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	[RH095 trade name][*]
Manufacturer of Prequalified Product	Ferring Pharmaceuticals (China) Co., Ltd. No. 6 HuiLing Lu (Ferring Road), National Health Technology Park, Zhongshan City, Guangdong Province, People's Republic of China Steril-Gene Life Sciences Private Ltd. 45, Main Road, Mangalam Village, Villianur, Puducherry 605110, India
Active Pharmaceutical Ingredient(s) (API)	Carbetocin
Pharmaco-therapeutic group (ATC Code)	Oxytocin and analogues (H01BB03)
Therapeutic indication	[RH095 trade name] is indicated for the prevention of postpartum haemorrhage due to uterine atony.

1. Introduction

[RH095 trade name] is indicated for the prevention of postpartum haemorrhage due to uterine atony.

Carbetocin is intended for use only by appropriately skilled and trained health care providers.

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)

Carbetocin, cyclo 1-6(carba-deamino-cysteinyl-O-methyl-tyrosyl-isoleucyl-glutaminyl-asparaginyl-cysteinylprolyl- leucyl-glycineamide), is a white fluffy powder. It is soluble in water, acetic acid 0.1% in water, freely soluble in ethanol and dimethylsulfoxide.

The manufacturing process consists of the following main steps; solid phase synthesis of a linear deprotected peptide, cyclisation of linear deprotected peptide to crude carbetocin, purification and lyophilisation of crude carbetocin. The specifications for the starting material and the intermediate

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

ensure adequate control thereof. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

The API specifications include tests for appearance, identification (HPLC and MS), related substances, assay (HPLC), specific optical rotation, acetic acid content, water content, residual solvents and microbial limits.

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 L-methionine, succinic acid, mannitol, water for injections and sodium hydroxide for adjusting the pH to 5.1-5.8. 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 and colourless solution, practically free of foreign matter other than gas bubbles filled in 1 mL one-point-cut (OPC) clear colourless Type I glass ampoule with a white OPC dot.

The room-temperature stable carbetocin solution for injection has been developed based on the knowledge gained from an isotonic saline carbetocin solution that has been on the market for more than 15 years.

The manufacturing process is a standard process – conducted under appropriate aseptic conditions – including the steps of compounding, aseptic filtration, filling and sealing of the solution in glass ampoules. Satisfactory operating parameters have been defined at each stage of manufacture. Process validation have been conducted on three consecutive batches. Based on the satisfactory data of optimization trials, the formulation was finalized resulting in a product matching the quality target product profile. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for description, colour of solution, particulate contamination (visible particles and sub-visible particles), pH, osmolality, extractable volume, identification of the API and L-methionine (LC/UV), assay (LC/UV), degradation products (LC/UV), bacterial endotoxins and sterility.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated conditions. The product appeared to be quite stable at both long term and accelerated storage conditions with no apparent negative trend. 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

[RH095 trade name] is identical to Pabal® 100 µg/ml, solution for injection (the current commercialised product marketed by Ferring and launched worldwide, which is the same formulation but presented in a vial).

Pabal® 100 µg/ml, solution for injection, is currently marketed under different names worldwide. Pabal® 100 µg/ml, solution for injection, is the listed WHO comparator product for carbetocin 100 µg/ml, solution for injection.

4. Summary of product safety and efficacy

[RH095 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. According to the submitted data on quality, [RH095 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Pabal® 100 µg/ml, solution for injection (Ferring Pharmaceuticals Ltd) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [RH095 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 [RH095 trade name] is used in accordance with the SmPC.

Bioequivalence

[RH095 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, [RH095 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 [RH095 trade name] was acceptable for the following indication: 'prevention of postpartum haemorrhage due to uterine atony', and would allow inclusion of [RH095 trade name], manufactured at Ferring Pharmaceuticals (China) Co., Ltd., Zhongshan City, Guangdong Province, People’s Republic of China, and Steril-Gene Life Sciences Private Ltd., Puducherry 605110, India, in the list of prequalified medicinal products.