This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	Santocyn[1]
Manufacturer of Prequalified Product:	PT SANBE FARMA Jl. Taman Sari No.10, Bandung 40116- Indonesia
Active Pharmaceutical Ingredient (API):	Oxytocin
International Nonproprietary Name:	Oxytocin
Pharmaco-therapeutic group (ATC Code):	Posterior pituitary lobe hormones (H01BB02)
Therapeutic indication:	Indicated in women for the active management of the third stage of labour, prevention and treatment of postpartum haemorrhage and for managing pregnancy complications where uterine contraction is clinically desirable

[1] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

Santocyn is indicated for women for the active management of the third stage of labour, prevention and treatment of postpartum haemorrhage and for managing pregnancy complications where uterine contraction is clinically desirable. Santocyn should not be used in women with significant hypersensitivity to oxytocin or to any of the components in the formulation. It must also not be used when vaginal delivery might be problematic or in case of hypertonic uterine contractions or fetal distress.

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 (European Directorate for the Quality of Medicines and HealthCare) was submitted, ensuring good manufacturing control and applicability of the Ph.Eur monograph to control quality of the API.

Other ingredients

Other ingredients include chlorobutanol hemihydrate, glacial acetic acid, anhydrous sodium acetate, ethanol, sodium chloride and water for injections. No excipient with the risk of transmitting TSE (transmissible spongiform encephalopathy) or BSE (bovine spongiform encephalopathy) is used.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource Santocyn is a clear, colourless, sterile solution contained in a clear, colourless type I glass ampoule with a white colour break. The ampoule has double orange rings and red vertical "SANBE" print, containing 1 mL of the solution for injection. The ampoules should be stored refrigerated (2– 8°C) protected from light, to limit degradation of the API.

The development strategy was to obtain a product with a quality profile similar to that of the WHO recommended comparator product, Syntocinon® 10 units/ml injection (Novartis). The innovator was characterised in terms of e.g. description, pH, density and assay. The ingredients selected are the same as those used in the comparator, except for sodium chloride. The comparator product also contains the preservative chlorobutanol in its formula. The stability of the injection solution is pH-dependent, thus a buffering agent is included to attain a favourable pH. The comparator product is hypotonic while the multisource product has been formulated to the physiological tonicity with the inclusion of sodium chloride. Since this a SVP product, the differences in tonicity is not regarded an issue with respect to the safety or quality of the product.

The manufacturing process is a standard aseptic process, conducted under appropriate conditions, including the steps of mixing and dissolving all ingredients and water for injection, sterile filtration, followed by filling into empty sterile ampoules and sealing. Satisfactory operating parameters and in-process controls have been defined at each stage of manufacture. Process validation have been conducted on 3 consecutive batches.

Specifications

The finished product specifications are pharmacopoeial based and include tests for appearance, identification of the API (HPLC and TLC), pH, oxytocin assay (HPLC), particulate matter, sterility, weight per ml, osmolality, net volume per ampoule, ampoule leakage, preservative assay, bacterial endotoxins and related substances (HPLC).

Stability testing

Stability studies have been performed at 2–8°C as long-term storage conditions and for six months at 25°C/60% RH as accelerated conditions. A noticeable decrease in oxytocin assay value was observed at both long-term and accelerated storage conditions, though within agreed limits. Based on the available stability data, the proposed shelf life and storage conditions of the unopened ampoules as stated in the summary of product characteristics (SmPC) are acceptable. Oxytocin is light-sensitive, thus the product has to be protected from light.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The applicant requested a biowaiver as per WHO Technical Report Series, No. 992 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 Syntocinon (oxytocin 10 units/ml, solution for injection, Novartis). The proposed product, i.e. Santocyn, is also a solution for injection. Both formulations do not contain excipients which may affect the availability of oxytocin.

As the proposed product meets the biowaiver requirements described above, a biowaiver was granted.

4. Summary of Product Safety and Efficacy

Santocyn has been shown to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovators' products. According to the submitted data on quality and bioavailability it is pharmaceutically and therapeutically equivalent to the reference product, Syntocinon® (oxytocin 10 units/ml, solution for injection, Novartis).

The clinical safety of this product is considered acceptable when the guidance and restrictions in the SmPC are taken into consideration. Reference is made to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions stated in the summary of product characteristics (SmPC, Part 4 of this WHOPAR). Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Efficacy and Safety

Regarding clinical efficacy and safety, Santocyn is considered effective and safe when the guidance and restrictions presented in the SmPC are taken into consideration.

Benefit–risk Assessment

Based on the WHO assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered by consensus that the benefit–risk profile of Santocyn was acceptable for the indications shown in the SmPC and has advised including Santocyn, manufactured at PT SANBE FARMA, Bandung, Indonesia, in the list of prequalified medicinal products.