Annex I

List of the names, pharmaceutical form, strength of the veterinary medicinal product, animal species, route of administration, applicant / marketing authorisation holder in the member states

Member State EU/EEA	Applicant/Marketing Authorisation Holder	Name	Pharmaceutical form	Strengths	Animal species	Frequency and route of administration	Recommended dose
Austria	Dechra Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire SY4 4AS, United Kingdom	Clavudale 50 mg tablet for cats and dogs	Tablet	Amoxicillin 40 mg Clavulanic acid 10 mg	Cats and dogs	Oral administration, twice daily for 5-7 days	Standard dose rate of 10 mg amoxicillin/ 2.5 mg clavulanic acid/kg bodyweight
Belgium	Dechra Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire SY4 4AS, United Kingdom	Clavudale 50 mg tablet for cats and dogs	Tablet	Amoxicillin 40 mg Clavulanic acid 10 mg	Cats and dogs	Oral administration, twice daily for 5-7 days	Standard dose rate of 10 mg amoxicillin/ 2.5 mg clavulanic acid/kg bodyweight
Czech Republic	Dechra Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire SY4 4AS, United Kingdom	Clavudale 50 mg tablet for cats and dogs	Tablet	Amoxicillin 40 mg Clavulanic acid 10 mg	Cats and dogs	Oral administration, twice daily for 5-7 days	Standard dose rate of 10 mg amoxicillin/ 2.5 mg clavulanic acid/kg bodyweight
Denmark	Dechra Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire SY4 4AS, United Kingdom	Clavudale 40 mg / 10 mg tablet for cats and dogs	Tablet	Amoxicillin 40 mg Clavulanic acid 10 mg	Cats and dogs	Oral administration, twice daily for 5-7 days	Standard dose rate of 10 mg amoxicillin/ 2.5 mg clavulanic acid/kg bodyweight

Member State EU/EEA	Applicant/Marketing Authorisation Holder	Name	Pharmaceutical form	Strengths	Animal species	Frequency and route of administration	Recommended dose
Finland	Dechra Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire SY4 4AS, United Kingdom	Clavudale 40 mg / 10 mg tablet for cats and dogs	Tablet	Amoxicillin 40 mg Clavulanic acid 10 mg	Cats and dogs	Oral administration, twice daily for 5-7 days	Standard dose rate of 10 mg amoxicillin/ 2.5 mg clavulanic acid/kg bodyweight
France	Dechra Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire SY4 4AS, United Kingdom	Clavudale 50 mg tablet for cats and dogs	Tablet	Amoxicillin 40 mg Clavulanic acid 10 mg	Cats and dogs	Oral administration, twice daily for 5-7 days	Standard dose rate of 10 mg amoxicillin/ 2.5 mg clavulanic acid/kg bodyweight
Germany	Dechra Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire SY4 4AS, United Kingdom	Clavudale 40 mg / 10 mg tablet for cats and dogs	Tablet	Amoxicillin 40 mg Clavulanic acid 10 mg	Cats and dogs	Oral administration, twice daily for 5-7 days	Standard dose rate of 10 mg amoxicillin/ 2.5 mg clavulanic acid/kg bodyweight
Greece	Dechra Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire SY4 4AS, United Kingdom	Clavudale 40 mg / 10 mg tablet for cats and dogs	Tablet	Amoxicillin 40 mg Clavulanic acid 10 mg	Cats and dogs	Oral administration, twice daily for 5-7 days	Standard dose rate of 10 mg amoxicillin/ 2.5 mg clavulanic acid/kg bodyweight

Member State EU/EEA	Applicant/Marketing Authorisation Holder	Name	Pharmaceutical form	Strengths	Animal species	Frequency and route of administration	Recommended dose
Hungary	Dechra Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire SY4 4AS, United Kingdom	Clavudale 50 mg tablet for cats and dogs	Tablet	Amoxicillin 40 mg Clavulanic acid 10 mg	Cats and dogs	Oral administration, twice daily for 5-7 days	Standard dose rate of 10 mg amoxicillin/ 2.5 mg clavulanic acid/kg bodyweight
Iceland	Dechra Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire SY4 4AS, United Kingdom	Clavudale 40 mg / 10 mg tablet for cats and dogs	Tablet	Amoxicillin 40 mg Clavulanic acid 10 mg	Cats and dogs	Oral administration, twice daily for 5-7 days	Standard dose rate of 10 mg amoxicillin/ 2.5 mg clavulanic acid/kg bodyweight
Ireland	Dechra Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire SY4 4AS, United Kingdom	Clavudale 50 mg tablet for cats and dogs	Tablet	Amoxicillin 40 mg Clavulanic acid 10 mg	Cats and dogs	Oral administration, twice daily for 5-7 days	Standard dose rate of 10 mg amoxicillin/ 2.5 mg clavulanic acid/kg bodyweight
Luxembourg	Dechra Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire SY4 4AS, United Kingdom	Clavudale 50 mg tablet for cats and dogs	Tablet	Amoxicillin 40 mg Clavulanic acid 10 mg	Cats and dogs	Oral administration, twice daily for 5-7 days	Standard dose rate of 10 mg amoxicillin/ 2.5 mg clavulanic acid/kg bodyweight

Member State EU/EEA	Applicant/Marketing Authorisation Holder	Name	Pharmaceutical form	Strengths	Animal species	Frequency and route of administration	Recommended dose
The Netherlands	Dechra Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire SY4 4AS, United Kingdom	Clavudale 40 mg / 10 mg tablet for cats and dogs	Tablet	Amoxicillin 40 mg Clavulanic acid 10 mg	Cats and dogs	Oral administration, twice daily for 5-7 days	Standard dose rate of 10 mg amoxicillin/ 2.5 mg clavulanic acid/kg bodyweight
Norway	Dechra Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire SY4 4AS, United Kingdom	Clavudale 40 mg / 10 mg tablet for cats and dogs	Tablet	Amoxicillin 40 mg Clavulanic acid 10 mg	Cats and dogs	Oral administration, twice daily for 5-7 days	Standard dose rate of 10 mg amoxicillin/ 2.5 mg clavulanic acid/kg bodyweight
Poland	Dechra Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire SY4 4AS, United Kingdom	Clavudale 50 mg tablet for cats and dogs	Tablet	Amoxicillin 40 mg Clavulanic acid 10 mg	Cats and dogs	Oral administration, twice daily for 5-7 days	Standard dose rate of 10 mg amoxicillin/ 2.5 mg clavulanic acid/kg bodyweight
Portugal	Dechra Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire SY4 4AS, United Kingdom	Clavudale 40 mg / 10 mg tablet for cats and dogs	Tablet	Amoxicillin 40 mg Clavulanic acid 10 mg	Cats and dogs	Oral administration, twice daily for 5-7 days	Standard dose rate of 10 mg amoxicillin/ 2.5 mg clavulanic acid/kg bodyweight

Member State EU/EEA	Applicant/Marketing Authorisation Holder	Name	Pharmaceutical form	Strengths	Animal species	Frequency and route of administration	Recommended dose
Slovak Republic	Dechra Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire SY4 4AS, United Kingdom	Clavudale 50 mg tablet for cats and dogs	Tablet	Amoxicillin 40 mg Clavulanic acid 10 mg	Cats and dogs	Oral administration, twice daily for 5-7 days	Standard dose rate of 10 mg amoxicillin/ 2.5 mg clavulanic acid/kg bodyweight
Spain	Dechra Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire SY4 4AS, United Kingdom	Clavudale 40 mg / 10 mg tablet for cats and dogs	Tablet	Amoxicillin 40 mg Clavulanic acid 10 mg	Cats and dogs	Oral administration, twice daily for 5-7 days	Standard dose rate of 10 mg amoxicillin/ 2.5 mg clavulanic acid/kg bodyweight
Sweden	Dechra Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire SY4 4AS, United Kingdom	Clavudale 40 mg / 10 mg tablet for cats and dogs	Tablet	Amoxicillin 40 mg Clavulanic acid 10 mg	Cats and dogs	Oral administration, twice daily for 5-7 days	Standard dose rate of 10 mg amoxicillin/ 2.5 mg clavulanic acid/kg bodyweight
United Kingdom	Dechra Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire SY4 4AS, United Kingdom	Clavudale 50 mg tablet for cats and dogs	Tablet	Amoxicillin 40 mg Clavulanic acid 10 mg	Cats and dogs	Oral administration, twice daily for 5-7 days	Standard dose rate of 10 mg amoxicillin/ 2.5 mg clavulanic acid/kg bodyweight

Annex II

Scientific conclusions for granting of the marketing authorisation

Overall summary of the scientific evaluation of Clavudale 50 mg tablet for cats and dogs and associated names *(see Annex I)*, hereinafter referred to as Clavudale 50 mg

1. Introduction

Clavudale 50 mg tablets contain amoxicillin and clavulanic acid in a ratio of 4:1, thus the 50 mg tablet contains 40 mg amoxicillin/10 mg clavulanic acid. The proposed indications are a range of diseases including deep and superficial pyoderma, soft tissue infections, dental infections, urinary tract infections, respiratory disease and enteritis in dogs and cats. The proposed standard dose rate is 12.5 mg/kg twice daily for 5-7 days. For a minority of cases (refractory cases), a dose rate of 25 mg/kg twice daily for up to 28 days is proposed.

Clavudale 50 mg was authorised in the United Kingdom on 08/01/2010 under Article 13(1) of Directive 2001/82/EC. Bioequivalence is claimed with the reference product, Synulox Palatable Tablets 50 mg, marketed by Pfizer Ltd and authorised in the United Kingdom since 20/08/1990.

The application was submitted to the Concerned Member States (Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Luxembourg, the Netherlands, Norway, Poland, Portugal, Slovak Republic, Spain and Sweden) under the mutual recognition procedure. During the procedure, there was disagreement between the Reference Member State and Concerned Member States on the demonstration of bioequivalence in the cat target species. Two Concerned Member States (the Netherlands and Sweden) considered that the authorisation of Clavudale 50 mg in cats may present a potential serious risk to animal health since the safety and efficacy of the product had not been sufficiently demonstrated. Consequently the matter was referred to the CVMP.

The CVMP was asked to give its opinion on the concerns raised by the Concerned Member States and to conclude on the benefit/risk balance for Clavudale 50 mg.

2. Assessment of the data submitted

This referral under Article 33(4) of Directive 2001/82/EC was made on the basis that the applicant had not satisfactorily demonstrated bioequivalence between the generic product, Clavudale 50 mg tablet for cats and dogs, and the reference product, Synulox Palatable Tablets 50 mg, in the cat target species.

The applicant had conducted a two-period crossover *in vivo* bioequivalence study in cats. In addition, a comparative *in vitro* dissolution study was conducted between the generic and reference products. In the *in vivo* bioequivalence study conducted in cats, the 90% confidence interval for the ratio of geometric means of the pivotal pharmacokinetic parameters for demonstrating bioequivalence fell within pre-defined acceptance limits of 0.8 to 1.25 for clavulanic acid. However, in the case of the amoxicillin, the lower limit of the 90% confidence interval for the ratio of geometric means for maximum plasma concentration (C_{max}) and area under the plasma concentration/time curve (AUC) fell just below the acceptance limit. When data from one particular cat, considered an outlier by the applicant, were excluded from the analysis, the 90% confidence internal fell within the acceptance limits. However, the CVMP considered that it was inappropriate to exclude results from a bioequivalence analysis if provision for this had not been made in the study protocol. The reason for the anomalous pharmacokinetic profile in this cat is not known.

It was considered that, given the similar variability that was seen between the cat study and the larger dog bioequivalence study, the smaller size of the cat study may have made it more vulnerable to the effects of one cat with an anomalous pharmacokinetic profile. The failure to demonstrate bioequivalence may well have been influenced by the study design (lack of power) rather than by true non-bioequivalence of the generic and reference products.

The guideline on the conduct on bioequivalence studies indicates that bioequivalence (based on *in vivo* data) should always be established based on conclusive studies in each major animals species for which an indication is claimed. Notwithstanding, the bioequivalence study in dogs provides reassurance that the formulation of the product is unlikely to be a contributing factor impacting on bioavailability in cats given that the 50 mg and 250 mg tablets are directly proportional and bioequivalence was satisfactorily demonstrated in dogs for both active substances. It was shown that, in dogs, the commonly used excipients present in the generic formulation did not affect the rate or extent of absorption of amoxicillin.

The dissolution studies presented by the applicant demonstrated similar dissolution profiles when different strengths of the generic and reference products were compared, which provides further reassurance on the pharmaceutical quality of the tablets.

Given the above, as well as current efforts to reduce the number of animals taking part in studies, it was considered unnecessary and unjustifiable to request the applicant to conduct another, larger, study in cats.

Grounds for recommendation of the granting of marketing authorisations

Having considered all of the data submitted in writing, the CVMP concludes that there is no rigorous scientific basis for a conclusion of serious risk in the cat target species based on a lower confidence limit for the AUC of amoxicillin which fell only narrowly below the pre-specified lower limit. Given,

- the well-known active substances and excipients;
- the similarity of the generic and reference product formulations;
- accepted demonstration of bioequivalence within the 0.8-1.25 acceptance limits in dogs with a different tablet strength;
- the similar and very rapid dissolution profiles of the generic and reference products at three pHs;

the weight of evidence is considered to support that the benefits of this product when used in the cat outweigh the potential risks.

Therefore, the CVMP recommends the granting of the marketing authorisations for Clavudale 50 mg tablets for cats and dogs and associated names (see Annex I) for which the summary of product characteristics, labelling and package leaflet are set out in Annex III.

Annex III

Summary of product characteristics, labelling and package leaflet

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