This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product	[CV004 trade name][*]
Manufacturer of Prequalified Product	Farmak JSC 74 Kyrylivska St. Kyiv Ukraine
Active Pharmaceutical Ingredient(s) (API)	Dexamethasone phosphate
Pharmaco-therapeutic group (ATC Code)	Corticosteroids for systemic use, Glucocorticoid (H02AB02)
Therapeutic indication	Corticosteroid used in a wide range of conditions for its anti-inflammatory and immunosuppressant effects.

1. Introduction

[CV004 trade name] is indicated for the management of conditions responsive to parenteral treatment with a potent glucocorticoid, including: cerebral oedema and raised intracranial pressure; adjunctive management of refractory shock; postoperative or chemotherapy-induced nausea and vomiting; in palliative care for the management of symptoms such as anorexia, dsypnoea, dysphagia, pain and neoplastic spinal cord compression; and in the acute management of severe corticosteroid-responsive allergic, inflammatory and autoimmune disorders.

Local (intra-articular or intralesional) injection of [CV004 trade name] may be given as part of the short-term management of inflammatory joint and tendon disorders, and localised inflammatory and hypertrophic skin lesions including those of lichen simplex, lichen planus, granuloma annulare, discoid lupus erythematosus, and keloids.

[CV004 trade name] may also be used in the treatment of coronavirus disease 2019 (COVID-19) in adult and adolescent patients (aged 12 years and older with body weight of at least 40 kg) who require supplemental oxygen therapy.

2. Assessment of quality

The assessment was done in accordance with the requirements of WHO's *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part.*

Active pharmaceutical Ingredient (API)

A CEP (Certificate of Suitability) issued by the EDQM was submitted, ensuring good manufacturing control and applicability of the Ph.Eur monograph to control quality of the API.

[*] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is stored in the original packaging.

Other ingredients

Other ingredients include sodium citrate, disodium edetate, creatinine, water for injections and 1 M sodium hydroxide for adjusting the pH to 7.0-8.5. No excipient with the risk of transmitting TSE/BSE is used.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a clear colourless or yellowish solution filled in a type 1 hydrolytic, amber glass ampoule with a break ring or break point. The solution for injection is administered by the intravenous or intramuscular route.

The goal of the formulation development strategy was to develop a product with a similar quality profile to that of the comparator product. The excipients used are identical to the excipients in the WHO recommended comparator product: Fortecortin® Injection 4 mg/mL solution for injection manufactured by Merck.

The manufacturing process is a standard process – conducted under appropriate aseptic conditions – including the steps of preparation of the solution with adjustment of pH, sterile filtration, filling of the solution in ampoules and sealing. The headspace of the ampoules is replaced with nitrogen during the filling process to prevent oxidation of the API. Satisfactory operating parameters and in-process controls have been defined at each stage of manufacture. Process validation have been conducted on 3 consecutive batches. Satisfactory in-process controls have been established.

Specifications

The finished product specifications include tests for description, identification of the API (HPLC and UV), identification of disodium edetate and creatinine (HPLC), pH, clarity, coloration, extractable volume, particulate matter, related substances (HPLC), sterility, bacterial endotoxins and assay of the API, disodium edetate and creatinine (HPLC).

Stability testing

Stability studies have been conducted at 30°C/65%RH, 25°C/60%RH and 5°±3°C as long-term storage condition and for six months at accelerated conditions in the packaging intended for marketing of the product. The data provided show that the product is not stable at 30°C and it should be stored at not above 25°C, with avoidance of excursions above this temperature. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The applicant requests a biowaiver as per WHO Technical Report Series, No. 1003 which indicates that no bioequivalence study is necessary when the pharmaceutical product is to be administered parenterally (e.g. intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations as in the comparator product.

The appropriate comparator product is Fortecortin 4 mg/ml, solution for injection (Merck, Europe). The proposed product is also a solution for injection, i.e. Dexametasone phosphate 4 mg/mL. The formulations contain comparable excipients.

As the proposed product meet the biowaiver requirements described above, a biowaiver can be granted.

4. Summary of product safety and efficacy

[CV004 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. The clinical safety of [CV004 trade name] is considered acceptable when guidance and restrictions stated in the summary of product characteristics (SmPC) are considered. Refer to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

Physicochemical and biological aspects relevant to the uniform pharmaceutical characteristics have been investigated and are controlled in a satisfactory way. The quality of this product is considered to lead to an acceptable clinical performance when [CV004 trade name] is used in accordance with the SmPC.

Bioequivalence

[CV004 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

Efficacy and Safety

Regarding clinical efficacy and safety, [CV004 trade name] is considered effective and safe to use when the guidance and restrictions in the SmPC are taken into consideration.

Benefit Risk Assessment

Based on WHO's assessment of data on quality, safety and efficacy the team of assessors considered that the benefit–risk profile of [CV004 trade name] was acceptable for the management of conditions responsive to parenteral treatment with a potent glucocorticoid, and would allow inclusion of [CV004 trade name], manufactured at Farmak JSC, 74 Kyrylivska St., Kyiv, Ukraine, in the list of prequalified medicinal products.