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MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR UTROGESTAN 100 AND UTROGESTAN 200 (PROGESTERONE 100 MG AND 200 MG) SOFT GELATIN CAPSULES

Version number 1.0
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1. Introduction

Utrogestan 100/200 is an innovator medicine/generic medicine of Progesterone Soft Gelatin Capsules. Utrogestan Vaginal 100/200 is a progestin medicine belonging to G03DA04-Sex hormones and modulators of the genital system, progestogens. Utrogestan 100/200 exerts is activity by mimicking the action of endogenous progesterone on the endometrium to convert the proliferating phase to the secretory phase. Utrogestan Vaginal 200 is approved in Tanzania for use in adults women.

1.1 Product details

Registration number	Utrogestan 200: TAN 20 HM 0410 Utrogestan 100: TAN 20 HM 0408
Brand name	Utrogestan 200 Utrogestan 100
Generic name, strength and form	Progesterone 200 mg Soft Gelatin Capsules Progesterone 100 mg Soft Gelatin Capsules
ATC classification	G03DA04-Sex hormones and modulators of the genital system, progestogens
Distribution category	POM
Country of origin	Spain
Associated product	State any other product of formulation, strength or site that is linked or associated with the product if applicable
Marketing Authorization Holder	BESINS HEALTHCARE SA Avenue Louise 287, B-1050 Brussels Belgium Belgium
Local Technical Representative	CFAO Motor Complex, P.O. Box 70032, Sokoine, Plot No. 89-90 Nyerere Road, Dar es Salaam,Tanzania.

1.2 Assessment procedure

The application for registration of Utrogestan 100/200 was submitted on 25/04/2019. The product underwent abridged assessment. Assessment was completed in 2 rounds of evaluation. Utrogestan was registered on 25/09/2020.

1.3 Information for users

Visual description of the finished product	Utrogestan 200: Ovoid slightly yellow soft capsules containing whitish oily suspension Utrogestan 100: Round and slightly yellow soft capsules, containing whitish oily suspension
Primary packing material	PVC/ALU blister

Secondary packing materials	
Shelf-life and storage condition	36 Months Do not store above 30°C
Route of administration	Oral
Therapeutic indications	**Gynaecological:** - Disorders related to progesterone deficiency, In particular: - premenstrual syndrome, - menstrual disorders due to poor ovulation or anovulation, - benign breast disease, - premenopause. - Treatment of the menopause (as an adjuvant to oestrogen therapy). - Sterility due to luteal phase deficiency. **Obstetric:** - Threat of miscarriage or prevention of recurrent miscarriages due to proven luteal phase deficiency. - Threat of premature delivery.

2. Labelling and product information

Summary of product characteristics

The SmPC included all the relevant information to ensure correct and safe use of the medicine by healthcare providers. The complete SmPC can be accessed here.

Package insert/leaflet

The package insert is confirmed to be derived from the SmPC and contains sufficient data for the end user. Since the product is POM that is intended for long term use, the package insert contains both full prescribing information as per SmPC and simplified information for patients.

Container labels

The product label information is presented in English. Details in the secondary pack label include:

Brand name:
Composition: <generic name & strength, list of excipients (if applicable)>
Pack size: <primary & secondary pack>
Manufacturing details: <batch number, manufacturing date, expiry date>
Storage conditions: <state the condition as it appears on the label>
Manufacturer address: <physical address of release site>
Unique identifier: <state the unique identification used>
Special warnings/precautions or instructions for use: <include warnings or IFU if applicable>

The details of the primary pack include:
Brand name and strength:
Manufacturing details: <batch number, manufacturing date, expiry date>
Name of manufacturer: <name only>

The content of the primary and secondary labels was aligned to the requirements of the Part V of the Compendium: Guidelines on Format and Content of Product Labels for Medicinal products. The label contains sufficient information for proper identification of the medicine and post marketing follow up of the product.
Describe any approved deviation to the requirements and the justification for the deviation.

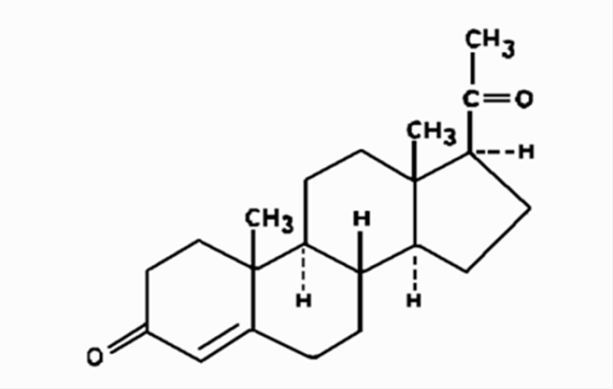
3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

Jiangsu Jiaerke Pharmaceuticals Group Corp, Ltd

Information on the quality of the API was submitted in form of CEP.

General properties
Progesterone API is compendia in BP/Ph.Eur.
Molecular formula: $C_{21}H_{30}O_2$
Chemical name: Pregn-4-ene-3, 20-Dione
Structure:



Critical physico-chemical properties of the API were practically insoluble in water, freely soluble in ethanol and sparingly soluble in acetone and in fatty oils. The API is micronized before manufacturing the finished product.

Manufacture
The API manufacturing site Jiangsu Jiaerke Pharmaceuticals Group Corp Ltd, Sanhuangmiao Zhenglu, Wujin, Changzhou, Jiangsu 213 111, China was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by <state the issuing authority>.Progesterone API is manufactured by chemical synthesis using conventional

techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The API specifications were set as per BP standards and ICHQ3A. The parameters monitored during quality control are: appearance, identification, specific optical rotation, assay, related substances, loss on drying, residual solvents, residual catalysts by AAS. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Progesterone API is 36 months when packed in LDPE bag and stored at <storage conditions>.

Symbiotec Pharmalab Private Limited

Information on quality of the API was submitted in form of CEP.

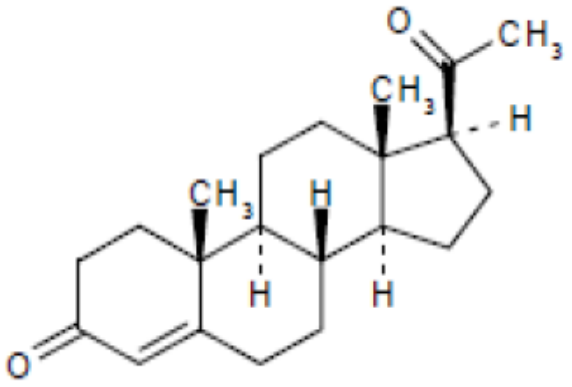
General properties

Progesterone API is compendia in BP/Ph.Eur.

Molecular formula: $C_{21}H_{30}O_2$

Chemical name: Pregn-4-ene-3, 20-Dione

Structure:



Critical physico-chemical properties of the API were practically insoluble in water, freely soluble in ethanol and sparingly soluble in acetone and in fatty oils. The API exists in two polymorphic forms and is micronized before manufacturing the finished product.

Manufacture

The API manufacturing site Symbiotec Pharmalab Private Limited, Plot No. 5, 6, 7 & 8, Special Economic Zone Phase -II, Pharma Zone, District Dhar India-454 774 Pithampur, Madhya Pradesh, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by <state the issuing authority>. Progesterone API is manufactured by

chemical synthesis using conventional techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications
The API specifications were set as per BP standards and ICHQ3A. The parameters monitored during quality control are: appearance, identification, specific optical rotation, assay, related substances, loss on drying, residual solvents, residual catalysts by AAS. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system
The re-test period of Progesterone API is 36 months when packed in LDPE bag and stored at <storage conditions>.

Quality of the Finished Pharmaceutical Product

Formulation

Utrogestan 200 is an ovoid slightly yellow soft capsules containing whitish oily suspension, Utrogestan 100 is a round and slightly yellow soft capsules, containing whitish oily suspension. Utrogestan contains micronized progesterone and other ingredients listed hereafter sunflower oil, soybean lecithin, shell (gelatin, glycerol, titanium dioxide,purified water). The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition <number> in terms of function and quantities. Ingredient, <excipient> is of safety concern therefore appropriate warnings were included in the product label.

Manufacture
The finished product was manufactured at Cyndea Pharma, Poligono Industrial Emiliano Revilla Sanz - Avenida de Agreda, 31 - Olvega 42110 (Soria), Spain. The compliance of the site to TMDA GMP standards was confirmed through <site inspection/desk-review> on <date of GMP compliance.

Specifications
The FPP is <non-compendia/compendia in BP/USP/JP/International Ph>. The manufacturer controls the quality of the finished product as per <reference monograph(BP/USP/JP/International Ph/in-house)> and ICHQ3B requirements. The parameters monitored during quality control are: appearance, average mass of filled capsules, uniformity of dosage units, uniformity of capsule mass, micronized progesterone particle size, disintegration time, identification, assay, related substances and antimicrobial integrity. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on 3 batches of the finished product stored at 30°C ± 2°C / 75% RH ± 5% RH for 24 months and 40°C ± 2°C / 75% RH ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 36 months when stored in PVC/aluminium blister at below 30°C.

Safety and efficacy information

Safety and efficacy of Utrogestan 100/200 was established through regulatory reliance as the product is registered in countries with stringent regulatory authorities (SRAs) and in the country of origin, Spain.

4. Benefit-Risk Assessment and Conclusion

On basis ofthe data submitted, the current state of knowledge and compliance to Good Manufacturing Practice, the benefit of the product outweighs the risks associated with its use when used in accordance to the summary of product characteristics. Utrogestan 100/200 is recommended for registration.

5. Post-approval updates

Variation applications

Reference number	Date submitted	Change requested	Recommendation	Granting date

Feedback from pharmacovigilance, post marketing surveillance and enforcement activities

Type of feedback	Impact	Response

Re-registration applications

Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

Version number	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up label