterinarian should be sought.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder <or its local representative> or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy:
Do not use in pregnant sows.

3.8 Interaction with other medicinal products and other forms of interaction

Concurrent administration of diuretics or potentially nephrotoxic drugs should be avoided since there is an increased risk of renal disturbances. This is secondary to the diminished blood flow caused by the inhibition of prostaglandins.
This veterinary medicinal product should not be administered concurrently with other NSAIDS or glucocorticosteroids due to the risk of exacerbating gastrointestinal ulceration.
Concurrent treatment with other anti-inflammatory substances may result in additional or increased adverse effects. Consequently, a period of at least 24 hours should be observed between treatment with other anti-inflammatories and this veterinary medicinal product.
The treatment-free period should, however, take into account the pharmacological properties of the products used previously.
Anticoagulants, particularly coumarin derivatives such as warfarin, should not be used in combination with ketoprofen.
Ketoprofen is highly bound to plasma proteins. The concomitant administration of substances that are also highly plasma protein bound may compete with ketoprofen with the possibility of consequent toxic effects due to the unbound fraction of the drug.

3.9 Administration routes and dosage

In drinking water use.

Cattle (calf)
3 mg ketoprofen/kg body weight/day (equivalent to 1 ml of the veterinary medicinal product/100 kg b.w./day)

Pigs (for fattening)
1.5 - 3 mg ketoprofen/kg body weight/day (equivalent to 0.5 - 1 ml of the veterinary medicinal product/100 kg b.w/day). The dose of 1.5 mg/kg is effective in the treatment of mild to moderate processes (body temperature <41°C). The dose must be increased up to 3 mg ketoprofen/kg b.w. to treat more severe cases.
Treatment should be administered for one day. It can be extended for another 1-2 days after a risk/benefit assessment has been carried out by the responsible veterinarian; see also sections 3.4 and 3.6.

Method of Administration:
The veterinary medicinal product is administered by the oral route, diluted in drinking water. Administration over a 24 hour period is recommended. Medicated water should be the only water supply during the period of treatment and should be refreshed every 24 hours. The product may be put directly into the header tank or introduced via a water proportioner pump.
Once the treatment period has finished, the animals should be given unmedicated water. Any medicated water which is not consumed within 24 hours should be discarded.
The animals must have *ad libitum* access to food and medicated water before and during treatment.
Start the treatment of recumbent animals with the parenteral form. To ensure a correct dosage, body weight should be determined as accurately as possible.

The water intake of the animals to be treated should be measured before calculating the total amount of product to be administered each day. In order to calculate accurately the rate of incorporation of the product in drinking water, it is necessary to estimate the mean weight and the consumption of water of the animals to be treated, based on the average for the days immediately before treatment.

If it is administered by adding the product directly into the drinking water tank, this must contain enough water for the level of consumption that is anticipated for the following 24 hours.

Based on the recommended dose and the number and weight of animals to be treated, the exact daily concentration of the veterinary medicinal product should be calculated according to the following formula:

$$\frac{\frac{ml\ veterinary\ medicinal\ product}{kg\ body\ weight\ day} / \ x \ \frac{average\ body\ weight\ (kg)}{of\ animals\ to\ be\ treated}}{average\ daily\ water\ intake\ (l/animal)} = \frac{ml\ veterinary\ medicinal\ product}{per\ litre\ of\ drinking\ water}$$

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

Overdose with NSAIDs can lead to gastro-intestinal ulceration, loss of proteins, hepatic and renal impairment. In tolerance studies performed with the veterinary medicinal product when administered in drinking water to cattle and pigs, up to 25% of the animals treated at five times the maximum recommended dose (15 mg/kg) for three days or at the recommended dose (3 mg/kg) for triple the maximum recommended time (9 days) showed gastric ulcerative lesions. Early signs of toxicity include loss of appetite and pasty faeces or diarrhoea. In case of overdosage, symptomatic treatment

should be initiated. The occurrence of ulcers is dose dependent to a limited extent.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

3.12 Withdrawal periods

Cattle: Meat and offal: 1 day
Pigs: Meat and offal: 1 day

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code
QM01AE03

4.2 Pharmacodynamics

Ketoprofen, 2-(phenyl 3-benzoyl) propionic acid is a non-steroidal anti-inflammatory drug belonging to the arylpropionic acid group. Ketoprofen inhibits the biosynthesis of prostaglandins (PGE2 and PGF2α) without affecting the ratio PGE2/PGF2α and thromboxanes. This mechanism of action results in its anti-inflammatory, antipyretic and analgesic activity. These properties are also attributed to its inhibiting effect of bradykinin and superoxide anions together with its stabilizing action on lysosomal membranes. The anti-inflammatory effect is enhanced by the conversion of the (R)-enantiomer to (S)-enantiomer. It is known that the (S)-enantiomer supports the anti-inflammatory effect of ketoprofen.

4.3 Pharmacokinetics

Following oral administration, ketoprofen is readily absorbed and binds strongly to plasma proteins. Ketoprofen is metabolised in the liver and is converted into a carbonil-reduced derivation, the RP69400 metabolite. It is excreted primarily through the kidneys and, to a lesser extent, in the faeces.

Cattle:
Following oral gavage administration at a dosage of 3 mg/kg to fattening calves, ketoprofen is absorbed readily (F = 100%). Maximum concentrations (C_{max}) of 3.7 µg/ml (2.5 to 4.5 µg/ml) are achieved at 72 min (0.33 to 2 h) after administration (T_{max}). Following absorption, the pharmacokinetics of ketoprofen are characterised by a low volume of distribution (0.5 l/kg) and a short plasma elimination half-life (2.2 h).

After repeated oral administration in drinking water in calves, the kinetic profile presents mainly two different phases per administration day, clearly related to the day-night cycle, which influenced the animal's water consumption. The first phase (first 9 hours post-treatment) corresponded to the absorption phase of the product. Considering the rapid absorption phase for the single administration, the longer phase observed for repeated administrations is due to the administration route: ketoprofen administered via drinking water is consumed by the animals sparsely during the day. The elimination phase observed in the following hours is directly related to the low drinking water consumption by the animals during the night time. When administering the product at 3 mg ketoprofen/kg/day during 3 days in drinking water, the C_{max} observed was 1.9 µg/ml (1.6 to 2.4 µg/ml) and the T_{max} was of 32 h(9 to 57 h) after beginning of administrations.

Pigs:
In swine, after oral gavage administration at a dosage of 3 mg ketoprofen/kg, a maximum mean concentration (C_{max}) of 10.6 µg/ml is reached (2.2 to 17.2 µg/ml), in average, at 60 minutes (0.33 to 2 h) after administration (T_{max}). Absolute bioavailability is high (84%). Volume of Distribution

following intravenous administration is low (Vd=0.2 l/kg) and its elimination half-life is short ($t_{½}$ = 2.0 h). Plasma clearance is 0.06 l/kg.h.

When administering the product at 3 mg ketoprofen/kg/day during 3 days in drinking water in pigs, the kinetic profile is similar to the one observed in cattle. The C_{max} observed was 2.7 µg/ml (1.4 to 4.2 µg/ml) and the T_{max} was of 16 h (6 to 57 h) after beginning of administrations.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years
Shelf life after first opening the immediate packaging: 3 months
Shelf life after dilution according to directions: 24 hours

5.3. Special precautions for storage

Keep the bottle tightly closed.

5.4 Nature and composition of immediate packaging

High density polyethylene bottles (HDPE) heat-sealed with a polyethylene foil (PE) and a screw cap of HDPE equipped with a security system to give an airtight sealing.

Package size:
Bottle of 500 ml

5.5 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater or household waste.
Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Industrial Veterinaria, S.A.

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: <{DD/MM/YYYY}><{DD month YYYY}.

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

{MM/YYYY}

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).