

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

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| Name of the Finished Pharmaceutical Product | [RH084 trade name]* |
| Manufacturer of Prequalified Product | Incepta Pharmaceuticals Limited Unit-1, Injectable Potent Drug (IPD) Krishnapura, Sahabelishor Dhamrai, Dhaka Bangladesh |
| Active Pharmaceutical Ingredient(s) (API) | Medroxyprogesterone acetate |
| Pharmaco-therapeutic group (ATC Code) | Progestogens (G03AC06) |
| Therapeutic indication | [RH084 trade name] is used for long-term contraception in women aged over 18 years. [RH084 trade name] may be used in adolescents aged over 12 years if there is compelling reason for contraception and other methods are unsuitable or unacceptable. |

1. Introduction

[RH084 trade name] is used for long-term contraception in women aged over 18 years (see Part 4 for full indications).

[RH084 trade name] should be initiated by a health care provider experienced in the management of female contraception.

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)

The API manufacturer supplies micronized, sterile medroxyprogesterone acetate for manufacture of the finished product. Medroxyprogesterone acetate (sterile) used in the manufacture of [RH084 trade name] has been prequalified by WHO according to WHO's *Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products* (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.
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medroxyprogesterone acetate (sterile), used in the manufacture of [RH084 trade name], is of good quality and manufactured in accordance with WHO good manufacturing practices (GMP). API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

The API is of BCS low solubility and formulated as a suspension, hence particle size distribution (PSD) is considered a critical parameter and forms part of the FPP manufacturer's API specifications, with acceptance criteria set on the information of the API lot used in the FPP biobatch. Polymorphic forms are not known.

Other ingredients

Other ingredients used in the suspension for injection include polyethylene glycol 3350, polysorbate 80 (tween 80), sodium chloride, methyl paraben, propyl paraben, sodium hydroxide and/or hydrochloric acid (for adjustment of pH) and water for injections, all being pharmacopoeia controlled. There are no excipients of animal or human origin. BSE/TSE compliance declarations were provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off- white suspension for injection, filled in 3 mL type I clear glass vial sealed with 13mm grey chlorobutyl rubber stopper and red flip-off aluminium seal.

The *Additional Guidance on Submission Requirements for Medroxyprogesterone Acetate Depot Injection Products Using the Common Technical Document (CTD) Format* (WHO Guidance) posted on the WHO PQM website was used extensively as guidance during development of the product. The WHO Guidance recommends that a first approach to deal with the rather complex situation in targeting the QTPP of the comparator product would be adoption of the composition of the comparator product. The qualitative and quantitative composition of the excipients selected for this multisource product is actually the same as listed for the WHO recommended comparator product, Depo-Provera® Contraceptive Injection obtained from the EU market. As part of the pharmaceutical development studies, the comparator product was characterized in terms of critical attributes such as pH, viscosity, and PSD. Detailed studies on redispersibility / resuspendability, syringeability, and sedimentation volume of the proposed finished product were performed in accordance with the WHO Guidance.

The manufacturing process is a standard aseptic process, conducted under appropriate conditions, including the steps of compounding (vehicle and final suspension preparation), followed by filling into empty sterile vials, stoppering and sealing. Satisfactory operating parameters and in-process controls have been defined at each stage of manufacture. Process validation has been conducted on 3 consecutive batches.

For selection of a dissolution method, Test 1 (USP Apparatus IV, flow through cell method) and Test 2 (USP Apparatus II modified, paddle method) of the USFDA OGD recommended dissolution methods were investigated in light of the extended release properties of the depot injection. Test 2 showed discriminatory power and was selected and optimised as QC test. As per the WHO Guidance the discriminatory power of the selected dissolution method was tested in relation to PSD variation, varying of polyethylene glycol grade and varying of polyethylene glycol 3350 quantity was studied. The discrimination power with respect to PSD was demonstrated.

Specifications

The finished product specifications are pharmacopoeial based and include tests for description,

identification of the API (IR, HPLC) and parabens (HPLC), extractable volume, particle size distribution, pH, specific gravity, content of methyl and propyl parabens (HPLC), dissolution (USP type II apparatus, UV detection), related substances (HPLC), assay (HPLC), uniformity of dosage units (content uniformity), sterility, bacterial endotoxins, resuspendability, clumping, seal integrity, antimicrobial effectiveness, sodium chloride content, osmolality, sedimentation volume and sub-visible particulate matter.

These tests are regarded acceptable for the suspension for injection as per the WHO Guidance. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated condition. Based on the available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable. The vials should be stored in the cartons to protect from light.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2017 according to internationally accepted guidelines.

A randomized, open label, balanced, two-treatment, single dose, parallel, bioequivalence study of Medroxyprogesterone acetate injection 150 mg/mL manufactured by Incepta Pharmaceuticals Ltd, Bangladesh with Depo-Provera[®] Contraceptive Injection (medroxyprogesterone acetate) 150 mg/mL of Pfizer, Belgium NV 0746-02 in normal, healthy, adult, female human subjects (study no. ARL/15/545).

The objective of the study was to compare the bioavailability of the stated Medroxyprogesterone acetate 150 mg/mL suspension for injection, manufactured by/for Incepta Pharmaceuticals Ltd, Bangladesh (test drug) with the reference formulation Depo-Provera[®] (Pfizer) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, parallel study in healthy subjects under fasting conditions. Each subject was assigned to receive one of the following two treatments:

Treatment T: Test – 1 mL injection [RH084 trade name]
(medroxyprogesterone acetate 150 mg)
Batch no. 16006.

Treatment R: Reference – 1 mL injection Depo-Provera[®]
(medroxyprogesterone acetate 150 mg)
Batch no. M11349.

Serial blood samples (1 pre-dose sample and 39 samples within 3 360h (140 days) post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for medroxyprogesterone acetate were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 0.15 ng/mL for medroxyprogesterone acetate.

The study was performed with 150 participants (75 subjects per study arm); data generated from a total of 142 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for medroxyprogesterone acetate as well as statistical results are summarised in the following tables:

Medroxyprogesterone acetate

| Pharmacokinetic Parameter | Test formulation (T) arithmetic mean ± SD (geometric mean) | Reference (R) arithmetic mean ± SD (geometric mean) | log-transformed parameters | |
|------------------------------------|--|---|----------------------------|--------------------------------------|
| | | | Ratio T/R (%) | Conventional 90% CI (ANOVAlog) |
| t _{max} (h) | 234 ± 545 | 306 ± 683 | – | – |
| C _{max} (pg/mL) | 2299 ± 1051 (2079) | 2819 ± 3752 (2186) | 95.1 | 81.8 – 110.5 |
| AUC _{0-21d} (ng·h/mL) | 685 ± 314 (624) | 653 ± 266 (604) | 103.3 | 91.4 – 116.8 |
| AUC _{21-49d} (ng·h/mL) | 545 ± 234 (494) | 560 ± 238 (524) | 94.4 | 83.0 – 107.2 |
| AUC _{49-90d} (ng.h/mL) | 590 ± 205 (554) | 745 ± 933 (618) | 89.9 | 79.1 – 101.6 |
| AUC _{0-90d} (ng.h/mL) | 1932 ± 642 (1823) | 2061 ± 1102 (1903) | 95.8 | 86.3 – 106.4 |
| AUC _{0-140d} (ng.h/mL) | 2504 ± 669 (2405) | 2653 ± 1172 (2503) | 96.0 | 87.9 – 105.0 |
| AUC _{0-inf} (ng·h/mL) | 3275 ± 774 (3167) | 3507 ± 1910 (3230) | 98.0 | 89.8 – 107.0 |

The results of the study show that pre-set acceptance limits of 80 -125 % are met by both the pivotal AUC_{0-90d}, AUC_{0-140d} and C_{max} values regarding medroxyprogesterone acetate. Accordingly, the test Medroxyprogesterone acetate injection 150 mg/mL meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulation Depo-Provera® (Pfizer).

4. Summary of product safety and efficacy

[RH084 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 and bioavailability, [RH084 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Depo-Provera® (Pfizer, Belgium) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [RH084 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 [RH084 trade name] is used in accordance with the SmPC.

Bioequivalence

[RH084 trade name] has been shown to be bioequivalent with Depo-Provera[®] (Pfizer, Belgium).

Efficacy and Safety

Regarding clinical efficacy and safety, [RH084 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, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [RH084 trade name] was acceptable for the following indication: **'long-term contraception in women aged over 18 years'**, and has advised that the quality, efficacy and safety of [RH084 trade name] allow inclusion of [RH084 trade name], manufactured at Incepta Pharmaceuticals Limited, Unit-1, Injectable Potent Drug (IPD), Krishnapura, Sahabelishor, Dhamrai, Dhaka, Bangladesh, in the list of prequalified medicinal products.