Taiwan Food and Drug Administration

Assessment Report

Trade Name：康紓為(柳菩林) 42 毫克注射乳劑 /
CAMCEVI (Leuprolide) injectable emulsion, 42 mg

Active Ingredient：Leuprolide mesylate

License Number：MOHW-PI 028546

Applicant：逸達生物科技股份有限公司

Approval Date：2023.09.15

Indication：
用於晚期攝護腺癌紓解治療，以及併用放射療法治療高風險局部和局部晚期荷爾蒙依賴型攝護腺癌。

Indicated for the palliative treatment of adult patients with advanced prostate cancer and for the treatment of high-risk localized and locally advanced hormone dependent prostate cancer in combination with radiotherapy.

Background Information

Trade Name	康紓為(柳菩林) 42 毫克注射乳劑 / CAMCEVI (Leuprolide) injectable emulsion, 42 mg
Active Ingredient(s)	Leuprolide mesylate
Applicant	逸達生物科技股份有限公司
Dosage Form & Strengths	注射乳劑 Leuprolide 42 mg
Indication	用於晚期攝護腺癌紓解治療，以及併用放射療法治療高風險局部和局部晚期荷爾蒙依賴型攝護腺癌。 **Indicated for the palliative treatment of adult patients with advanced prostate cancer and for the treatment of high-risk localized and locally advanced hormone dependent prostate cancer in combination with radiotherapy.**
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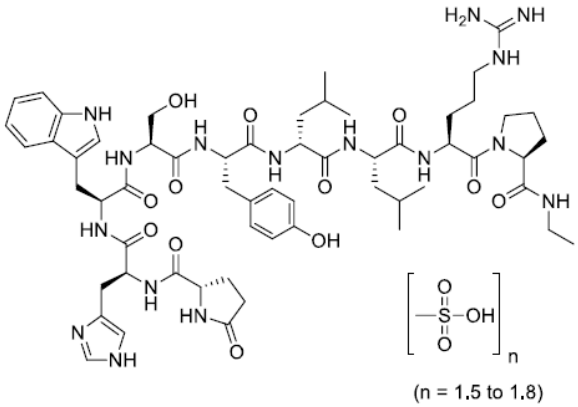
Pharmacological Category **ATC Code**	L02AE02

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, leuprolide mesylate, is chemically designated as 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide mesylate (salt). The molecular formula and the molecular weight for leuprolide mesylate are $C_{59}H_{84}N_{16}O_{12}\bullet(CH_4O_3S)_n$, n = 1.5 to 1.8 and 1209.41 g/mol (free base), respectively. The chemical structure of leuprolide mesylate is shown below:



It is a white to off-white powder. The structure of leuprolide mesylate is confirmed by IR spectrum, nuclear magnetic resonance (NMR) spectroscopy, ultraviolet (UV) and mass spectrum (MS). The specification for the drug substance includes tests for appearance, identification, solubility, amino acids analysis, assay, purity, alkyl methanesulfonate, acid content, residual solvent, water content, specific rotation, ROI, bacterial endotoxins and microbial enumeration tests.

2.1.2 Drug product

The drug product is supplied for injection use as an emulsion containing 50 mg leuprolide mesylate (42 mg leuprolide free base). All excipients are well known ingredients and suitable for proposed formulation. The specification for the drug product includes appearance, identification, deliverable weight in container, content uniformity, residual alkyl mesylates, impurities, water content, particulate matter, average molecular weight by weight of polymer, polydispersity ratio, break loose force, glide force, sterility, bacterial endotoxins and extended release. Analytical methods are described well and validated. Stability studies of drug product under long term condition (5±3°C) and accelerated condition (25°C/60% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Leuprolide is a synthetic nonapeptide analog of GnRH. Leuprolide acetate has been approved to treat prostate cancer, endometriosis, and breast cancer before menopause. This product deviates from the reference drug Eligard® 45 mg in the salt used for the proposed drug product (mesylate), which differs from the one used in the currently approved products (acetate). The *in vivo* pharmacology studies showed that a single subcutaneous administration of leuprolide mesylate emulsion stimulated testosterone production shortly and suppressed testosterone release continuously for 6 months, like the prolonged exposure of GnRH.

2.2.2 Toxicological Studies

In the toxicity studies, a single dose of leuprolide mesylate emulsion also decreased serum

testosterone levels for 6 months. Slight decreases in body weight and prothrombin time were observed in the treatment groups. The organ weights of male reproductive organs, kidney, heart, and liver decreased in the treatment groups, and the pituitary weight increased. The findings in the leuprolide mesylate-treated groups were similar to the leuprolide acetate-treated group. Based on the pharmaceutical effects of leuprolide, the impacts of leuprolide mesylate on reproductive organs and fetuses are expectable and could be supported by the information of leuprolide acetate. The genotoxicity and carcinogenicity are also supported by the information of leuprolide acetate. The safety of the impurities was supported by the pivotal 6-month toxicity study.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The PK profile of leuprolide mesylate 42 mg exhibited two phases: after dosing, an initial rapid increase of serum leuprolide concentration was observed, followed by a rapid decline over the first 3 days post-dose. Leuprolide appeared to be released continuously by the third day after dosing with steady serum concentrations ("plateau" phase) through the 24-week dosing interval (mean concentration: 0.370 to 2.97 ng/mL). The mean serum leuprolide C_{max} was 94-100 ng/mL and it was reached after approximately 2 to 4 hours after the first and second dose of leuprolide mesylate 42 mg. Serum leuprolide concentrations and the associated PK following the first and second doses of leuprolide mesylate 42 mg were similar, suggesting lack of significant accumulation with repeated dosing at 24-week intervals.

The mean V_{ss} of leuprolide was 26.5 L (SD: 10.1 L) following intravenous bolus administration and 37.1 L (SD: 16.8 L) following subcutaneous administration of leuprolide acetate (Lupron® 1 mg for daily injection). *In-vitro* binding to human plasma proteins ranged from 43% to 49%. No dedicated clinical study on the metabolism of leuprolide with administration of leuprolide mesylate 42 mg has been conducted, and no drug metabolism study was conducted with leuprolide acetate depot formulations (e.g., Eligard® 45 mg). In healthy male subjects, a 1-mg bolus of leuprolide acetate administered intravenously (Lupron® 1 mg) revealed a mean systemic plasma clearance of 139 mL/min (SD: 30 mL/min), with a terminal elimination half-life of 2.9 hours (SD: 0.5 h) as based on a two-compartment, open PK model with elimination from the central compartment.

2.3.2 Interaction Studies

No specific drug-drug interaction studies have been carried out on leuprolide following administration of leuprolide mesylate 42 mg. No drug-drug interaction studies have been conducted with leuprolide acetate. However, as leuprolide base is a peptide that is primarily degraded by peptidases and not by cytochrome P-450 enzymes, and due to the drug’s low plasma protein binding (about 46%), significant drug interactions would not be expected to

occur.

As described in the product information of the reference product, androgen deprivation therapy (ADT) is reported to potentially prolong the QT interval. Therefore, the concomitant use of leuprolide with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated.

2.3.3 Special Populations

No investigations have been conducted with leuprolide mesylate 42 mg in pediatric populations. As drug intended for use in prostate cancer, leuprolide mesylate 42 mg is not indicated for use in children. In the clinical trials on leuprolide, the majority of subjects studied were of higher age, which is to be expected in prostate cancer. Serum leuprolide peak levels as well as overall exposure were higher in subjects aged > 79 years compared to subjects aged < 60 years. However, median serum testosterone concentration-time profiles were comparable among age categories (< 60, 60-69, 70-79 or > 79 years old).

No investigations have been conducted with leuprolide mesylate 42 mg in women. As a drug intended for use in prostatic cancer, leuprolide mesylate 42 mg is not indicated for use in women. Subjects >100 kg body weight showed decreased serum leuprolide peak levels and overall exposure as compared to subjects < 40 kg. However, median serum testosterone concentration time profiles were comparable among body weight categories (< 75, 75-84, 85-100 or > 100 kg body weight).

The PK of leuprolide following leuprolide mesylate 42 mg in renally impaired subjects has not been determined. The PK characteristics of leuprolide following leuprolide mesylate 42 mg in subjects with hepatic impairment has not been investigated. There are no investigations on leuprolide in renal impairment and in hepatic impairment.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

One Phase 3, open-label, single arm, multinational clinical study, FP01C-13-001, was provided and evaluated in male subjects with advanced prostate carcinoma judged to be appropriate candidates for medical androgen ablation therapy. All subjects received leuprolide mesylate injectable suspension LMIS 50 mg (equivalent to 42 mg of leuprolide free base) every 24 weeks (approximately 6 months; over the course of 2 doses on Day 1 and Day 168) in an unblinded fashion.

For efficacy variables used to assess the efficacy of LMIS 50 mg, the percentage (95% CI) of subjects with a serum testosterone concentration suppressed to castrate levels (≤ 50 ng/dL) by Day 28 and from Day 28 through Day 336 (remaining duration of the study) was 98.5% (135 out of total 137 subjects; 95% CI: 94.8-99.8) and 97.0% (133 out of total 137 subjects; 95% CI: 92.2-98.9) in the ITT population.

2.4.2 Safety Results

Common TEAEs include hot flash, hypertension, pain of extremity, injection sites pain, arthralgia, fatigue, nocturia, back pain and nasopharyngitis.

2.5 Bridging Study Evaluation

The currently approved leuprolide acetate products have been marketed in Taiwan for treating prostate cancer. Camcevi® is developed in a different salt form (mesylate). Camcevi® (48 mg leuprolide mesylate, eq. as 42 mg leuprolide free base) is claimed to possess similar drug release profile *in vivo* with marketed leuprolide acetate depot products, Eligard® 45 mg (eq. as 41.9 mg leuprolide free base).

In the phase 3 study (Study FP01C-13-001), 131 male subjects with advanced prostate carcinoma had evaluable PK data. Though moderate PK difference was observed following the first dose between Asian and overall population, it was reduced following the 2nd dose. The ethnic difference was not significant after pooling the PK parameters of 1st and 2nd dose. In addition, no clinically significant difference of PD marker, serum testosterone concentrations, was observed between Asian and non-Asian population after Camcevi® 42 mg administration.

Moreover, mean PK parameters derived from Study FP01C-13-001 (Camcevi®) and literature review of Eligard® was cross-study compared. Systemic exposures including C_{max}, C_{avg}, AUC are comparable. For cross-study comparison on PD, Camcevi® and Eligard® showed comparable therapeutic effect and onset time, reaching the castration level of serum testosterone < 0.5 ng/mL.

Overall, the PK and PD properties of Camcevi ® and Eligard® were similar. Ethnicity is not considered a sensitive factor on Camcevi® PK.

There is no clinical bridging data. Camcevi® is a new salt as compared to approved product Eligard®, the clinical evaluation of ethnic difference could be extrapolated from Eligard®.

2.6 Conclusion

Approval of Camcevi® is recommended, the approved indication should be in consistent with

that of Eligard® 45 mg as below:
Indicated for the palliative treatment of adult patients with advanced prostate cancer and for the treatment of high-risk localized and locally advanced hormone dependent prostate cancer in combination with radiotherapy.

3. Post-Marketing Requirements

Routine pharmacovigilance.