# Annex I

# List of the names, pharmaceutical form, strength of the veterinary medicinal products, animal species, routes of administration, applicant in the Member States

| Member State EU/EEA | Applicant | Name | INN | Strength | Pharmaceutical form | Animal species | Route of administration |
|---|---|---|---|---|---|---|---|
| Austria | CP- Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Catophos 100 mg/ml + 0.05 mg/ml injektionslösung für pferde, rinder, hunde und katzen | Butafosfan Cyanocobalamin | 100 mg/ml + 0.05 mg/ml | Solution for injection | Cattle, horse, dog, cat | Cattle, horse: intravenous use<br>Dog, cat: intravenous, intramuscular, subcutaneous use |
| Belgium | CP- Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Catophos 100 mg/ml + 0.05 mg/ml solution injectable pour chevaux, bovins, chiens et chats | Butafosfan Cyanocobalamin | 100 mg/ml + 0.05 mg/ml | Solution for injection | Cattle, horse, dog, cat | Cattle, horse: intravenous use<br>Dog, cat: intravenous, intramuscular, subcutaneous use |
| Czechia | CP- Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Catophos 100 mg/ml + 0.05 mg/ml injekční roztok pro koně, skot, psy a kočky | Butafosfan Cyanocobalamin | 100 mg/ml + 0.05 mg/ml | Solution for injection | Cattle, horse, dog, cat | Cattle, horse: intravenous use<br>Dog, cat: intravenous, intramuscular, subcutaneous use |
| Denmark | CP- Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Catophos Vet 100 mg/ml + 0.05 mg/ml injektionsvæske opløsning til heste, kvæg, hunde og katte | Butafosfan Cyanocobalamin | 100 mg/ml + 0.05 mg/ml | Solution for injection | Cattle, horse, dog, cat | Cattle, horse: intravenous use<br>Dog, cat: intravenous, intramuscular, subcutaneous use |

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|---|---|---|---|---|---|---|---|
| Estonia | CP- Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Catophos | Butafosfan Cyanocobalamin | 100 mg/ml + 0.05 mg/ml | Solution for injection | Cattle, horse, dog, cat | Cattle, horse: intravenous use<br>Dog, cat: intravenous, intramuscular, subcutaneous use |
| Germany | CP- Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Catophos 100 mg/ml + 0.05 mg/ml injektionslösung für pferde, rinder, hunde und katzen | Butafosfan Cyanocobalamin | 100 mg/ml + 0.05 mg/ml | Solution for injection | Cattle, horse, dog, cat | Cattle, horse: intravenous use<br>Dog, cat: intravenous, intramuscular, subcutaneous use |
| Finland | CP- Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Catophos Vet 100 mg/ml + 0.05 mg/ml injektioneste, liuos hevosille, naudoille, koiralle ja kissoille | Butafosfan Cyanocobalamin | 100 mg/ml + 0.05 mg/ml | Solution for injection | Cattle, horse, dog, cat | Cattle, horse: intravenous use<br>Dog, cat: intravenous, intramuscular, subcutaneous use |
| France | CP- Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Catophos 100 mg/ml + 0.05 mg/ml solution injectable pour chevaux, bovins, chiens et chats | Butafosfan Cyanocobalamin | 100 mg/ml + 0.05 mg/ml | Solution for injection | Cattle, horse, dog, cat | Cattle, horse: intravenous use<br>Dog, cat: intravenous, intramuscular, subcutaneous use |

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|---|---|---|---|---|---|---|---|
| Hungary | CP- Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Catophos 100 mg/ml + 0.05 mg/ml oldatos injekció szarvasmarhák, lovak, kutyák, és macskák részére A.U.V. | Butafosfan Cyanocobalamin | 100 mg/ml + 0.05 mg/ml | Solution for injection | Cattle, horse, dog, cat | Cattle, horse: intravenous use<br>Dog, cat: intravenous, intramuscular, subcutaneous use |
| Ireland | CP- Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Catophos 100 mg/ml + 0.05 mg/ml solution for injection for horses, cattle, dogs and cats | Butafosfan Cyanocobalamin | 100 mg/ml + 0.05 mg/ml | Solution for injection | Cattle, horse, dog, cat | Cattle, horse: intravenous use<br>Dog, cat: intravenous, intramuscular, subcutaneous use |
| Italy | CP- Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Catophos 100 mg/ml + 0.05 mg/ml soluzione iniettabile per cavalli, bovini, cani e gatti | Butafosfan Cyanocobalamin | 100 mg/ml + 0.05 mg/ml | Solution for injection | Cattle, horse, dog, cat | Cattle, horse: intravenous use<br>Dog, cat: intravenous, intramuscular, subcutaneous use |
| Latvia | CP- Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Catophos | Butafosfan Cyanocobalamin | 100 mg/ml + 0.05 mg/ml | Solution for injection | Cattle, horse, dog, cat | Cattle, horse: intravenous use<br>Dog, cat: intravenous, intramuscular, subcutaneous use |

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|---|---|---|---|---|---|---|---|
| Lithuania | CP- Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Catophos | Butafosfan Cyanocobalamin | 100 mg/ml + 0.05 mg/ml | Solution for injection | Cattle, horse, dog, cat | Cattle, horse: intravenous use<br>Dog, cat: intravenous, intramuscular, subcutaneous use |
| Netherlands | CP- Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Catophos 100 mg/ml + 0.05 mg/ml oplossing voor injectie voor paarden, runderen, honden en katten | Butafosfan Cyanocobalamin | 100 mg/ml + 0.05 mg/ml | Solution for injection | Cattle, horse, dog, cat | Cattle, horse: intravenous use<br>Dog, cat: intravenous, intramuscular, subcutaneous use |
| Norway | CP- Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Catophos Vet 100 mg/ml + 0.05 mg/ml injeksjonsvæske, oppløsning til hester, storfe, hunder og katter | Butafosfan Cyanocobalamin | 100 mg/ml + 0.05 mg/ml | Solution for injection | Cattle, horse, dog, cat | Cattle, horse: intravenous use<br>Dog, cat: intravenous, intramuscular, subcutaneous use |
| Poland | CP- Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Catophos 100 mg/ml + 0.05 mg/ml roztwór do wstrzykiwań dla koni, bydła, psów i kotów | Butafosfan Cyanocobalamin | 100 mg/ml + 0.05 mg/ml | Solution for injection | Cattle, horse, dog, cat | Cattle, horse: intravenous use<br>Dog, cat: intravenous, intramuscular, subcutaneous use |

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|---|---|---|---|---|---|---|---|
| Portugal | CP- Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Catophos 100 mg/ml + 0.05 mg/ml solução injetável para cavalos, bovinos, cães e gatos | Butafosfan Cyanocobalamin | 100 mg/ml + 0.05 mg/ml | Solution for injection | Cattle, horse, dog, cat | Cattle, horse: intravenous use<br>Dog, cat: intravenous, intramuscular, subcutaneous use |
| Slovakia | CP- Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Catophos 100 mg/ml + 0.05 mg/ml injekčný roztok pre kone, hovädzí dobytok, psy a mačky | Butafosfan Cyanocobalamin | 100 mg/ml + 0.05 mg/ml | Solution for injection | Cattle, horse, dog, cat | Cattle, horse: intravenous use<br>Dog, cat: intravenous, intramuscular, subcutaneous use |
| Spain | CP- Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Catophos 100 mg/ml + 0.05 mg/ml solución inyectable para caballos, bovino, perros y gatos | Butafosfan Cyanocobalamin | 100 mg/ml + 0.05 mg/ml | Solution for injection | Cattle, horse, dog, cat | Cattle, horse: intravenous use<br>Dog, cat: intravenous, intramuscular, subcutaneous use |
| Sweden | CP- Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Catophos Vet 100 mg/ml + 0.05 mg/ml injektionsvätska, lösning för hästar, nötkreatur, hundar och katter | Butafosfan Cyanocobalamin | 100 mg/ml + 0.05 mg/ml | Solution for injection | Cattle, horse, dog, cat | Cattle, horse: intravenous use<br>Dog, cat: intravenous, intramuscular, subcutaneous use |

| Member State EU/EEA | Applicant | Name | INN | Strength | Pharmaceutical form | Animal species | Route of administration |
|---|---|---|---|---|---|---|---|
| United Kingdom (Northern Ireland)[1] | CP- Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Catophos 100 mg/ml + 0.05 mg/ml solution for injection for horses, cattle, dogs and cats | Butafosfan Cyanocobalamin | 100 mg/ml + 0.05 mg/ml | Solution for injection | Cattle, horse, dog, cat | Cattle, horse: intravenous use<br>Dog, cat: intravenous, intramuscular, subcutaneous use |

[1] For the United Kingdom, as from 1 January 2021, EU Law applies only to the territory of Northern Ireland (NI) to the extent foreseen in the Protocol on Ireland/NI.

# Annex II

# Scientific conclusions and grounds for the granting of the marketing authorisation

# Overall summary of the scientific evaluation of Catophos 100 mg/ml+0.05 mg/ml solution for injection for horses, cattle, dogs and cats and associated names (see Annex I)

## 1. Introduction

Catophos 100 mg/ml + 0.05 mg/ml solution for injection for horses, cattle, dogs and cats and associated names (thereafter called 'Catophos') contains 100 mg of butafosfan per ml and 0.05 mg of cyanocobalamin (vitamin B12) per ml as active substances, and 2% benzyl alcohol as an excipient.

The proposed indications for 'Catophos' are: supportive treatment of metabolic or reproductive disorders when supplementation of phosphorus and cyanocobalamin is needed; in case of peri-parturient metabolic disorders, tetany and paresis (milk fever), the product should be administered in addition to magnesium and calcium, respectively; it may be used also to support muscle function in the presence of deficiencies of phosphorus and/or cyanocobalamin.

'Catophos' may be administered intravenously in cattle and horses and via intravenous, intramuscular and subcutaneous routes in dogs and cats.

The applicant CP-Pharma Handelsgesellschaft mbH submitted a marketing authorisation application via the decentralised procedure under Article 13(3) of Directive 2001/82/EC for the veterinary medicinal product Catophos 100 mg/ml+0.05 mg/ml solution for injection for horses, cattle, dogs and cats and associated names. This was a hybrid marketing authorisation application since there was a change in the therapeutic indication and routes of administration compared to the reference veterinary medicinal product 'Catosal' authorised in Czechia since 1994. The formulation of 'Catosal' contains 100 mg of butafosfan per ml and 0.05 mg of cyanocobalamin per ml as active substances and 3% butanol as an excipient.

The marketing authorisation application was submitted to the reference Member State (RMS): Czechia and the concerned Member States (CMS): Austria, Belgium, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, the Netherlands, Norway, Poland, Portugal, Slovakia, Spain, Sweden and the United Kingdom (Northern Ireland).

During the decentralised procedure (CZ/V/0172/001/DC), the CMS Germany raised concerns on bioequivalence. In particular, Germany considered that the applicant had not adequately justified that the difference in the excipients (preservatives) and their concentration as well as the differences in physico-chemical properties (i.e., pH, osmolality and viscosity) of the reference and test formulations have no influence on the rate and/or extent of absorption of the active substances. Therefore, Germany considered that the conditions for the 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.4)[2] regarding the subcutaneous and intramuscular administration in dogs and cats were not fulfilled and could not accept the claimed biowaiver. These concerns 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 for veterinary medicinal products (CMDv). Since no agreement was reached during the CMDv referral procedure, on 25 August 2022 the matter was referred to the Committee for Veterinary Medicinal Products (CVMP) under Article 33(4) of Directive 2001/82/EC.

[2] CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4) - link

The CVMP was asked to consider the concerns raised by Germany and to conclude whether a marketing authorisation for 'Catophos' should be granted.

# 2. Assessment of the data submitted

In this referral procedure, the CVMP was asked to consider whether 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.4)[2] could be accepted for the veterinary medicinal product Catophos 100 mg/ml + 0.05 mg/ml solution for injection and associated names regarding the intramuscular and subcutaneous routes of administration in the target species dogs and cats.

The formulation of the reference product 'Catosal' contains 100 mg of butafosfan per ml and 0.05 mg of cyanocobalamin (vitamin B12) per ml as active substances and 3% butanol as an excipient. 'Catophos' is an aqueous solution for injection containing the same active substances as the reference product and in the same concentration, but substitutes 2% benzyl alcohol as an excipient instead of 3% butanol.

According to section 7.1.b) of the above-mentioned CVMP guideline, studies to compare the rate and extent of absorption between the reference medicinal product and the test product are generally not required for veterinary medicinal products intended for intramuscular, subcutaneous or systemically-acting topical administration when the products are of the same type of solution, contain the same concentration of the active substance and comparable excipients in similar amounts, if it can be adequately justified that any difference(s) in the excipient(s) and/or their concentration have no influence on the rate and/or extent of absorption of the active substance.

No in vivo experimental data was made available to the Committee to demonstrate that bioavailability of the active substances butafosfan and cyanocobalamin is not influenced by the changes of preservatives. However, detailed information on the chemical properties of each excipient and on the physico-chemical properties of the reference and test formulations were provided. Furthermore, published literature was also provided by the applicant.

Although slight differences in physico-chemical properties (i.e., viscosity, osmolality and pH value) between 'Catophos' and 'Catosal' were noted, they were not considered meaningful and their impact on the rate and extent of absorption of butafosfan and cyanocobalamin from the subcutaneous and intramuscular injection site was considered relatively small and not clinically relevant in terms of bioequivalence.

Considering an overall high bioavailability of the active substances and a fast absorption from the injection site, in addition to the claimed indications and a large margin of safety of the active substances butafosfan as well as cyanocobalamin, the CVMP considered that the relatively small differences observed have no impact on the safety and efficacy of the veterinary medicinal product.

The CVMP considered that exemption from the requirement for bioequivalence studies for intramuscular and subcutaneous administration in dogs and cats in accordance with section 7.1.b) of the above-mentioned CVMP guideline was adequately justified on the basis of data and explanations provided regarding physico-chemical characteristics of the individual components and the final formulation.

# 3. Benefit-risk assessment

**Introduction**

CP-Pharma Handelsgesellschaft mbH submitted a marketing authorisation application via the decentralised procedure under Article 13(3) of Directive 2001/82/EC (i.e. a hybrid application) for the veterinary medicinal product Catophos 100 mg/ml+0.05 mg/ml solution for injection for horses, cattle, dogs and cats and associated names. 'Catophos' is an aqueous solution for injection that contains 100 mg of butafosfan per ml and 0.05 mg of cyanocobalamin (vitamin B12) per ml as active substances and 2% benzyl alcohol as an excipient. It differs from the reference product 'Catosal' which contains 3% butanol as an excipient.

The applicant for 'Catophos' claimed exemption from bioequivalence studies for the intramuscular and subcutaneous routes of administration on the basis of biowaiver section 7.1.b) of the CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4)[2].

During this referral procedure the CVMP discussed whether a biowaiver according to the above-mentioned section of the CVMP guideline could be accepted for 'Catophos' for the intramuscular and subcutaneous routes of administration in dogs and cats.

**Benefit assessment**

The efficacy of 'Catophos' has not been assessed as part of this referral. As a hybrid application, the benefits of 'Catophos' are extrapolated from those of the reference product 'Catosal', given that the biowaiver, and consequently bioequivalence, has been accepted by the CVMP. The proposed indications for 'Catophos' are: supportive treatment of metabolic or reproductive disorders, when supplementation of phosphorous and cyanocobalamin is needed; in case of peri-parturient metabolic disorders, tetany and paresis (milk fever), the product should be administered in addition to magnesium and calcium, respectively; to support muscle function in the presence of deficiencies of phosphorous and/or cyanocobalamin.

**Risk assessment**

The safety of 'Catophos' has not been assessed as part of this referral. As a hybrid application, the risks of 'Catophos' are extrapolated from those of the reference product 'Catosal', given that the biowaiver, and consequently bioequivalence, has been accepted by the CVMP.

With regards to quality, the Committee acknowledged that no in vivo experimental data was available to demonstrate the effect of the excipient benzyl alcohol on the rate or extent of absorption of the active substances butafosfan or cyanocobalamin. However, physico-chemical properties of the test and reference formulations were provided. Based on the available data, the impact on the bioavailability of the active substances by the change in the preservative system is expected to be relatively small considering the high bioavailability of the active substances and a fast absorption from the injection site, in addition to the claimed indications and a large margin of safety of the active substances butafosfan as well as cyanocobalamin.

**Risk management or mitigation measures**

Since the biowaiver, and consequently bioequivalence, can be accepted by the CVMP, no additional risk management or mitigation measures compared to those already in place for the reference product were proposed for 'Catophos' as a consequence of this referral.

**Evaluation and conclusions on the benefit-risk balance**

The data submitted by the applicant confirmed that, when the veterinary medicinal product is used in accordance with the summary of product characteristics, the benefit-risk profile for the intramuscular or subcutaneous routes of administration in the target species dogs and cats is favourable.

Overall, the Committee concluded that the concerns expressed by Germany should not prevent the granting of a marketing authorisation for the veterinary medicinal product 'Catophos'. A satisfactory justification was provided by the applicant that the impact on the bioavailability of the active substances by the change in the excipient is relatively small and not clinically relevant in terms of bioequivalence. In addition, this change have no impact on the efficacy and safety of this veterinary medicinal product compared to the reference product.

# Grounds for the granting of the marketing authorisation

Whereas

- On the basis of the available data the Committee concluded that despite the difference in the formulation between 'Catophos' and the reference product, effects on bioavailability of the active substances butafosfan and cyanocobalamin after intramuscular and subcutaneous administration in the target species dogs and cats would be relatively small and not clinically relevant in terms of bioequivalence;
- The Committee consequently considered that exemption from the requirement for bioequivalence studies for the intramuscular and subcutaneous routes of administration in dogs and cats 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.4)[2] was adequately justified on the basis of the data and explanations provided regarding physico-chemical characteristics of the individual components and the final formulation;
- The Committee concluded that bioequivalence of 'Catophos' and the reference veterinary medicinal product 'Catosal' is considered demonstrated.

Therefore, the CVMP recommended the granting of the marketing authorisation for Catophos 100 mg/ml + 0.05 mg/ml solution for injection for horses, cattle, dogs and cats and associated names (see Annex I). The summary of product characteristics, labelling and package leaflet remain 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.