EDA Assessment Report for human medicinal product

(Scientific Discussion)

Dutamsuvitae Hard capsule

(Dutasteride 0.5 mg +Tamsulosin HCl 0.4 mg)

Date: September 2024

I. Introduction

Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Dutamsuvitae Hard Capsule from Pharma Solutions Egypt.

The product is indicated for:
- Treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH).
- Reduction in the risk of acute urinary retention (AUR) and surgery in patients with moderate to severe symptoms of BPH.

II. Quality Aspects

Drug Substance
- Dutasteride from the first supplier:

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is white to off white colored powder soluble in methanol. It exhibits polymorphism and isomerism.
- The synthesis of drug substance includes 2 stages with the formation of 7 intermediates. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via Mass spectroscopy, IR,1H-NMR, P-XRD, 13C-NMR, Elemental Analysis and the structure is well characterized.
- The drug substance specifications are in accordance with Dutasteride European Pharmacopeia monograph/In-House and include the following tests: Description, Solubility, Identification with (IR, HPLC, specific optical rotation), Specific Optical Rotation, water content, sulphated ash, Heavy metals, X-ray powder diffraction pattern, Methyl trifluoromethane sulfonate content by GC, Benzene content by GC, Carbon tetra chloride and 1,1 Dichloroethene content by GC, assay by HPLC, related substances and residual solvents. All limits are acceptable.
- Analytical methods were adequately described and validated.
- The applicant provided batch analysis results of 3 drug substance batches demonstrating compliance with the current drug substance specification.
- Dutasteride is packed in Clear poly bag and flushed with nitrogen and tied (primary pack) then placed in Black poly bag, flushed with Nitrogen and tied (secondary pack) then placed in triple laminated bag, silica gel bag is placed in between the triple laminated bag and black poly bag, flushed with nitrogen and sealed with liner sealer. This bag is finally placed in the HDPE container with a HDPE

lid. HDPE container is closed with lid, followed by sealing with tamper evident seal and QA release labels will be pasted.

- Container closure system is suitable to store drug substance and comply with food grade packaging material and the specifications are acceptable
- Stability of drug substance is submitted as (accelerated at 40°C ± 2°C, RH 75% ± 5%) and (long term at 25°C ± 2°C, RH 60% ±5%), and conclude the conformity of specifications during the retest period and storage conditions.

-Dutasteride from the second supplier:

- A CEP (R1-CEP 2014-019) has been submitted for evaluation.
- The drug substance is white or pale yellow powder practically insoluble in water, freely soluble in methylene chloride, soluble or sparingly soluble in anhydrous ethanol. It exhibits polymorphism and isomerism.
- The synthesis of drug substance includes 12 steps with the formation of 7 intermediates. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via Mass spectroscopy, IR, UV Spectroscopy,1H-NMR, P-XRD, 13C-NMR, Elemental Analysis and the structure is well characterized.
- The drug substance specifications are in accordance with Dutasteride European Pharmacopeia monograph/In-House and include the following tests: Description, Solubility, Identification with (IR and specific optical rotation), Specific Optical Rotation, water content, sulphated ash, Heavy metals, X-ray powder diffraction pattern, Methyl trifluoromethane sulfonate content by GC, Benzene content by GC, Carbon tetra chloride and 1,1 Dichloroethene content by GC, Assay by HPLC, Related substances and Residual solvents. All limits are acceptable.
- Analytical methods were adequately described and validated.
- The applicant provided batch analysis results of 3 drug substance batches demonstrating compliance with the current drug substance specification.
- Dutasteride is packed in virgin, non-toxic, clear low-density polyethylene bag (primary pack) then placed in black color low density polyethylene bag (secondary pack) then ach bag is individually tied with a thread/ strip. This double polyethylene bag is placed inside a triple laminated bag and sealed. This triple laminated bag is kept inside a HDPE container.
- Container closure system is suitable to store drug substance and comply with food grade packaging material and the specifications are acceptable
- Stability of drug substance is submitted as (accelerated at 40°C ± 2°C, RH 75% ± 5%) and (long term at 25°C ± 2°C, RH 60% ±5%), and conclude the conformity of specifications during the retest period and storage conditions.

- The storage conditions for Dutasteride are Preserve in well closed containers at controlled room temperature i.e., between 20°C and 25°C (excursion is allowed between 15°C and 30°C).

2- Tamsulosin HCl:

- A CEP (R1-CEP 2008-206-Rev 00) has been submitted for evaluation.
- The drug substance is white or almost white or powder, slightly soluble in water, freely soluble in formic acid, slightly soluble in anhydrous ethanol.
- The drug substance specifications are in accordance with Dutasteride European Pharmacopeia monograph/In-House and include the following tests: Description, Melting point, Solubility, Identification with (IR and specific optical rotation and chemical test), Loss on drying, water content, sulphated ash, Heavy metals, Assay by Potentiometry, Related substances and Residual solvents. All limits are acceptable.
- Analytical methods are in line with the current version of the European pharmacopeia monograph and the certificate of suitability (CEP).
- The applicant provided batch analysis results of 3 drug substance batches demonstrating compliance with the current drug substance specification.
- Container closure system is triple polybag, placed in a polyethylene drum.
- As per the CEP issued by the EDQM, the retest period of the drug substance is 60 months if stored in triple polybag, placed in a polyethylene drum.

Medicinal Product

- **Product Description**
- Dutasmavitae Hard Capsule is available as hard capsules with brown body and orange cap.

  The hard capsules contain: one dutasteride 0.5 mg oblong soft gelatin capsule, opaque, yellow, containing an oily and yellowish liquid and tamsulosin HCL white to off-white pellets in the equivalent weight of 0.4 of tamsulosin HCL.

- The product is packed in HDPE Bottles, sealed with an aluminium foil with child resistant closure or Aluminium/Aluminium blisters in cardboard box.

- **The excipients used in manufacture of dutasteride soft capsule are**: Glycerol monocaprylocaprate Type I and Butylhydroxytoluene (BHT)-(E-321)
- **The soft capsule shell consists of**: Gelatin, Glycerol, Purified water, Titanium Dioxide (E-171), Yellow Iron Oxide (E-172), Triglycerides medium chain and Lecithin (soya)(E-322).

- **The excipients used in manufacture of Tamsulosin HCL Pellets are**: Microcrystalline Cellulose (PH 101), Magnesium Stearate, Methacrylic acid – Ethyl acrylate copolymer (1:1) dispersion (30%) and Purified water.
- **Enteric coat of Pellets consists of**: Methacrylic acid – Ethyl acrylate copolymer (1:1), Sodium Hydroxide, Triacetin, Purified Talc, Titanium Dioxide and Extra granular Talc.
- **The excipients used in manufacture of Hard Capsule are**:
- **Capsule cap consists of**: Hypromellose (substitution type 2208 (4mpa.s & 3mpa.s)) -(substitution type 2910 (6mpa.s & 4.5mpa.s), Potassium chloride, Carrageenan, Titanium Dioxide (E-171), Sunset Yellow (E-110) and Water.
- **Capsule body consists of**: Potassium chloride, Carrageenan, Titanium Dioxide (E-171), Hypromellose (substitution type 2208 (4mpa.s & 3mpa.s)) -(substitution type 2910 (6mpa.s & 4.5mpa.s), Red Iron Oxide (E-172) and purified water.

Pharmaceutical development

- The development of the product has been described, the choice of excipients is justified and their functions explained. It was aimed to develop a product equivalent to the reference product.
- Overall, the choices of the packaging, manufacturing process, compatibility, overage physicochemical properties and microbiological attributes are justified.

Manufacturing process

- The manufacturing process of dutasteride soft capsule consists of dissolution, heating, stirring, deareation, sieving, heating, dissolution, dissolution, dispersing, stirring, encapsulation, drying and inspection.
- The manufacturing process of tamsulosin HCL pellets consists of raw material quantity verification, sifting, granulation, drying, sifting and sizing, granulation, extrusion and spheronization, drying, coating of pellets, drying, sifting, blending and packaging.
- The manufacturing process of hard capsule consists of weighing, loading, capsule filling, blistering or bottle filling, sealing and packaging.
- The manufacturing process of soft capsule, enteric coated pellets and hard capsule were adequately validated according to relevant guidelines. Validation included validation of specific operating parameters for each step of manufacturing where applicable.
- All excipients used in manufacture of dutasteride soft capsule comply with Ph.Eur/ USP except for Yellow Iron Oxide (E-172) which has in-house specifications.
- All excipients used in manufacture of tamsulosin HCL pellets comply with Ph.Eur.

- All excipients used in manufacture of hard capsule comply with Ph.Eur except for Sunset Yellow(E-110) and Red Iron Oxide (E-172) which has in-house specifications.
- Specification for dutasteride soft capsule includes description, identification, uniformity of dosage units, dissolution, assay, related substances and microbial examination.
- Specification for tamsulosin HCL pellets includes description, identification, water content, dissolution, assay, related substances and microbial examination.
- Specification for hard capsule includes description, identification, uniformity of dosage units, dissolution, water content, assay, related substances and microbial examination
- Analytical methods were revised and found to be suitable for the required testing.
- Batch Analysis from the proposed production site were provided for 3 batches. The results of all tests are well within specification limits and batch data is acceptable
- Container closure system is suitable to store finished pharmaceutical product and comply with food grade packaging material and the specifications are acceptable.
- Stability of the finished pharmaceutical product is submitted and conclude the conformity of specifications during the shelf life and storage conditions. The finished pharmaceutical product is stable for 36 months if stored below 30°C.
- Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies.

  There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, except gelatine. A declaration/certificate of TSE/BSE free is provided for the gelatine present in the capsule shell.

Recommendation:

- Based on the review of CTD quality module and other supplementary documents; from the quality point, the product is approved

Summary basis of opinion:

From Chemistry, Manufacture and Control perspective, the main concerns found during the evaluation process were as follow:

For the Drug substance

- The acceptance criteria of B-isomer in test III of related substances for dutasteride soft capsule should be modified in drug product manufacturer compiled specifications to be matched with API manufacturer specifications.

For the Drug product:

- The Comparative dissolution profile of tamsulosin HCL pellets against the reference product in the

developed dissolution medium is missing.
- A justification for the high limit of water content in the specification of tamsulosin HCL pellets.

The Quality of the drug product has been found satisfactory after:
- The drug product manufacturer modified the acceptance criteria of B-isomer in test III of related substances for dutasteride soft capsule.
- The applicant submitted Comparative dissolution profile of tamsulosin HCL pellets against the reference product.
- The applicant narrowed down the limit of water content to be matching the supplier specification.

III. Non-Clinical

No new preclinical data have been submitted with this application. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application. An Environmental Risk Assessment has not been performed as this product is intended for generic substitution and therefore will not result in an increase of risk to the environment during use, storage and disposal.

IV. Clinical Aspects

Introduction

Dutasteride & Tamsulosin are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature.

Dutasteride is a 5α-reductase inhibitor that inhibits the conversion of testosterone to dihydrotestosterone (DHT) in the prostate gland.

Tamsulosin is an α1 adrenoceptor blocker that exhibits selectivity for α1A receptors in the human prostate.

This drug is indicated for the treatment of symptomatic Benign Prostatic Hyperplasia (BPH).

Bioequivalence Study

The bioequivalence study was conducted for Dutamsuvitae 0.5mg/0.4mg hard capsule from Pharma Solutions Egypt to Duodart® 0.5 mg/0.4 mg hard capsules marketed by GlaxoSmithKline S.A., Spain administered to healthy participants.

Design

Crossover, randomized bioequivalence clinical trial of one formulation of dutasteride/tamsulosin 0.5 mg/0.4 mg hard capsules versus Duodart® 0.5 mg/0.4 mg hard capsules after a single dose administration to healthy volunteers under fed & fasting conditions in a two-stage design.

Duration of treatment: single oral dose of Dutasteride/Tamsulosin in each period under fed and fasting condition.

The wash out period followed treatment between period 1 and period 2 was 28 days, it would be enough for the complete elimination of Dutasteride/Tamsulosin because their half-life is around 7-9 days and 10 hours respectively.

- Sampling time schedule as the following:
Baseline (before receiving the drug),0.5 h,1 h ,1.5 h ,2 h, 2.5 h, 3 h , 4 h , 5 h , 6 h ,7 h ,8 h ,9 h ,10 h ,12 h , 14 h ,16 h ,20 h ,24 h ,32 h ,48 h and 72 h after administration of each of the products.
All plasma samples were stored at -20º C ±5ºC.

Analytical Methods

All procedures used to perform the bio-analyses of Dutasteride & Tamsulosin in subject samples were executed according to international guidelines and official publications.

CRO developed an adequately validated method to ensure data integrity, Accuracy and Precision of data generated during sampling, sample treatment and bioanalyses. The bioequivalence study accordance with acceptable standards of Good Clinical Practice (GCP) and Good Laboratory Practice (GLP).

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of **Dutasteride** under **fed** conditions.

Treatment N=33	**AUC_{0-t} ng.h/ml**	**$AUC_{0-\infty}$ ng.h/ml**	**C_{max} ng/ml**	**t_{max} h**	**$t_{1/2}$ h**
Test	50898.65	98057.96	2640.79	3.5	64.83
Reference	49398.83	87436.75	2612.93	4	54.18
***Ratio (90%) CI**	102.32 (97.16 – 107.76)	110.54 (103.38 – 118.21)	100.18 (90.73-110.6)		
CV (%)	---	---	----		

*ln-transformed values

$AUC_{0-72\ h}$ of dutasteride has been evaluated according to a noncompartmental model. The obtained mean value (±SD) of Dutasteride/Tamsulosin test was 50898.65 (± 27161.04) pg/mL*h and Duodart® was 49398.83 (± 26770.68) pg/mL*h. The ratio between logarithmically transformed means of Dutasteride/Tamsulosin test and Duodart® was 102.32 with a 90% CI of 97.16 – 107.76, that is within the 80 to 125% interval proposed by the current regulations of the EMA for bioequivalence.

AUC_{0-inf} of dutasteride has been evaluated according to a non-compartmental model. The obtained mean value (±SD) of Dutasteride/Tamsulosin test was 98057.96 (± 63218.80) pg/mL*h and Duodart® was 87436.75 (± 56282.61). The ratio between logarithmically transformed means of Dutasteride/Tamsulosin test and Duodart® was 110.54 with a 90% CI of 103.38 – 118.21.

Cmax of dutasteride after administration of Dutasteride/Tamsulosin test was 2640.79 (± 959.80) pg/mL and Duodart® was 2612.93 (± 874.02) pg/mL. The mean ratio "test over reference" was calculated as of 100.18 with 90% confidence intervals of 90.73 – 110.60 for Dutasteride/Tamsulosin test versus Duodart® that is within the 80 to 125% interval proposed by the current regulations of the EMA for bioequivalence.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of **Tamsulosin** under **fed** conditions.

Treatment N=33	**AUC_{0-t} ng.h/ml**	**$AUC_{0-\infty}$ ng.h/ml**	**C_{max} ng/ml**	**t_{max} h**	**$t_{1/2}$ h**
Test	142438.75	147566.36	9464.05	7	10.96
Reference	150076.72	153979.75	10136.86	8	10.22
***Ratio (90%) CI**	94.07 (89.41 – 98.98)	108.46 (101.37 – 116.06)	93.72 (85.90–102.26)		
CV (%)	----	--------	----------		

*ln-transformed values

AUC_{0-t} of tamsulosin has been evaluated according to a noncompartmental model. The obtained mean value (±SD) of Dutasteride/Tamsulosin test was 142438.75 (± 62965.62) pg/mL*h and Duodart® was 150076.72 (± 63225.25) pg/mL*h. The ratio between logarithmically transformed means of Dutasteride/Tamsulosin test and Duodart® was 94.07 with a 90% CI of 89.41 – 98.98, that is within the 80.00 to 125.00% interval proposed by the current regulations of the EMA for bioequivalence.

AUC_{0-inf} of tamsulosin has been evaluated according to a non-compartmental model. The obtained mean value (±SD) of Dutasteride/Tamsulosin test was 147566.36 (± 67724.42) pg/mL*h and Duodart® was 153979.75 (± 65900.62). The ratio between logarithmically transformed means of Dutasteride/Tamsulosin test and Duodart® was 108.46 with a 90% CI of 101.37 – 116.06.

Cmax of tamsulosin after administration of Dutasteride/Tamsulosin test was 9464.05 (± 2925.85) pg/mL and Duodart® was 10136.86 (± 3439.51) pg/mL. The mean ratio "test over reference" was calculated as of 93.72 with 90% confidence intervals of 85.90 – 102.26 for Dutasteride/Tamsulosin test versus Duodart® that is within the 80.00 to 125.00% interval proposed by the current regulations of the EMA for bioequivalence.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of **Dutasteride** under **fast** conditions

DUTASTERIDE	Mean – SD				Bioequivalence assessment (n=35)	
	Dutasteride/Tamsulosin TEST (n=35)		Duodart® (n=35)		Ratio	90% CI
AUC_{0-72} (pg*h/mL)	38550.16	16847.73	38751.40	17975.10	100.51	95.20 – 106.34
Cmax (pg/mL)	2312.97	807.37	2276.55	914.02	104.14	95.83 – 113.17

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of **Tamsulosin** under **fast** conditions

TAMSULOSIN	Mean – SD				Bioequivalence assessment (n=35)	
	Dutasteride/Tamsulosin TEST (n=35)		Duodart® (n=35)		Ratio	90% CI
AUC_{0-t} (pg*h/mL)	173609.29	78711.05	187107.68	87997.99	93.33	87.26 – 99. 83
Cmax (pg/mL)	13309.29	3824.89	13879.40	5569.27	98.80	91.77 – 106.36

Conclusion

Based on this study demonstrated that Dutamsuvitae hard capsule applied by Pharma solutions Egypt & Duodart® 0.5 mg/0.4 mg hard capsules marketed by GlaxoSmithKline S.A., Spain are Bioequivalent after a single oral dose of test and reference administration under fasting & fed conditions on healthy participants.

The 90% confidence intervals calculated for AUC0-t, AUC0-inf and Cmax are within the bioequivalence acceptance range of 80-125%.