Annex I

List of the names, pharmaceutical form, strength of the veterinary medicinal product, animal species, route of administration, applicant in the Member States

Member State EU/EEA	Applicant	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Austria	Bela-Pharm GmbH & Co. KG Lohner Strasse 19 49377 Vechta Germany	Belatamin 100 mg/ml solution for injection	Ketamine	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats, horses, dogs, cats, guinea pigs, hamsters, rabbits, rats and mice	Intravenous, intramuscular and intraperitoneal use
Bulgaria	Bela-Pharm GmbH & Co. KG Lohner Strasse 19 49377 Vechta Germany	Ketabel 100 mg/ml solution for injection	Ketamine	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats, horses, dogs, cats, guinea pigs, hamsters, rabbits, rats and mice	Intravenous, intramuscular and intraperitoneal use
Czech Republic	Bela-Pharm GmbH & Co. KG Lohner Strasse 19 49377 Vechta Germany	Ketabel 100 mg/ml solution for injection	Ketamine	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats, horses, dogs, cats, guinea pigs, hamsters, rabbits, rats and mice	Intravenous, intramuscular and intraperitoneal use
Germany	Bela-Pharm GmbH & Co. KG Lohner Strasse 19 49377 Vechta Germany	Ketabel 100 mg/ml solution for injection	Ketamine	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats, horses, dogs, cats, guinea pigs, hamsters, rabbits, rats and mice	Intravenous, intramuscular and intraperitoneal use

Member State EU/EEA	Applicant	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Estonia	Bela-Pharm GmbH & Co. KG Lohner Strasse 19 49377 Vechta Germany	Ketabel 100 mg/ml solution for injection	Ketamine	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats, horses, dogs, cats, guinea pigs, hamsters, rabbits, rats and mice	Intravenous, intramuscular and intraperitoneal use
Greece	Bela-Pharm GmbH & Co. KG Lohner Strasse 19 49377 Vechta Germany	Ketabel 100 mg/ml solution for injection	Ketamine	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats, horses, dogs, cats, guinea pigs, hamsters, rabbits, rats and mice	Intravenous, intramuscular and intraperitoneal use
Finland	Bela-Pharm GmbH & Co. KG Lohner Strasse 19 49377 Vechta Germany	Ketabel vet. 100 mg/ml solution for injection	Ketamine	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats, horses, dogs, cats, guinea pigs, hamsters, rabbits, rats and mice	Intravenous, intramuscular and intraperitoneal use
France	Bela-Pharm GmbH & Co. KG Lohner Strasse 19 49377 Vechta Germany	Ketabel 100 mg/ml solution for injection	Ketamine	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats, horses, dogs, cats, guinea pigs, hamsters, rabbits, rats and mice	Intravenous, intramuscular and intraperitoneal use

Member State EU/EEA	Applicant	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Hungary	Bela-Pharm GmbH & Co. KG Lohner Strasse 19 49377 Vechta Germany	Ketabel 100 mg/ml solution for injection	Ketamine	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats, horses, dogs, cats, guinea pigs, hamsters, rabbits, rats and mice	Intravenous, intramuscular and intraperitoneal use
Ireland	Bela-Pharm GmbH & Co. KG Lohner Strasse 19 49377 Vechta Germany	Ketabel 100 mg/ml solution for injection	Ketamine	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats, horses, dogs, cats, guinea pigs, hamsters, rabbits, rats and mice	Intravenous, intramuscular and intraperitoneal use
Iceland	Bela-Pharm GmbH & Co. KG Lohner Strasse 19 49377 Vechta Germany	Ketabel vet. 100 mg/ml solution for injection	Ketamine	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats, horses, dogs, cats, guinea pigs, hamsters, rabbits, rats and mice	Intravenous, intramuscular and intraperitoneal use
Lithuania	Bela-Pharm GmbH & Co. KG Lohner Strasse 19 49377 Vechta Germany	Ketabel 100 mg/ml solution for injection	Ketamine	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats, horses, dogs, cats, guinea pigs, hamsters, rabbits, rats and mice	Intravenous, intramuscular and intraperitoneal use

Member State EU/EEA	Applicant	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Latvia	Bela-Pharm GmbH & Co. KG Lohner Strasse 19 49377 Vechta Germany	Ketabel 100 mg/ml solution for injection	Ketamine	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats, horses, dogs, cats, guinea pigs, hamsters, rabbits, rats and mice	Intravenous, intramuscular and intraperitoneal use
The Netherlands	Bela-Pharm GmbH & Co. KG Lohner Strasse 19 49377 Vechta Germany	Ketabel 100 mg/ml solution for injection	Ketamine	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats, horses, dogs, cats, guinea pigs, hamsters, rabbits, rats and mice	Intravenous, intramuscular and intraperitoneal use
Norway	Bela-Pharm GmbH & Co. KG Lohner Strasse 19 49377 Vechta Germany	Belatamin vet. 100 mg/ml solution for injection	Ketamine	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats, horses, dogs, cats, guinea pigs, hamsters, rabbits, rats and mice	Intravenous, intramuscular and intraperitoneal use
Portugal	Bela-Pharm GmbH & Co. KG Lohner Strasse 19 49377 Vechta Germany	Ketabel 100 mg/ml solution for injection	Ketamine	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats, horses, dogs, cats, guinea pigs, hamsters, rabbits, rats and mice	Intravenous, intramuscular and intraperitoneal use

Member State EU/EEA	Applicant	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Romania	Bela-Pharm GmbH & Co. KG Lohner Strasse 19 49377 Vechta Germany	Ketabel 100 mg/ml solution for injection	Ketamine	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats, horses, dogs, cats, guinea pigs, hamsters, rabbits, rats and mice	Intravenous, intramuscular and intraperitoneal use
Sweden	Bela-Pharm GmbH & Co. KG Lohner Strasse 19 49377 Vechta Germany	Ketabel vet. 100 mg/ml solution for injection	Ketamine	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats, horses, dogs, cats, guinea pigs, hamsters, rabbits, rats and mice	Intravenous, intramuscular and intraperitoneal use
Slovakia	Bela-Pharm GmbH & Co. KG Lohner Strasse 19 49377 Vechta Germany	Ketabel 100 mg/ml solution for injection	Ketamine	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats, horses, dogs, cats, guinea pigs, hamsters, rabbits, rats and mice	Intravenous, intramuscular and intraperitoneal use
Slovenia	Bela-Pharm GmbH & Co. KG Lohner Strasse 19 49377 Vechta Germany	Ketabel 100 mg/ml solution for injection	Ketamine	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats, horses, dogs, cats, guinea pigs, hamsters, rabbits, rats and mice	Intravenous, intramuscular and intraperitoneal use

Member State EU/EEA	Applicant	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
United Kingdom	Bela-Pharm GmbH & Co. KG Lohner Strasse 19 49377 Vechta Germany	Ketabel 100 mg/ml solution for injection	Ketamine	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats, horses, dogs, cats, guinea pigs, hamsters, rabbits, rats and mice	Intravenous, intramuscular and intraperitoneal use

Annex II

Scientific conclusions and grounds for the granting of the marketing authorisation

Overall summary of the scientific evaluation of Ketabel 100 mg/ml solution for injection and associated names (see Annex I)

1. Introduction

Ketabel 100 mg/ml solution for injection and associated names (thereafter called Ketabel) contains 100 mg ketamine as active substance per ml product. Ketamine belongs to the group of the dissociative anaesthetics. Ketabel is indicated in combination with a sedative for immobilisation, sedation and general anaesthesia for cattle, pigs, sheep, goats, dogs, cats, horses, guinea pigs, hamsters, rabbits, rats, and mice.

The applicant Bela-Pharm GmbH & Co. KG submitted a marketing authorisation application, via the decentralised procedure (FR/V/0338/001/DC), for Ketabel according to Article 13(1) of Directive 2001/82/EC, referring to the reference product Imalgene 1000 authorised in France since 1992. The marketing authorisation application was submitted to France as reference Member State (RMS) and Austria, Bulgaria, Czech Republic, Germany, Estonia, Greece, Finland, Hungary, Ireland, Iceland, Lithuania, Latvia, The Netherlands, Norway, Portugal, Romania, Sweden, Slovenia, Slovakia and the United Kingdom as concerned Member States.

During the decentralised procedure Germany considered that Ketabel may present a potential serious risk to human health. In particular, Germany considered that Ketabel is essentially different from the reference product Imalgene 1000 as it contains approximately 10% of the excipient propylene glycol and this difference could be sufficient to alter or interfere with residue depletion of the active substance at the injection site when Ketabel is administered via the intramuscular route to cattle, pigs, sheep and goats. These issues remained unsolved and they were referred under Article 33(1) of Directive 2001/82/EC to the Coordination group for Mutual recognition and Decentralised procedures (veterinary) (CMD(v)). Since the issues raised by Germany remained unsolved, the Member States concerned failed to reach agreement regarding the marketing authorisation for the product Ketabel and consequently the matter was referred to the CVMP on 5 July 2019 under Article 33(4) of Directive 2001/82/EC.

The Committee was asked to consider the issues raised by Germany and conclude whether a marketing authorisation for Ketabel should be granted.

2. Assessment of the data submitted

In this referral procedure, the Committee was asked to consider whether a meat and offal withdrawal period of 1 day with a limitation of the injection volume to 20 ml is sufficient to guarantee the consumer safety when Ketabel is administered via the intramuscular route to cattle, pigs, sheep and goats.

The formulation of Ketabel differs from the reference product, Imalgene 1000, as it contains 10% of propylene glycol. During the assessment in the context of the decentralised procedure for Ketabel (FR/V/0338/001/DC), it was concluded that the excipient propylene glycol was added in order to improve the formulation of the reference product in terms of antimicrobial preservation without differing qualitatively from the reference product in terms of preservative used (chlorobutanol).

The veterinary medicinal product Ketabel is administered by intramuscular route to the target species cattle, pigs, sheep and goats. During the assessment in the context of the decentralised procedure for Ketabel (FR/V/0338/001/DC), it was concluded that bioequivalence with the reference product (Imalgene 1000) was shown based on a biowaiver according to section 7.1.b) of the CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.3)[1]*: 'For products intended for intramuscular, subcutaneous or systemically acting topical administration, bioequivalence studies are not required in cases when the product is of the same type of solution, contains the same concentration of the active substance and comparable excipients in similar amounts as the reference product.'*

No product specific data in support of the meat and offal withdrawal period following intramuscular administration of Ketabel was made available to the Committee. However, in line with the CVMP aforementioned bioequivalence guideline (EMA/CVMP/016/2000-Rev.3), information on the behaviour of residues at the site of administration was provided.

Ketamine is a pharmacologically active substance included in table 1 of the Annex to Commission Regulation (EU) No 37/2010[2] with no maximum residue limits (MRL) required. Based on the residue study provided for the establishment of MRLs (no residue found at the injection site 24 hours post intramuscular administration), the fact that ketamine is used infrequently for treatment of individual animals, the fact that the animals are unlikely to be sent for slaughter during or immediately after treatment and the fact that ketamine is rapidly absorbed and rapidly and extensively excreted, the Committee did not consider it necessary to establish an MRL for ketamine (EPMAR, EMEA/MRL/315/97-FINAL)[3].

For the excipient propylene glycol an acceptable daily intake of 0-25 mg/kg bodyweight (equivalent to 1.5 g/day for a 60 kg adult), with a 'no maximum residue limits (MRL) required' status was established by the CVMP (EMEA/MRL/130/96-FINAL)[4].

According to a worst case-scenario, an injection site of cattle treated with Ketabel could contain up to 2 g propylene glycol (maximum intramuscular dose for cattle 4 mg ketamine per kg bodyweight, this would be 2000 mg ketamine for a cow of 500 kg, i.e. 20 ml of solution which contains 2000 mg propylene glycol [propylene glycol = 100 mg/ml]).

For pigs the intended intramuscular dose is up to 20 mg ketamine/kg bodyweight and this would lead to an absolute amount of 4000 mg of propylene glycol at the injection site (assuming a bodyweight of 200 kg).

The total amount of propylene glycol administered (2 g for cattle and 4 g for pigs) at the injection site at the time of product administration exceed the acceptable daily intake of 1.5 g per person per day. Based on these calculations, a withdrawal period of 1 day and a limitation of the injection volume to 20 ml has been proposed by the applicant as additional precautionary measures. The withdrawal period of 1 day is considered safe as it is not expected that the 2 g of propylene glycol remain at the injection site 24 hours post administration since, as discussed below, the absorption of propylene glycol is

[1] Guideline on the conduct of bioequivalence studies for veterinary medicinal products. www.ema.europa.eu/en/documents/scientific-guideline/guideline-conduct-bioequivalence-studies-veterinary-medicinal-products-revision-3_en.pdf
[2] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-5/reg_2010_37/reg_2010_37_en.pdf
[3] Ketamine MRL summary report. https://www.ema.europa.eu/en/documents/mrl-report/ketamine-summary-report-committee-veterinary-medicinal-products_en.pdf
[4] Propylene glycol MRL summary report. https://www.ema.europa.eu/en/documents/mrl-report/propylene-glycol-summary-report-committee-veterinary-medicinal-products_en.pdf

known to be very rapid (report of the International Program on Chemical Safety[5]; Kakemi *et al*. 1972[6]).

It can be predicted that the 10% propylene glycol will not slow down ketamine absorption at the injection site based on:

A. The very fast and high absorption of ketamine after intramuscular injection

Data from published literature were provided to emphasise that the absorption of ketamine following intramuscular administration is generally fast in humans and pigs, with approximately 100% bioavailability (WHO 2015[7], Löscher *et al*., 1990[8], Grant *et al*., 1981[9]).

The World Health Organisation (WHO) 2015 report on ketamine indicates that this active substance is rapidly absorbed when administered through the intramuscular route; the Tmax is reached between 5 to 15 minutes after intramuscular administration in humans.

The MRL summary report on ketamine (EMEA/MRL/315/97-FINAL) indicates that absorption from the injection site is rapid with a Tmax of 10 minutes.

The applicant has cited a pharmacokinetic study (Löscher *et al*. 1990) comparing intravenous and intramuscular administration of 15 mg ketamine per kg bodyweight to six healthy pigs (and two sows) and plasma concentrations were monitored over 8 hours. This study shows that ketamine absorption and elimination is very rapid after intramuscular administration in pigs (Tmax = 7.2 minutes and elimination half-life = 2.2 hours). A 100% bioavailability of intramuscular ketamine is determined. Data confirm that ketamine load is fully absorbed from the injection site following intramuscular administration.

B. The very rapid absorption of propylene glycol after intramuscular injection

In the report of the International Program on Chemical Safety, the absorption of propylene glycol administered by parenteral route is noted as immediate.

Propylene glycol's properties are compatible with a very quick absorption at the injection site as this is a solvent of low molecular weight (76.09 g/mol) which is very soluble in water. This was confirmed by Kakemi *et al*. (1972) who showed that absorption of propylene glycol at injection site in rats occurs within minutes (absorption rate around 0.4/min) for a 10% concentrated solution. This paper also showed that 10% of propylene glycol in a solution containing isonicotinamide only slightly modifies the absorption of propylene glycol and isonicotinamide (absorption rate constant of 0.4/min versus 0.5/min when there is no propylene glycol). Kakemi *et al*. (1972) also showed that the prediction of the absorption rate of a drug from an injectable solution could be possible by the viscosity of the solvent, provided that the solvents are of comparatively small weight and exert little local effect.

C. The fact that the physicochemical properties of the generic and the reference veterinary medicinal products are very similar.

Relevant physical-chemical characteristics of candidate and reference formulation have been analysed.

[5] Report of the International Program on Chemical Safety. Propylene glycol. http://www.inchem.org/documents/pims/chemical/pim443.htm
[6] Kakemi K., Sezaki H., Okumura K., Kobayashi H., Furusawa S. Absorption of drugs from the skeletal muscle of the rats. 3. Effect of water-soluble adjuvants and vehicles on the intramuscular absorption. Chem Pharm Bull (Tokyo) 1972 Mar; 20(3):443-51.
[7] Ketamine (INN) - Update Review Report. Agenda item 6.1. 37th Expert Committee on Drug Dependence (2015). https://api-cr.eudra.org/dossiers/Article%2033(4)/sequences/2019-10-08_3/documents/who-2015.pdf
[8] Löscher W., Ganter M. and Fassbender C.P. Correlation between drug and metabolite concentrations in plasma and anesthetic action of ketamine in swine. Am J Vet Res 1990 Mar; 51(3):391-8.
[9] Grant I.S., Nimmo W.S., Clements J.A. Pharmacokinetics and analgesic effects of i.m. and oral ketamine. Br J Anaesth. 1981 Aug; 53(8):805-10.

It should be noted that the viscosity and density of these aqueous products are similar to those of water. This can be explained by the fact that propylene glycol is only 10% of the formulation whereas water constitutes 80% of the formulation.

3. Benefit-risk assessment

Introduction

Bela-Pharm GmbH & Co. KG submitted a marketing authorisation application via the decentralised procedure under Article 13(1) of Directive 2001/82/EC (i.e. generic application) for Ketabel 100 mg/ml solution for injection and associated names. Ketabel is a solution for injection that contains 100 mg of ketamine per ml as active substance. Ketabel differs from the reference product Imalgene 1000 as it contains 10% of propylene glycol (as solvent for the preservative).

No specific residue data for Ketabel was made available to the CVMP. The appropriateness of the withdrawal period of 1 day with a limitation of the injection volume to 20 ml was discussed during this referral procedure.

Benefit assessment

The quality and efficacy of Ketabel has not been assessed as part of this referral but it was considered in the preceding decentralised procedure. The benefits of Ketabel are extrapolated from those of the reference product Imalgene 1000, given that bioequivalence has been accepted. The proposed indications for Ketabel are for immobilisation, sedation, general anaesthesia in combination with a sedative.

Given the legal basis of this marketing authorisation application (Article 13(1) of Directive 2001/82/EC – an application for a generic product) and the satisfactory justification for a waiver from the requirement to demonstrate bioequivalence with the reference product in accordance with section 7.1.b) of the CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.3), no pre-clinical or clinical data have been presented.

Risk assessment

Ketamine is a pharmacologically active substance included in table 1 of the Annex to Commission Regulation (EU) No 37/2010 with no maximum residue limits (MRL) required and no acceptable daily intake (ADI) established.

The Committee acknowledged that there is no data available on residue depletion of Ketabel. However, taking into account the very fast and high absorption of ketamine and propylene glycol after intramuscular injection as well as the close formulation and physicochemical properties between Ketabel and the reference product, it is expected that there will be no different rates of absorption from the injection site.

Risk management or mitigation measures

Having considered the grounds for referral and the data available, and to ensure the safety of consumers of food and food products derived from animals to be treated with Ketabel, the Committee is of the opinion that the proposed meat and offal withdrawal period of 1 day, with a restriction on the maximum injection volume to 20 ml, can be accepted as safe for the consumer.

Evaluation and conclusions on the benefit-risk balance

Overall, the Committee concludes that the concerns expressed by Germany should not prevent the granting of a marketing authorisation, where the withdrawal period is set at 1 day with a limitation of

the injection volume to 20 ml. A satisfactory justification has been provided that the excipient propylene glycol would not impact the safety of this veterinary medicinal product compared to the reference product.

Grounds for the granting of the marketing authorisation for Ketabel

Whereas

- On the basis of the available data the Committee concluded that the different formulation between Ketabel and the reference product will not impact the absorption of ketamine at the injection site after intramuscular administration;
- The Committee considered that a meat and offal withdrawal period of 1 day with a limitation of the injection volume to 20 ml is sufficient to guarantee the consumer safety when Ketabel is administered via the intramuscular route to cattle, pigs, sheep and goats.

Therefore, the CVMP has recommended the granting of the marketing authorisation for Ketabel 100 mg/ml solution for injection and associated names (see Annex I). The product information (summary of product characteristics, labelling and package leaflet) remains as per the final version achieved during the Coordination group procedure as mentioned in Annex III.

Annex III

The valid summary of product characteristics, labelling and package leaflet are the final versions achieved during the Coordination group procedure.