Australian Government
Department of Health
Therapeutic Goods Administration

Efficacy Evaluation Report

Complementary Medicines Evaluation Section

ProstateEZE Max – Caruso's Natural Health Pty Ltd

Complementary and OTC Medicines Branch

Evaluators: s22 [redacted]
Date of report: 19 May 2021
Verified by: s22 [redacted]**. 19 May 2021**
TRIM reference: D20-3523337

This report contains confidential information in Section 25.

TGA Health Safety Regulation

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List of abbreviations

Abbreviation	Meaning
PI	Product Information
CMI	Consumer Medicines Information
LUTS	lower urinary tract symptom
BPH	benign prostatic hyperplasia
EMA	European Medicines Agency
GCP	Good Clinical Practice
IPSS	International Prostate Symptom Score
PE	plasma electrolytes
LFT	liver function tests
PSA	Prostate Specific Antigen
ANOVA	analysis of variance
QoL	Quality of Life
RCT	randomized clinical trial
SD	standard deviations
ES	Effect size
WMD	Weighted Mean Difference

1. Introduction

1.1. Identifying information

Product name	Caruso's Prostate EZE Max
Active ingredient(s)	Prunus africana, Serenoa repens, Epilobium parviflorum, Cucurbita pepo and Lycopene
Sponsor	Caruso's Natural Health Pty Ltd.
Submission number	LM-2020-01113-1
Application category	L(A)3

1.2. Purpose of assessment

s47 (acting as an Agent for Caruso's Natural Health Pty Ltd) has submitted an L(A)3 application to the Complementary Medicines Evaluation Section of the TGA for the listing of an existing listed medicine, ProstateEZE Max (AUST L 231578), as an assessed listed medicine for the management of symptoms of medically diagnosed benign prostate hypertrophy. The product is presented in capsule form. s47

1.3. Information on the product

1.3.1. Active ingredient(s), excipients, dosage form and strength

The product contains the following active ingredients:

1. *Prunus africana* (Pygeum) dry stem bark extract – Standardised to 9.75mg Sitosterol (equiv. to 15g dry stem bark),
2. *Serenoa repens* (Saw Palmetto) dry seed extract – Standardised to 39.6mg Fatty Acids (equiv. to 660mg dry seed),
3. *Epilobium parviflorum* (Willow Herb) dry herb extract – 500mg,
4. *Cucurbita pepo* (Pumpkin seed) oil fixed – 160mg, and
5. Lycopene – 2.1mg

The product is presented in capsule dosage form (multi-active). The complete formulation details of the product are provided in Section 25, Confidential information.

1.3.2. Indications, directions for use, contraindications

Indications

The proposed indications for ProstateEZE Max are:

1. May assist in the management of symptoms of medically diagnosed benign prostatic hypertrophy.
2. For the symptomatic relief of medically diagnosed benign prostatic hypertrophy.

3. Pygeum Africana may provide support for the symptomatic relief [of] nocturia, nocturnal frequency, weak stream, after-dribbling, hesitation and interruption of flow when such symptoms are associated with medically diagnosed benign prostatic hypertrophy.

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Directions for use

Adults take 1 capsule a day with food or as advised by your health professional.

Warnings

The ProstateEZE Max draft label contains the following warnings/claims:

- KEEP OUT OF REACH OF CHILDREN
- Use only as directed.
- If symptoms persist see your Healthcare Professional.
- Contains Soya Oil and sulfites.
- Phenylketonurics - this product contains phenylalanine.
- Free from: sugar, lactose, yeast, gluten, salt and preservatives.
- Do not use if carton or blister seal is missing or damaged.

1.4. Label/product documentation

The label for the existing AUST L medicine Caruso's ProstateEZE Max (60 pack) has been provided as a mock-up draft of the proposed product label. The sponsor has not specified whether the mock label is for the carton or the immediate container, only one label is provided. The sponsor has not proposed to include a Product Information (PI) document or a Consumer Medicines Information (CMI) document.

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2. Background

2.1. Clinical rationale

The sponsor has provided the following product development rationale in Module 2.5:

BPH is a common urological issue that causes prostate enlargement in men after 40 years old. It is a non-cancerous augmentation of the prostate gland size, with stromal and glandular epithelial hyperplasia in the transition zone. It is estimated that 50% of 50 year old, and 75% of 80 year old men could have some lower urinary tract symptom (LUTS). In such condition the urethra can be partially or totally blocked, resulting in urinary retention, weak urination stream, incomplete bladder emptying and hesitancy; and so carrying secondary problems as urinary tract infections, bladder stones and chronic kidney disease, culminating in kidney failure. The LUTS is reflection of the hormonal changes rising with age, and resulting in abnormal stromal and epithelial cell proliferation (hyperplasia) in the transition zone of the prostate (Simoes, et al, 2018).

The severity of symptoms in people who have prostate gland enlargement varies, but symptoms tend to gradually worsen over time. The size of the prostate doesn't necessarily determine the severity of symptoms. Common signs and symptoms of BPH include (Skinder, et al, 2016):

- Frequent or urgent need to urinate
- Increased frequency of urination at night (nocturia)
- Difficulty starting urination
- Weak urine stream or a stream that stops and starts
- Dribbling at the end of urination
- Inability to completely empty the bladder
- Urinary tract infection
- Inability to urinate
- Blood in the urine

Many pharmacologic and surgical interventions have been approved for treating BPH, with the goals of improving patient symptoms and quality of life while slowing disease progression and reducing complications (Skinder, et al, 2016).

With the target population, condition and focus in mind a blend of herbal ingredients were identified and researched for their potential in assisting with the symptoms of BPH. The ingredients chosen for development of the product are:

***Cucurbita pepo* –** Pumpkin is a plant native to South America now grown worldwide. Packed with Tryptophan, unsaturated fatty acids and a high level of antioxidant substances as well as a high content of carotenoids and liposoluble vitamins. Orally, pumpkin is used for symptoms of benign prostatic hyperplasia, bladder irritation, overactive bladder, pyelonephritis, intestinal worms and androgenic alopecia (Natural Medicines Professional Monograph, 2019a).

***Epilobium parviflorum* –** Also known more commonly as small flowered willow-herb, is a perennial, flowering plant, growing wild across Europe. It has been utilized in the treatment of prostatic disorders and its application has been recommended especially for patients suffering from Benign Prostatic hyperplasia (Hevesi, et al, 2009).

Lycopene – is an unsaturated hydrocarbon carotenoid similar in structure to beta-carotene, but without provitamin A activity. It is a fat soluble red pigment synthesized by plants and microorganisms. Orally, lycopene is used for treating prostate cancer, benign prostatic

hyperplasia (BPH), prostatitis, male infertility, human papilloma virus and more (Natural Medicines Professional Monograph, 2019b).

***Prunus africana* –** Also referred to as Pygeum is a large, evergreen tree native to Africa. Its bark has been used medicinally for thousands of years by traditional African healers to treat bladder disorders, kidney disease, prostate disorders and malaria, as well as male baldness, and to enhance sexual functioning. Because of overharvesting, the plant is now considered an endangered species and efforts are underway to protect it (Braun & Cohen, 2014a).

***Serenoa repens* –** Common name Saw palmetto was traditionally used as a treatment for urogenital irritations, impotence and male infertility, among other conditions including benign prostatic hyperplasia (Braun & Cohen, 2014b).

2.2. Regulatory history

2.2.1. Local regulatory history

All active ingredients are included in the Therapeutic Goods (Permissible Ingredients) Determination (No. 2) 2020 and are included in a number of (standard) listed medicines.

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2.2.2. International regulatory history

The sponsor did not provide any information regarding international regulatory history.

2.3. Relevant guidelines

TGA: Assessed Listed Medicines Evidence Guidelines

EMA: Guideline on the clinical investigation of medicinal products for the treatment of urinary incontinence. European Medicines Agency (EMA), 27 June 2013 (CPMP/EWP/18/01/Rev. 1)

Note: The scope of the Guideline includes incontinence associated with benign prostatic hyperplasia (BPH), but post voiding dribbling in males associated with BPH is not covered by this guideline.

EMA: Guideline on the clinical assessment of fixed combinations of herbal substances / herbal preparations. European Medicines Agency (EMA), 11 January 2006 (EMEA/HMPC/166326/2005)

3. Contents of the efficacy package

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4. Pharmacokinetics

4.1. Pharmacokinetic studies

No clinical pharmacokinetic studies on the product were submitted.

4.2. Other pharmacokinetic information

Two bioavailability studies conducted in humans were provided – one each for Pygeum and Lycopene.

4.2.1. Emara et al., (1999). Bioavailability of β-sitosterol from *Pygeum africanum* extract in humans (Ref 12).

The study aimed to determine the rate and extent of absorption of β-sitosterol (BSS) in humans. This cross-over study had 18 healthy volunteers who were given a single dose of two different marketed capsules ('Tadenan' or 'Prostacure') with 150 mg dry *Pygeum africanum* (PA) extract, equivalent to 18 mg BSS. BSS serum concentrations were analysed by a validated HPLC-method.

The results are presented in the table below:

Table 1. Bioavailability of β-sitosterol from *Pygeum africanum* extract in humans

Parameter	Capsule 1	Capsule 2
C_{max} (µg/mL)	9.8	8.64
t_{max} (h)	2.86	2.92
AUC_{0-8} (µg.h/mL)	26.7	27.24
AUC0-∞ (µg.h/mL)	42.35	46.53
MRT (h)	3.08	3.22

$t_{1/2}$ (h)	2.53	3.41

In the study discussion, it was mentioned that the absorbability of dietary BSS can vary greatly. In a study where BSS was administered in a 50 mg single oral dose versus 250 mg in dietary daily intake, the highest BSS level in plasma of healthy volunteers was determined as 0.15 µg/mL and 4 µg/mL respectively. Even on providing 242-415 mg BSS, as a daily fat intake typical of American diet, to hypercholesterolemic patients, the highest concentration determined for BSS ranged 3-10 µg/mL plasma, and the absorption amounted to 5% or less. In contrast, cholesterol, although belonging with BSS to the same class of sterols, is much more efficiently absorbed (45-54%) from dietary fats. However, these studies only estimated BSS in blood at daily intervals rather than hourly intervals.

The only other report of BSS pharmacokinetics was in the beagle dog, where two experimental formulations were administered orally at 0.6 mg/kg body weight, with reported C_{max} values of 0.148 and 0.171 µg/mL blood, and t_{max} values of 0.71 and 0.96 h. The current study showed that BSS behaved differently in man with a much higher C_{max} (9.0ug/mL) with a smaller dose of 0.25 mg/kg, which could be due to species variability and/or the effect of *Pygeum africanum* extract on its bioavailability.

The authors concluded that the present work underlines the necessity for pharmacokinetic evaluation of other medicinally active agents that are administered in dosage forms containing plant extracts.

Note: This study only studied the bioavailability of one active ingredient (*Pygeum africana*) and not the finished product.

4.2.2. Ross et al., (2011). Lycopene bioavailability and metabolism in humans: an accelerator mass spectrometry study (Ref 13).

The objective of this study was to quantify the long-term human bioavailability of lycopene in plasma and skin after a single dose of 14C-lycopene, and to profile the metabolites formed.

Method: Two male subjects were pre-selected as lycopene absorbers and were given an oral dose of 10 mg synthetic lycopene combined with ≈6 µg [6,6',7,7'-^{14}C]lycopene (≈30,000 Bq; 92% trans lycopene). The appearance of ^{14}C in plasma, plasma triacylglycerol–rich lipoprotein (TRL) fraction, urine, expired breath carbon dioxide, and skin biopsies was measured over 42 d. The 14C in lycopene-isomer fractions from plasma and TRL fraction was measured to assess the isomerization of lycopene in vivo.

Results: The time to maximum concentration (t_{max}) of total ^{14}C-lycopene in plasma was 6 h, and the elimination half-life ($t_{1/2}$) was 5 d, which were different from the t_{max} and $t_{1/2}$ of unlabelled lycopene (0.5 and 48 d, respectively). ^{14}C-Lycopene was extensively isomerized after dosing as a 92% all-trans isomer at dosing but changed to 50% trans, 38% 5 cis, 1%9cis, and 11% other cis isomers after 24 h. A similar pattern of isomerization was seen in plasma TRL fractions.

Conclusion: Lycopene was extensively isomerized after dosing and rapidly metabolized into polar metabolites excreted into urine with the rapid peak of $^{14}CO_2$ after dosing, which implies that β-oxidation was involved in the lycopene metabolism. Lycopene or its metabolites were detected in skin for up to 42 d.

The authors also commented that both ^{14}C-lycopene and unlabelled lycopene in plasma followed first-order kinetics overall. The absolute pharmacokinetic results generally differed from previous studies, although the C_{max} was similar to that in a study with a similar study design and dose of lycopene, with the diverse range of study designs, doses, and matrices used being the likely reason for differences in lycopene kinetics. The finding of ^{14}C from lycopene in plasma 1004

h after the dose was unexpected, although there was evidence for a slow-turnover tissue compartment that may have explained this finding.

Note: This study only studied the bioavailability of one active ingredient (Lycopene) and not the finished product.

4.3. Evaluator's conclusions on pharmacokinetics

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The Emara et al., study discussed that the absorption of β-sitosterol can vary greatly depending on the dosage and sterol form. β-sitosterol appears to have a relatively short half-life of around 3 hours. The amount of BSS examined in the study was nearly double the amount that is in ProstateEze Max (18mg c.f. 9.75 mg). s47 [redacted]

In the Ross et al., study, lycopene was reported to have a half-life of 5 days for a 10 mg dose. The current product has 2.1 mg of lycopene.

Overall, the pharmacokinetics data provided is insufficient to make a conclusion on the pharmacokinetics of the product. Given that the product is a combination of multiple herbal ingredients, it is unclear how each of the herbal ingredients and their components could potentially affect the absorption, distribution, metabolism and elimination processes.

5. Pharmacodynamics

5.1. Pharmacodynamic studies

No clinical pharmacodynamics studies were submitted.

5.2. Other pharmacodynamic information

5.2.1. Hevesi et al., (2008). Antioxidant and Anti-inflammatory Effect of *Epilobium parviflorum* Schreb.

This paper reported on different aspects of the antioxidant and anti-inflammatory effects *Epilobium parviflorum*.

The antioxidant capacity of *E. parviflorum* was investigated from various angles with three distinct methods: DPPH assay, lipid peroxidation assay, and an *in vitro* test for protecting fibroblast cells against free radical induced oxidative damage. The anti-inflammatory effect was examined using the COX-inhibition assay (PGE_2 assay).

The aqueous acetone extract of *E. parviflorum* showed higher antioxidant effect in the DPPH assay than well-known antioxidants and inhibited the lipid peroxidation determined by the TBA assay (IC50 = 2.37 ± 0.12 mg/mL). In concentrations of 0.2–15.0 µg/mL the extract possessed a protective effect, comparable to catalase (250 IU/mL), against oxidative damage, generated in fibroblast cells. In the COX inhibition assay, E. parviflorum decreased the PGE2 release, thereby showing inhibition of the COX-enzyme (IC50 = 1.4 ± 0.1 µg/mL).

The authors concluded that the extract of *E. parviflorum* possesses antioxidant and anti-inflammatory properties, which are likely to contribute to its beneficial effect in BPH.

5.3. Evaluator's conclusions on pharmacodynamics

One *in vitro* pharmacodynamics study on antioxidant and anti-inflammatory effect of *Epilobium parviflorum* was provided (Hevesi et al., 2009). There were antioxidant and anti-inflammatory properties shown by *Epilobium,* though not in relation to BPH. No other information on mechanism of action was provided. The extract investigated (aqueous acetone) is different from the extract in ProstateEze Max (aqueous).

Overall, the pharmacodynamics data provided is insufficient to come to a conclusion on the pharmacodynamics of the product. Given that the product is a combination of multiple herbal ingredients, it is unclear how each of the herbal ingredients and their components could potentially impact the effect of the product in the body.

6. Clinical efficacy

6.1. Developmental and pilot studies

No developmental and pilot studies were submitted.

6.2. Pivotal or main efficacy studies

6.2.1. Coulson, S., Rao, A., Beck, SL., Steels, E., Gramotnev, H. & Vitetta, L (2013)., A phase II randomised double blind placebo-controlled clinical trial investigating the efficacy and safety of ProstateEZE Max: A herbal medicine preparation for the management of symptoms of benign prostatic hypertrophy. Complementary Therapies in Medicine, Vol 21 pp172-179.

6.2.1.1. Study design, objectives, locations and dates

The aim of this study was to investigate the efficacy and safety of ProstateEZE Max, an oral herbal preparation containing *Cucurbita pepo*, *Epilobium parviflorum*, lycopene, *Pygeum africanum* and *Serenoa repens*, in the management of symptoms of medically diagnosed benign prostate hypertrophy (BPH) in otherwise healthy men.

This study was a double-blind, randomized, placebo-controlled clinical trial conducted in Brisbane, Australia by the School of Medicine in University of Queensland and Princess Alexandra Hospital. The clinical trial was registered on 19 February 2010. No details were provided on dates of enrolment or completion.

The clinical trial study was carried out according to the principles expressed in the declaration of Helsinki and was approved by the Human Research Ethics Committees [ACNM HREC Number 023], and registered with the Australian New Zealand Clinical Trials Registry (ACTRN 12610000168055).

There are no details on whether the study was conducted in accordance with Good Clinical Practice (GCP). Participants were asked to provide informed consent before enrolment in the trial.

6.2.1.2. Methods

Potential participants were preliminarily screened via local media advertising and clinical trial databases. Then via telephone, requested to attend an information question session where they were informed of the trial process and asked to provide their consent prior to further involvement in the trial.

Severity of BPH symptoms was measured at baseline and at the end of the study (3 months), using the international prostate symptom score (IPSS). Day-time and Night-time micturition frequencies were measured using daily record in a patient diary, with frequency averaged over each of the 3 months.

Inclusion/exclusion criteria

Inclusion criteria:

1. Healthy males aged between 40-80 years.
2. Medically diagnosed with BPH (histologically).
3. With a minimum score of 8 in the IPSS. A maximum IPSS score was not set.

Exclusion criteria:

Men were excluded if they:

1. Had used a pharmaceutical or natural therapy for BPH or other urological symptoms within the last 30 days.
2. Recently started a bladder-training program.
3. Had urogenital surgery within the last 6 months.
4. Had bladder biopsy and/or cystoscopy and biopsy within the past 30 days.
5. Had an indwelling catheter or practiced self-catheterisation.
6. Had been medically diagnosed with chronic persistent local pathology (i.e. interstitial cystitis, bladder stones).
7. Were receiving/prescribed anticoagulation therapy.
8. Had been diagnosed with hypertension and were receiving prescribed antihypertensive medications.
9. Had been diagnosed with severe renal and/or hepatic insufficiency.
10. Had been diagnosed with genital anatomical deformities, uncontrolled diabetes mellitus, a history of spinal cord injury, an uncontrolled psychiatric disorder and/or abnormal secondary sexual characteristics.
11. Had been diagnosed with prostate cancer.
12. Had history of chronic alcohol and/or illicit drug abuse.
13. Had participated in other clinical trial within the past 30 days.

Study treatments, randomisation and blinding

The included participants were randomised to the active treatment or placebo group. Randomisation was performed independently to the investigators, using the Random Allocation Software version 1.0 and was based on 70 participants randomly allocated into 2 arms of equal numbers (n= 35). The treatment was the TGA listed capsule ProstateEZE Max (TGA ARTG details not provided) containing *C. pepo* seed oil (160 mg), *E. parviflorum extract (equivalent to 500 mg dry herb)*, lycopene (2.1 mg), *Prunus africana* (equivalent to 15 g dry stem, standardized to _-sitosterol) and *S. repens (equivalent to 660 mg of dry leaf per capsule)* with the excipients lecithin, hydrogenated vegetable oil and beeswax and soya oil in a blue softgel capsule. The placebo product contained the same amounts of lecithin, hydrogenated vegetable oil, beeswax and but had higher levels of soya oil in the same soft gel capsule. The treatment product and placebo capsules were identical in capsule odour, texture, hardness and packaging. Both capsule types were administered as 1 capsule per day with food. The randomisation code was maintained by the independent company. Product containers were returned at the end of the study.

Variables and outcomes

Total prostate function and severity of individual symptoms were measured at baseline and at 1, 2 and 3-month time period, using the validated self-reporting questionnaire: international prostate symptom score (IPSS). Changes in day-time and night-time micturition frequency were measured by a daily record in a patient diary. Participant plasma electrolytes (PE), liver function

tests (LFT) and the Prostate Specific Antigen (PSA) was also recorded at baseline and at 3-months (±14 days). The participants provided fasting blood sample at a pathology collection centre.

The IPSS questionnaire is a widely used validated instrument to measure the severity of lower urinary tract symptoms. It is based on seven questions concerning urinary symptoms associated with BPH. Each question is rated on a six-point scale, where the ratings for each question are: 0: not at all; 1: less than 1 time in 5; 2: less than half the time, 3: about half the time; 4: more than half the time; 5: almost always. IPSS uses the following rating system: 0—8 (mild symptoms), 9—19 (moderate symptoms) and 20—35 (severe symptoms). The IPSS also includes a question relating to quality of life due to symptoms rated on a seven-point scale where 0: Delighted; 1: Pleased; 2: Mostly satisfied; 3: Mixed; 4; Mostly unhappy; 5: Unhappy; 6; Terrible.

Analysis populations

The authors indicated that the data was analysed according to an intention-to-treat approach.

Sample size

The authors mentioned that a minimum number of 23 participants per group was required to achieve a statistical power of 80% based on a 25% reduction in average symptoms severity as measured by the total IPSS score.

Statistical methods

Clinical study analyses were completed at an alpha level of 0.05. The group medians of scores at baseline and 1/2/3-month were calculated for each symptom measure and the total IPSS score. The group means (along with the 95% CI) of day/night-time urinary frequency for active and placebo were calculated at baseline and 1/2/3-month time period. Kolmogorov-Smirnoff test was performed to test for normality of the different data sets.

The group means of scores at the 3-month timeframe were used to assess the statistical difference between both groups by Wilcoxon signed ranks test. Paired *t*-tests were performed on daytime and night-time urinary frequency to compare baseline with 1, 2 and 3 month within the groups. The authors also analysed the day and night-time urinary frequency data for time (baseline, month 1, month 2 and month 3) and treatment (ProstateEZE Max and placebo) effects using a mixed-design (Split-Plot) repeated-measures analysis of variance (ANOVA).

6.2.1.3. Results

Participant flow

The authors declared that the final sample size of minimum 23 participants per group was adequate. Power analysis details were provided for TGA assessment. Overall, 60 eligible participants were enrolled, out of which 3 withdrew immediately after randomisation due to unwillingness to participate further. These men were excluded from the final analysis. The active group had 32 participants while the placebo group has 25.

Baseline data/characteristics

The authors indicated that active treatment groups and placebo group were evenly matched at baseline in all demographics, with no significant differences in age (mean±SD, 63.0±10.1 years, and 64.9±9.6 years respectively), weight (85.7±11.6 kg and 88.9±15.5 Kg), body mass index (27.8±3.6 and 27.0±6.1), and PSA score (2.8±2.0 and 3.3±2.5).

The authors indicated that there were no significant correlation between symptom severity (total IPSS severity rating) and the above parameters in either the active or placebo groups.

Treatment compliance

According to the authors, participants returned unused containers of product at the final interview, and compliance was high (95%). Compliance data was not provided for TGA assessment.

Efficacy

The authors provided the IPSS symptom severity scores (scale and subscale) for active and placebo groups over the 3-month intervention period. Scores were expressed as median values (Table 2).

Table 2. Individual IPSS symptom severity scores in the active and placebo groups over the 3-month intervention.

IPSS symptom severity item.	Active treatment group (n= 32) Median IPSS scores				Placebo treatment group (n= 25) Median IPSS scores				Significance between groups at 3-month[a]
	Baseline	1-Month	2-Months	3-Months	Baseline	1-Month	2-Months	3-Months	
Had a sensation of not emptying your bladder completely after you finished urinating?	3	2.5	2	1.5	3.5	3	3	3	p=0.06
Had to urinate again less than two hours after you finished urinating?	4	3.5	3	3	3	3.5	3	3	p=0.29
Stopped and started again several times when you urinated?	2	2	1	1	3	2	2	2	p=0.06
Found it difficult to postpone urination?	3	3	3	3	3.5	3	2	3.5	p=0.07
Had a weak urinary stream?	3	3	3	3	4	3	2	3.5	p=0.1
Had to push or strain to begin urination?	2	1	1	1	1	1	1	1	p=0.2
Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?		2	2	2	2	2	2	2.5	p<0.05
Total score	19.5	15.5	14	12.5	18	16.5	16.5	16.5	p<0.05

[a] Wilcoxon signed ranks test.

Total prostate function

There was no significant difference in the total IPSS median score between active and placebo groups at baseline. The author stated the difference at baseline to be 3 vs 3.5 as per table 1 above.

There was a progressive reduction in the total IPSS scores for the active group across the 3-month period. At the end of the 3-month intervention period the decrease in the total IPSS median score for the active group (35.9%) was significantly greater than that in the placebo group (8.3%).

There was no significant difference in the total prostate function in the placebo group at months 2 and 3.

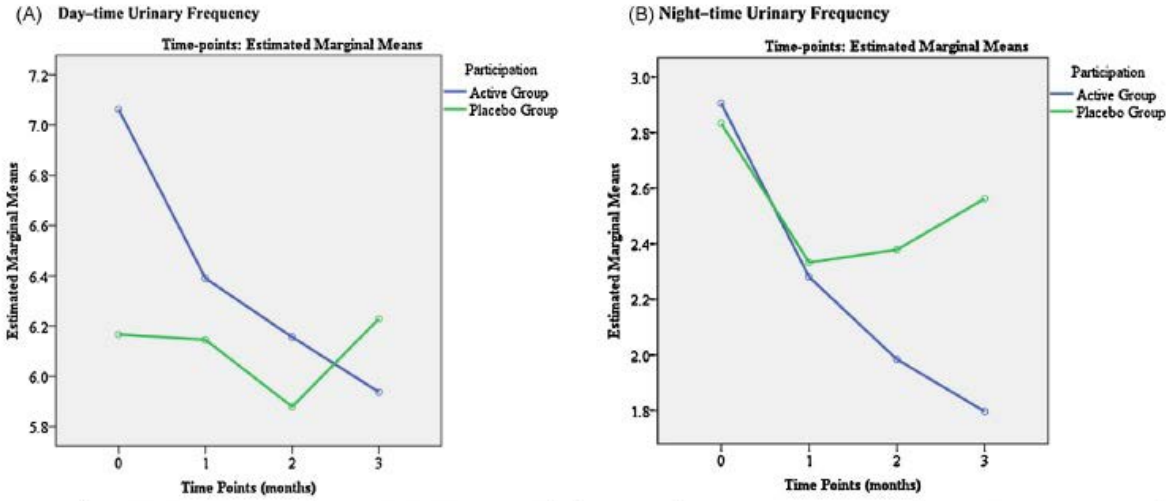
Individual BPH symptoms

According to the authors, the results for the active group showed a significant percentage decrease in mean severity for all questions, except *weak urinary stream* after 1 month of treatment. There was a significant improvement in *urinary stream* by month 2 and all symptoms remained significant at month 3. The authors proposed that the most positive improvement was observed in the questions (symptoms) relating to *pushing & straining* and *stopping & starting*.

For the placebo participants, the authors reported that the individual questions (symptoms) *weak urinary stream* and *sensation of not emptying fully* were reduced at month 1 and 2 but reverted to baseline levels by month 3, and that they reported greater severity to the question *had to push and strain* over the trial period.

Urinary frequency:

The authors provided the day and night-time urinary frequency plots along with the mean values (along with the 95%CI) for the active and placebo groups across the 3-month intervention period (Figure 1).



Time Point Intervention Day–time	Treatment Group			Placebo Group		
	Mean	95%CI Lower Bound	95%CI Upper Bound	Mean	95%CI Lower Bound	95%CI Upper Bound
Baseline	7.1	6.1	8.1	6.2	5.0	7.3
1–month	6.4	5.5	7.3	6.2	5.2	7.2
2–month	6.2	5.3	6.9	5.9	4.9	6.9
3–month	5.9	5.0	6.9	6.3	5.2	7.3

Time Point Intervention Day–time	Treatment Group			Placebo Group		
	Mean	95 %CI Lower Bound	95% CI Upper Bound	Mean	95 %CI Lower Bound	95% CI Upper Bound
Baseline	2.9	2.5	3.4	2.8	2.3	3.4
1–month	2.3	1.8	2.8	2.3	1.8	2.9
2–month	2.0	1.5	2.5	2.4	1.8	2.9
3–month	1.8	1.4	2.2	2.6	2.1	3.1

Figure 1. Day-time (A) and night-time (B) trends in urinary frequency for the active group over the placebo group during the 3-month intervention period.

The authors report that at baseline the average day-time urinary frequencies were similar for active and placebo groups (mean±SD, 7.0±3.2, and 6.2±2.0; respectively). There was significant reduction in day-time urinary frequencies in the active group from baseline to month 1, 2 and 3. 9.1% reduction at 1-month ($p<0.018$); 12.6% at 2-month ($p<0.003$); and 15.6% at 3-month ($p<0.016$). Placebo group experienced reduction in day-time frequency at 1 and 2-month but returned to baseline at 3-month.

The authors reported a significant reduction in night-time urinary frequency for the active group after 1-month (20.4% reduction, $p<0.001$). With progressive reduction after 2-month (36.7%, $p<0.001$) and 3-month (39.3%, no p value reported) compared to baseline.

Based on a repeated measures analysis with a mixed design ANOVA, the active group showed a statistically significant trend of reduction in both day-time ($F=3.052$, $p<0.03$) and night-time ($F=4.601$, $p<0.004$) urinary frequencies over placebo.

Safety

There were no significant changes to the plasma electrolytes (PE) or liver function tests (LFT) in either group after 3 months of treatment. The prostate specific antigen levels for each participant remained in the healthy reference range for all participants in both active and placebo groups. There were no adverse reactions reported in the trial and ProstateEZE Max was well tolerated.

6.2.1.4. Study author's conclusions

The study results indicated a significant reduction in severity of lower urinary tract symptoms (LUTS) associated with benign prostate hypertrophy (BPH) as a result of 3 months treatment with the product, compared to placebo. Both day and night-time urinary frequencies reduced in the treatment/active group. There were consistent positive effects across the IPSS scales.

The authors concluded that overall, the results indicate the effectiveness of ProstateEZE Max®, in management of histologically diagnosed benign prostate hypertrophy (BPH), without any adverse effects.

The authors noted the following limitations to their study:

- The study has a relatively low sample size and lacks comparative studies that have investigated the herbal combination.
- The study did not perform a flow rate measurement. However, given that this was a preliminary investigation only, the aim was mostly to assess if the herbal combination could improve symptom relief, especially day and night-time urinary frequency.

The authors recommended future research into efficacy of the herbal combination medicine for managing symptoms of medically diagnosed benign prostate hypertrophy.

6.2.1.5. Funding/conflicts of interest

Funding and study medication for the project was received from the clinical trial sponsor, Totally Natural Products, Sydney, Australia. The sponsor had no involvement in the collection, analysis or interpretation of the data; writing the report; or the decision to submit the paper for publication.

6.2.1.6. Evaluator's comments

The aim of this study was to evaluate the clinical efficacy and safety of ProstateEZE Max® for improving/management of symptoms of medically diagnosed benign prostate hypertrophy (BPH). These objectives were relevant to the indications sought for use in otherwise healthy adults.

The authors claimed that the study population was otherwise healthy adults with mild to moderate symptoms of BPH. However, there was no upper limit of the baseline IPSS scores mentioned in the recruitment process, only that all participants had a minimum score of 8. As the range for mild to moderate symptoms IPSS score is 1-19 (1-7: Mild; 8-19 Moderate), the lack of an upper limit could indicate that participants with severe symptoms may have also been included. Additionally, the authors did not report the Quality of Life (QoL) scores in the study, which are an integral part of IPSS. Without this information, it is not possible to ascertain whether the improvements in the total IPSS scores or even in the individual symptom scores had a significant clinical impact on quality of life.

The exclusion criteria were overall appropriate for the conduct of a clinical trial to study a highly specific population and exclude any other conditions requiring concurrent medications or other extenuating variables.

The authors claimed that the data was analysed according to the intention to treat approach, however there were 3 participants who withdrew from the study after randomisation. These participants were not included in the statistical analyses. There was no discussion about what impact that may have on the analyses, however the evaluator notes that these participants were reported to have withdrawn *immediately* after randomisation, which may have been before the first time point measurement at 1 month.

Based on Table 1 in the published study, the median IPSS scores were recorded for the individual BPH symptoms as well as the total. The evaluator considers this appropriate given that the IPSS variables data were not normally distributed. According to the authors, there was no significant difference in the total IPSS medians between active and placebo at baseline, however no numerical statistical results were provided. Additionally, the authors appear to have erroneously reported the difference to be 3 vs 3.5, which the evaluator notes relates to one of the BHP symptoms and not the total IPSS score (as per table 1). There is a general trend of reduction of the total IPSS score from baseline to 3-month for the active/treatment group, while the placebo group showed a slight reduction at 1-month and did not change further at the 2/3-month time point. There was a significant reduction in the total IPSS score at the end of the trial (i.e. 3-month) for the active group (35.9% reduction) when compared to the placebo group (8.3% reduction), based on the Wilcoxon signed ranks test.

The authors reported that the mean severity of all individual symptoms (IPSS subscale questions) showed a significant percentage decrease for the active group. No numerical statistical data was provided to justify this interpretation, especially noting that in the majority of the cases (refer to table 1) the scores did not change or only changed by a factor of 1 across the 3-month period. Similar unsubstantiated interpretations (i.e. without numerical statistical data) were made by the authors with regards to improvement in *urinary stream*, *pushing & straining* and *stopping & starting* symptoms/questions. Additionally, the Wilcoxon signed ranks tests did not reveal a statistically significant reduction in any of the individual symptoms except one (night-time urinary frequency) for the active group relative to placebo. Hence the evaluator concludes that the efficacy of treatment in reducing 6 of the 7 individual symptoms is unclear.

The authors claimed that the average day-time urinary frequencies were similar for active and placebo. However, there was no inferential statistical measure used to support this claim. The evaluator notes from Figure 1(A) that the baseline day-time urinary frequencies are mismatched between the active/treatment and placebo groups such that the validity of the overall analysis (of impact of treatment on day-time frequency relative to placebo) may be uncertain. More information should be provided to clarify the assertion that baseline (day-time) urinary frequencies were indeed similar for active and placebo.

The evaluator notes and concurs with the significant reduction in day-time urinary frequency from baseline to month 1, 2 and 3 in the active group as reported by the authors based on the p values of <0.05 generated using paired *t*-tests. The results from the paired *t*-tests for the placebo group were not provided even though the authors reported a reduction at 1 and 2 month time points.

There was also a significant reduction in night-time urinary frequency from baseline to month 1, and month 2 in the active group as reported by the authors based on the paired *t*-tests p-values of <0.05. The p-value for month 3 frequency was not provided. Hence the evaluator is unable to confirm the statistical significance of reduction. The evaluator does, however, note a general trend of reduction for the night-time frequency in the active/treatment group. Again, no numerical statistical results were provided for the change in night-time urinary frequency of the placebo group.

The authors also provided a repeated measures ANOVA analysis results, mainly the F statistic and accompanying p value, for an effect for the active group in reducing the day and night-time urinary frequencies. Due to the lack of additional information and/or numerical statistical data relating to the repeated measures ANOVA, the evaluator is not able to assess whether the authors' conclusion is related to a time effect or a time x treatment effect or a treatment effect. Additional information is required to make any clear interpretations from the results currently presented in the published trial.

The authors further suggest that the reduction of nocturia from 2.9 times to 1.8 times was clinically significant. However, this was not based on any validated clinical practice evidence or published scientific information.

Finally the authors briefly discuss the evidence from scientific literature that supports the use of the different active herbal constituents (albeit in varying amounts, preparations, extractions). The evaluator notes the authors' implications from this scientific evidence that:

- Some men may not respond to particular herbal extracts/medicines, hence a mixture may be a plausible alternative for treatment.
- There needs to be more comprehensive dosing studies on individual/combination products.
- Direct comparisons of trials can only be conducted if the extracts have similar chromatographic profiles.
- Herbal remedies are likely to be more effective in treating mild to moderate symptoms, rather than severe cases.

The evaluator agrees with the authors' conclusion that the major limitation of this study is the relatively low sample size and the lack of comparative studies that have investigated the herbal combination, and a further weakness is the absence of a flow rate measurement. However, the evaluator also notes that this study was a preliminary investigation.

Overall, this study has missing information and inconsistencies in reporting which need to be clarified in order for a more reliable conclusion to be made regarding efficacy.

6.3. Other (non-pivotal) efficacy studies

The sponsor provided two published clinical trials (Ref. 20, 21) based on the active ingredient *Pygeum africanum* extract. Both the clinical trials investigated the efficacy of a commercially available extract of *Pygeum africanum* – Tadenan®.

The evaluator has not described these trials in detail here as they both did not include a placebo control group and the amount of extract used in both trials was different to that used in the proposed product (i.e. the proposed product contains 75mg of *Pygeum* extract), while the studies assessed 50 and 100mg extracts. Additionally, these were considered in the meta-analysis conducted by the Cochrane collaboration on the use of *Pygeum africanum* for benign prostate hyperplasia (see section 6.4).

6.4. Meta-analyses and systematic reviews

The sponsor provided a published systematic review that included a quantitative meta-analysis (Ref. 16) on the active ingredient *Pygeum africanum* extract.

6.4.1. (Wilt TJ and Ishani A, 2011; Reference 16)

Wilt Timothy J and Ishani Areef (2011) Pygeum africanum for benign prostatic hyperplasia. *Cochrane Database of Systematic Reviews 1998*, Issue 1. Art. No.: CD001044.

6.4.1.1. Study design, objectives, and locations

Wilt and Ishani, 2011 conducted a systematic review including a quantitative meta-analysis of 18 randomized clinical trials (RCTs) with the purpose of investigating the efficacy and safety of *Pygeum africanum* extract in BPH in comparison to placebo.

All of the studies were conducted outside the United States. Study design included RCTs, thirteen of which compared *Pygeum africanum* with a placebo and seven of which compared *Pygeum*

africanum with an 'active control'. The 'active controls' used in the studies have not been conclusively demonstrated to be effective in treating symptomatic BPH. There were no studies comparing *Pygeum africanum* to standard pharmacologic interventions such as alpha-adrenergic blockers or 5-alpha reductase inhibitors. The mean study duration was about 64 days (range 30-122 days). The majority of the studies (n=14 studies) utilised a standardised extract of Pygeum africanum at doses of 75 to 200 mg per day. For studies that provided baseline data, results did not vary between treatment arms and were consistent with men typically presenting with moderate benign prostatic hyperplasia. The mean age was 66.± 6.9 years (9 studies, n = 845, range 42 to 89); nocturia = 3 ± 0.7 times per evening (4 studies, n = 413); peak urine flow = 12 ± 3.6 mL/sec (5 studies, n = 416); residual urine volume = 40 ± 25.6 mL (2 studies, n = 284). Not all studies could be pooled because of differences in reporting methods.

6.4.1.2. Methods

Search Strategy

The authors searched MEDLINE for 1996 – 2000 using the following MeSH headings: prostatic hyperplasia, phytotherapy, plant extracts, pygeum africanum, tadenan, docosonal and pigenil, including all subheadings. A search of EMBASE, years 1974 to 1999 was done by using a similar approach to that for Medline. The authors also searched the private database Phytodok (Munich Germany), and the Cochrane Library, including the database of Cochrane Prostate Diseases and Urologic Malignancies Review Group. Two investigators independently screened all identified studies to determine if they met the inclusion criteria below.

Inclusion and exclusion criteria

Trials were eligible if they (1) were randomized (2) included men with BPH (3) compared preparations of *Pygeum africanum* (alone or in combination) with placebo or other BPH medications (4) included clinical outcomes such as urologic symptom scales, symptoms, or urodynamic measurements.

Statistical methods

Two investigators independently determined if the identified studies met the inclusion criteria. Study quality was assessed using the method outlined by Schulz et al, 1995.

For the meta-analysis: Two methods were used for combining data as no common outcome measure was available from all eighteen studies. One method assessed treatment effect size for continuous variables by the difference of the mean change for each outcome divided by the pooled standard deviation for each outcome when trials report different outcome measures of effectiveness (e.g. symptom scale scores, nocturia, peak urine flow rate). The other method calculated a summary measure for individual outcomes using studies that provided similar outcome measures and utilised standard meta-analytic techniques.

The effect size was determined using an a priori method of determining the outcome that was most clinically significant (order of clinical importance: symptom scale score > nocturia > peak urine flow > residual urine volume). One outcome from each study was then transformed into units of standard deviations (SD), giving a comparable effect size for each study. The study-specific overall effect size was the difference in mean outcome for the *Pygeum africanum* and placebo groups, divided by the pooled SD of the outcome measure. The summary effect size across studies was calculated as the weighted average of the study-specific effect size, with weights equal to the inverse of the estimated variance of each using standard meta-analytic methodology as developed by DerSimonian and Laird. The statistical significance of the summary effect size was assessed by comparing it with the standard normal distribution and the Cohen effect size was used (0.8 = large, 0.5 = moderate, 0.2 = small).

Additional meta-analyses considered the difference between *Pygeum africanum* treatment and the control treatment in the mean change from baseline to end of follow-up for each separate continuous outcome. Weighted relative risks and 95% CI were calculated using standard meta-analytic techniques for categorical outcome measures.

Chi squared tests were used for analysis of bivariate comparisons (adverse events and dropouts) using simple pooling of data. To assess the percentage of patients having improvement in urologic symptoms, a modified intention-to-treat analysis was performed (i.e., men who dropped out or were lost to follow-up were considered to have had worsening symptoms). A test for heterogeneity was calculated according to standard formulas and a random effects model utilized for all summary estimates.

6.4.1.3. Results

Study identification

The authors identified 31 trials, 18 of which met the inclusion criteria. N=11 studies examined *Pygeum africanum* alone versus placebo. N=2 trials comparing *Pygeum africanum* against an anti-inflammatory drug. One study comparing *Pygeum africanum* to placebo included an additional treatment arm of *Pygeum africanum* in combination with a steroid. N=2 studies compared *Pygeum africanum* alone to one or more herbal agents and versus placebo. One trial compared *Pygeum africanum* to another herbal agent, one trial compared different daily dosage forms of *Pygeum africanum*, and one trial compared two different doses of *Pygeum africanum* in combination with another herbal extract.

Risk of bias

The authors identified these risks of bias in the included studies:

- Only one of the studies reported a method for concealment of treatment allocation (score = 2) but 17 of the 18 studies were double-blinded.
- Most studies did not provide baseline patient information nor provide clinically relevant baseline or outcomes data in a standardized fashion.
- No placebo-controlled studies utilized standardized, validated symptom scales (the outcome measure of greatest clinical significance).
- No information on patient race, comorbid conditions, prostate size or standardized/validated urologic symptom scale scores.
- All studies were of short treatment duration with none having a follow up greater than four months.

The authors were not able to assess for publication bias using funnel plot analysis due to the small number of studies.

Results for summary effect sizes (primary outcome)

The results for summary effect sizes are as outlined in the Table below:

Table 3. Summary of effect size for *Pygeum africanum* in urologic symptoms

Outcome measures	No. of studies	Summary effect size (ES)
Weighted estimate of effectiveness	6	ES = -0.8 SD (95% CI -1.4 to -0.3) (large improvement)
Nocturia	3	ES = -0.8 SD (95% CI -1.4 to -0.1) (moderate to large improvement)

Peak urine flow	4	ES = 0.7 SD (95% CI 1.3 to 0.0) (moderate improvement)

Overall, *Pygeum africanum* improves the outcome measures and the point estimate for the effect size is moderate in magnitude.

Results for the urinary symptoms and flow measures

Consistent with the results seen in the summary effect sizes, *Pygeum africanum* improved specific urinary symptoms and flow measures.

In 5 double-blind trials involving 430 participants, men receiving *Pygeum africanum* were more than twice as likely to be rated by their physician as having overall improvement in symptoms compared to men taking placebo (65% vs. 30%; RR = 2.1; 95% CI = 1.4 to 3.1).

Table 4. Weighted Mean Difference for the *Pygeum africanum* in urologic symptoms

Outcome measures	Change	Weighted Mean Difference (WMD)
Nocturia	Reduced by 19%	WMD = - 0.9 times per evening; 95% CI = -2.0 to 0.1) (not statistically significant)
Peak urine flow	Increased by 23%	WMD = 2.5 mL/sec (95%CI = 0.3 to 4.7)
Residual urine volume	Reduced by 24%	WMD = -13 mL; 95%CI = -23.3 to -3.0

Safety

All studies provided information on the percentage of men who dropped-out or were lost to follow up, potentially the most reliable indicator of tolerability. The mean percentage of participants who dropped out was 12% (n = 179), ranged from 0% to 45% and did not differ between *Pygeum africanum* (13%), placebo (11%) and other controls (8%) (P=0.4 vs placebo and P=0.5 vs other control).

Three studies (two placebo controlled) had dropout rates > 20%. The reason for the high dropout rate was not reported but two of the trials (Barth 1981; Chatelain 1999) indicated that adverse effects were “infrequent and mild” in participants completing the trial. None of these three trials reported outcome data in a method suitable for incorporation into the effect size analyses.

Thirteen of the eighteen studies provided information on specific adverse events. Adverse events due to *Pygeum africanum* were generally mild in nature and comparable in frequency to placebo. The most frequently reported adverse events were gastrointestinal and occurred among seven men in five trials.

6.4.1.1. Study author’s conclusions

The authors concluded that the overall standardized effect size and the summary improvement in global symptoms, nocturia, peak urine flow and residual urine volume suggests that *Pygeum africanum* is effective in men with symptomatic benign prostatic hyperplasia. This benefit is of modest size and appears to be clinically significant. *Pygeum africanum* is well tolerated and costs less than most prescription medications. A standardized preparation of *Pygeum africanum*, may be a useful treatment option, at least in the short term, for men with lower urinary symptoms consistent with benign prostatic hyperplasia.

The authors noted the following limitations to their study:

- No study was conducted in the United States.
- Many studies did not report means and standard deviations.

- No information provided to determine if *Pygeum africanum* prevented long-term complications of benign prostatic hyperplasia such as acute urinary retention, renal insufficiency or the need for surgical intervention.
- No studies compared *Pygeum africanum* with medical interventions of demonstrated effectiveness including alpha adrenergic blockers and 5-alpha reductase inhibitors.
- The "active controls" used in the studies have not been convincingly demonstrated to have beneficial effects.

The authors recommended that additional placebo-controlled trials are needed as well as studies that compare *Pygeum africanum* to active controls that have been convincingly demonstrated to have beneficial effects on lower urinary tract symptoms related to BPH. Future trials should be of sufficient size and duration (e.g. > 6 months).

6.4.1.2. Funding/conflicts of interest

The authors noted internal sources as sources of support - Department of Veterans Affairs Health Services Research and Development (HSRD) Office, USA and Minneapolis/VISN-13 Center for Chronic Diseases Outcomes Research (CCDOR), USA.

The authors reported no conflicts of interest for this work.

6.4.1.3. Evaluator's comments

The aim of this systematic review/meta-analysis was to investigate the efficacy and safety of *Pygeum africanum* extract in BPH in comparison to placebo.

The evaluator performed an assessment of the overall quality of the meta-analysis using the PRISMA 2009 Checklist. The meta-analysis addressed 24 out of 27 of the items on the checklist. Three of the missing items were the methods and results if additional analyses were performed, and the authors did not indicate if a review protocol exists and its accessibility.

In terms of study design, all studies were randomized, double-blinded clinical trials. The majority of the studies compared *Pygeum africanum* with placebo; other studies compared *Pygeum africanum* with active controls such as anti-inflammatory drugs, steroids and other herbal agents. The search strategy, selection criteria, data extraction, and quality assessment were appropriate.

The statistical methods used were appropriate. The tests for heterogeneity were not found in the pdf document provided by the sponsor, but they were found in the (full) pdf document available on the Cochrane library website (sourced by evaluator; https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001044/epdf/full). There was moderate heterogeneity reported for overall symptoms improvement and peak urine flow. There was considerable heterogeneity for nocturia but no heterogeneity for residual volume. The authors did not note the possible causes of heterogeneity but it is likely that variation in daily dosage amounts and treatment duration could contribute to the heterogeneity seen.

The evaluator concurs with the author's approach in the choice of pooled studies.

The authors reported that the adverse events were generally mild in nature and comparable in frequency to placebo. The most frequently reported adverse events were gastrointestinal and occurred among seven men in five trials.

The evaluator notes and concurs with the limitations presented by the authors.

Overall, this meta-analysis was performed with sufficient rigor. The evaluator agrees with the conclusion of this meta-analysis that *Pygeum africanum* is suggested to be effective in improving urinary symptoms in men with symptomatic benign prostatic hyperplasia. It should be noted that the pooled studies were few in number and that placebo-controlled studies did not use

standardized, validated symptom scales for the outcome measures of greatest clinical significance. The short treatment duration is also a limitation of the studies.

The evaluator also notes that the publication states that this review is out of date and has been withdrawn.

6.5. Other efficacy information

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Secondary supporting information (provided by sponsor)

The evaluator has summarised the secondary supporting information provided by the sponsor from their search strategy (see Table 5, below). Some of this information cites similar supporting references, some of which have been assessed in this application e.g. the pivotal study (Coulson, 2013) and also the meta-analysis on *Pygeum* (Wilt, 2002). As such, some of these pieces of supporting information are not entirely independent sources of information for evaluation of this application. The information is on the individual active ingredients and not the proposed product, hence it is unclear how each ingredient would interact to contribute to the efficacy of the product for the proposed indications. Furthermore, the extracts and/or doses used are sometimes different or not identified.

Table 5. Summary of secondary supporting information provided.

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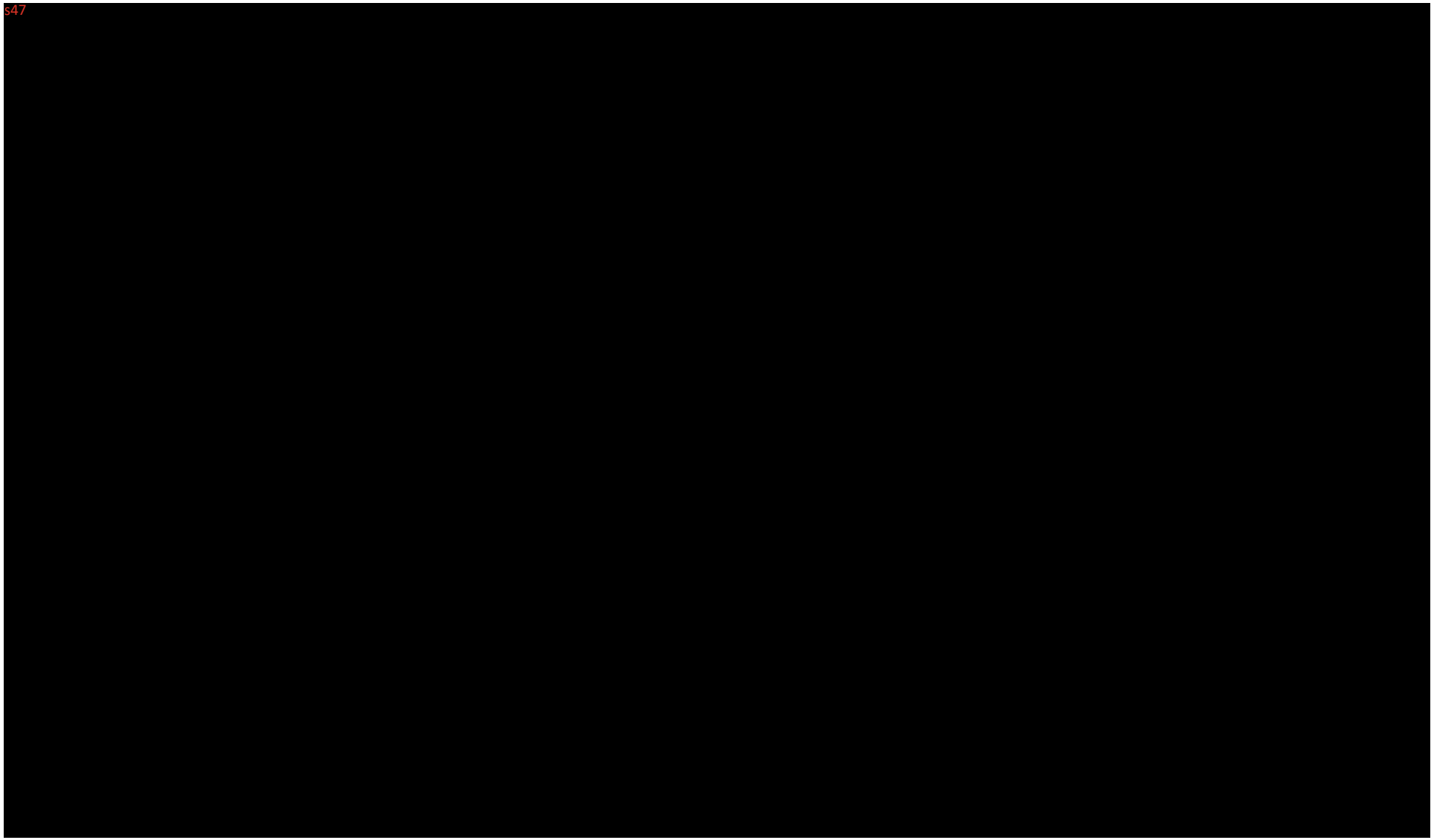

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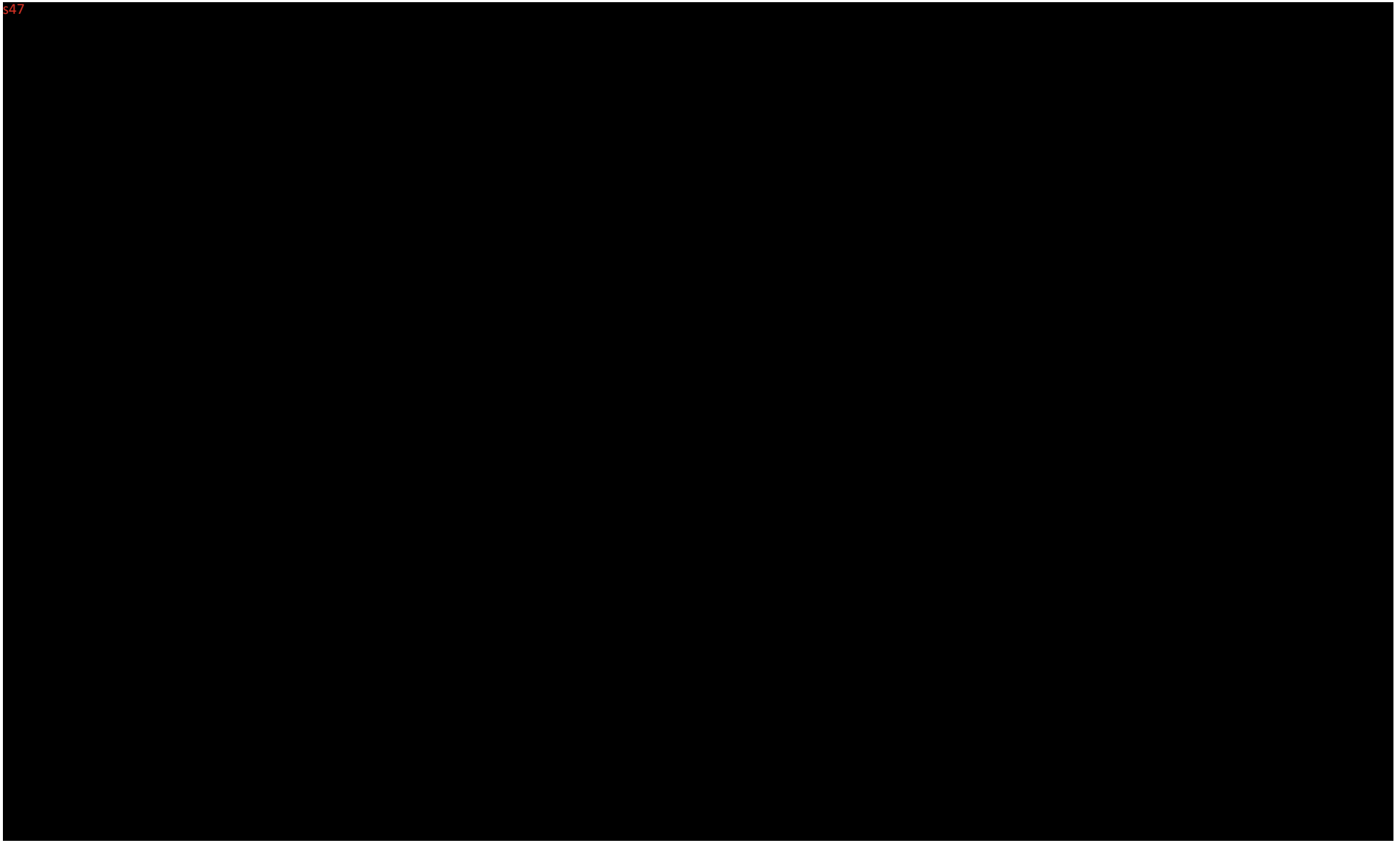

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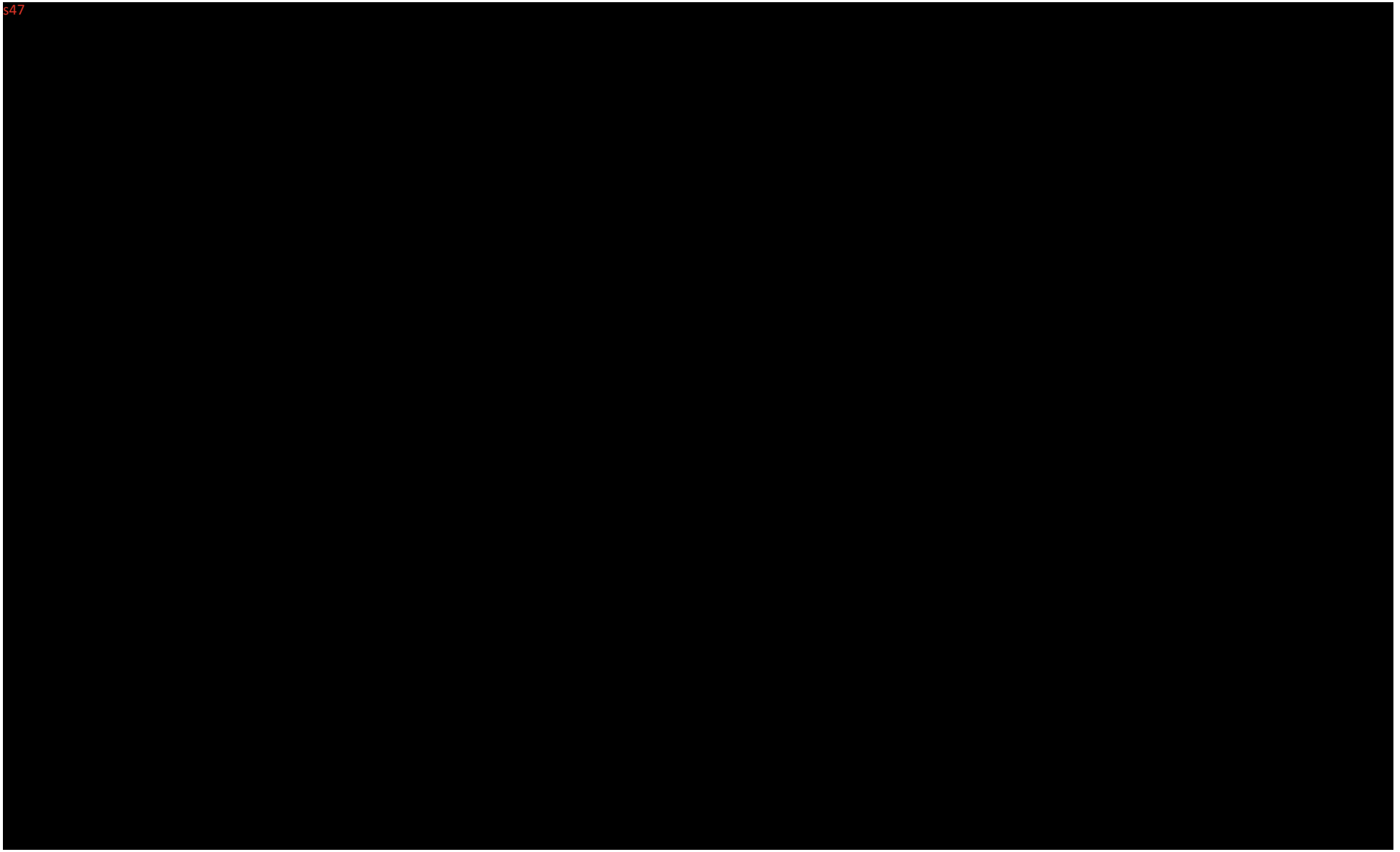

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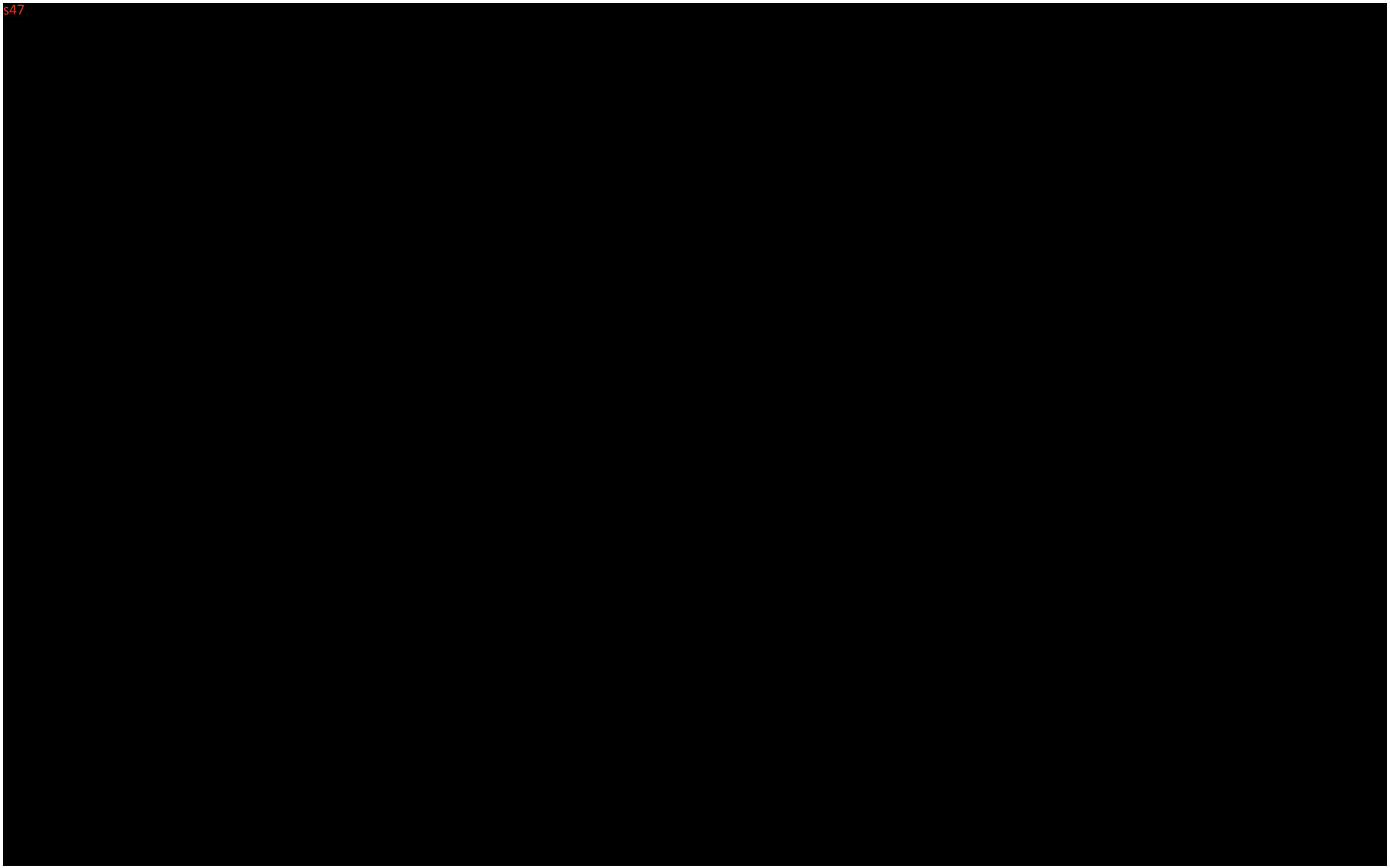

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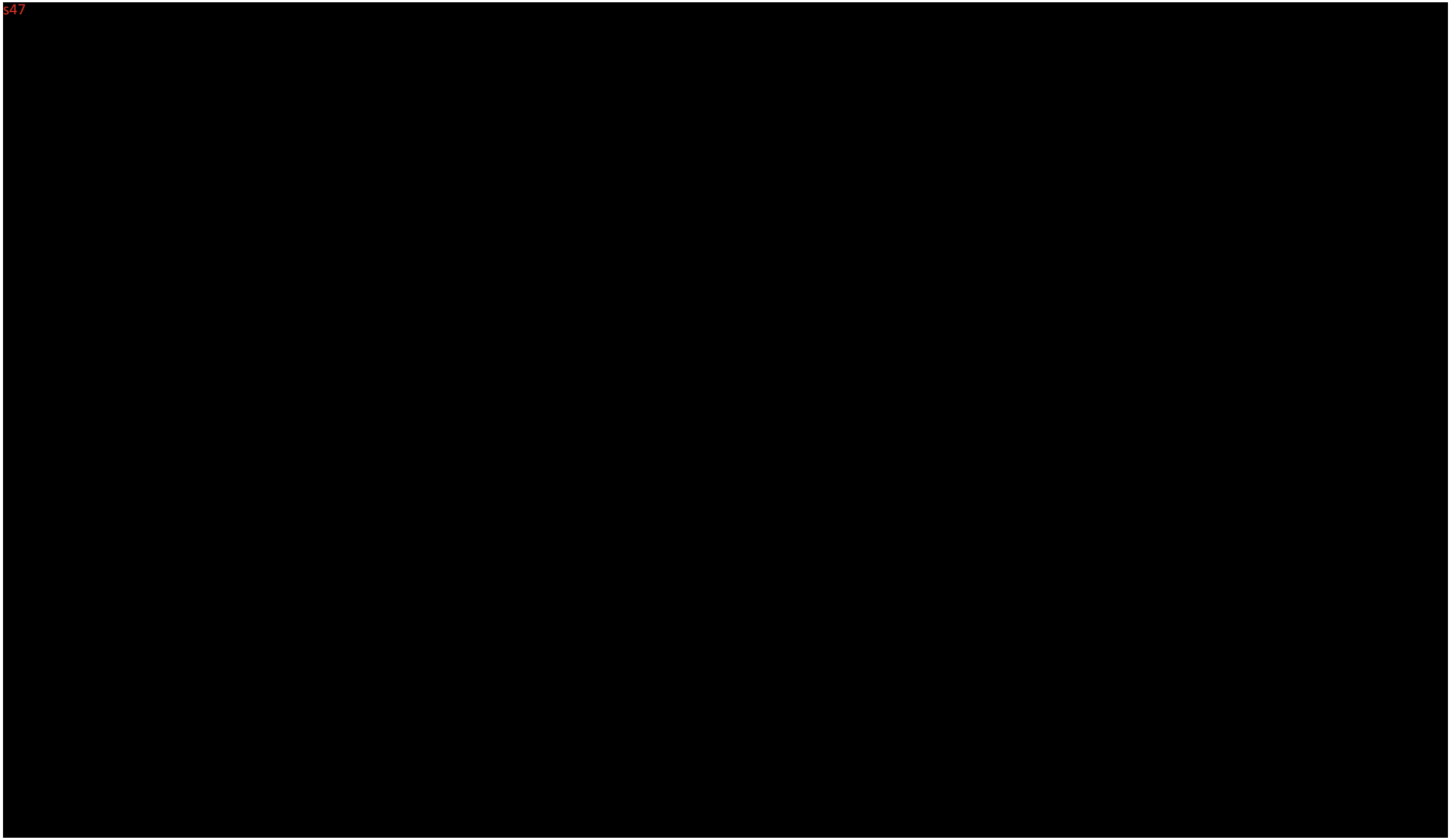

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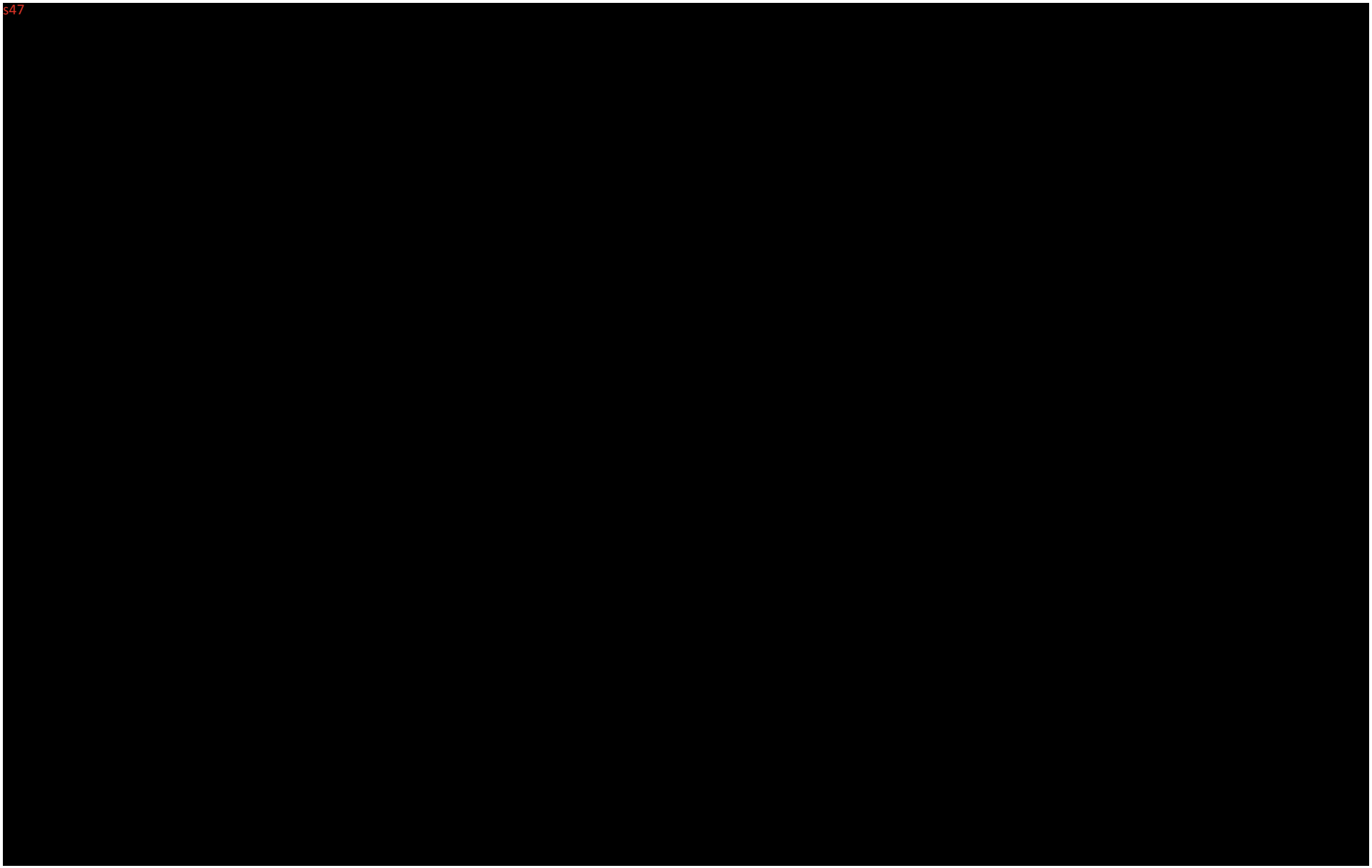

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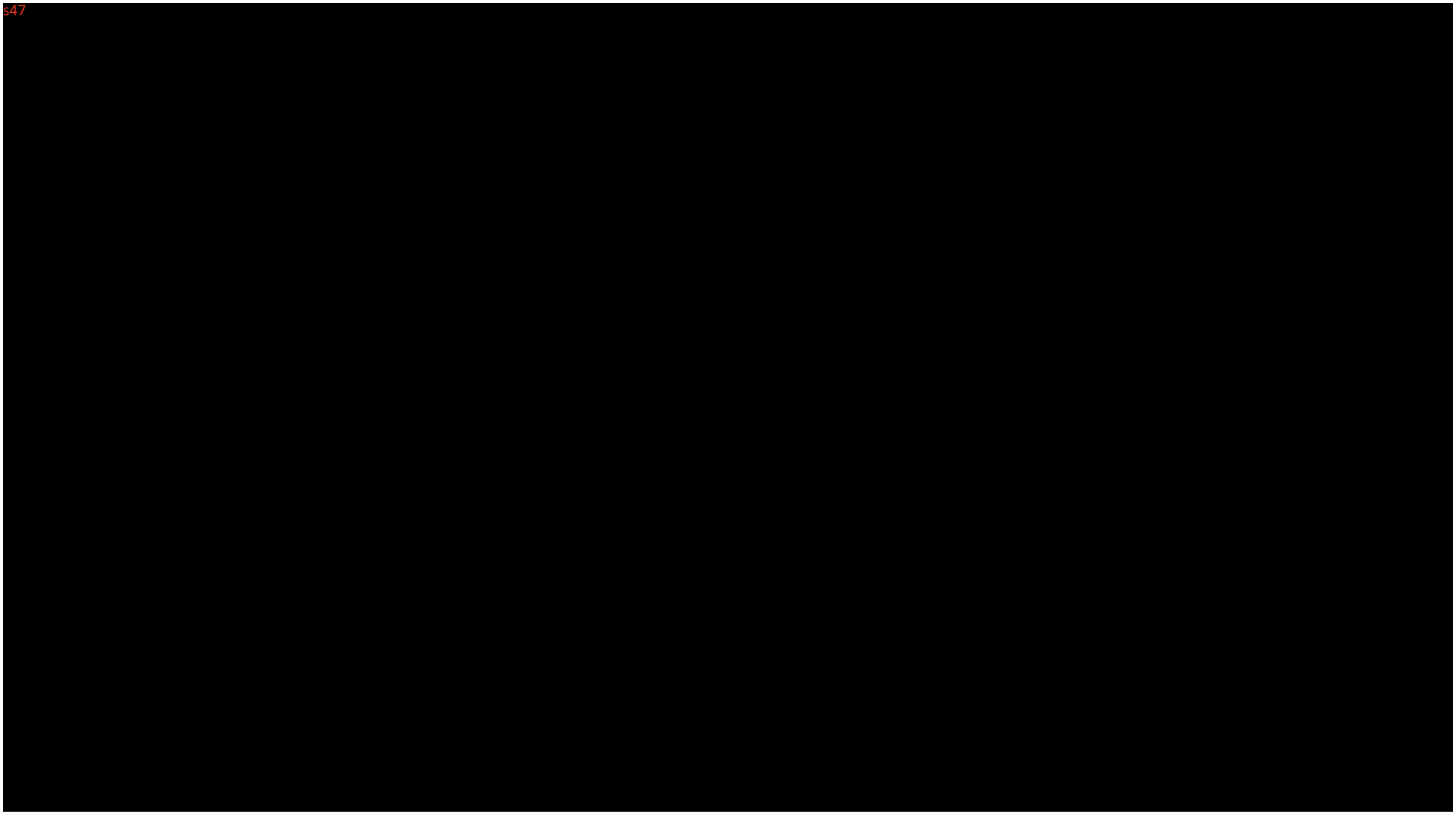

Cochrane reviews (sourced by evaluator)

The sponsor provided a Cochrane review on the *Prunus africana* for Benign Prostatic Hyperplasia, which is discussed in Section 6.4.

The evaluator sourced two additional Cochrane reviews: the most recent review on *Serenoa repens* for Benign Prostatic Hyperplasia (Tacklind et al, 2012) and a review on Lycopene for the prevention of prostate cancer (Ilic et al, 2011). There were no Cochrane reviews available for *Cucurbita pepo* and *Epilobium parviflorum*.

The *Serenoa repens* Cochrane review noted that *Serenoa repens* is widely used in Europe and the US to treat lower urinary tract symptoms associated with benign prostatic hyperplasia. The review concluded that even at escalating doses, *Serenoa repens* is not superior to placebo, a conclusion based on two high quality, clinical trials, one with a follow-up of six years.

The conclusion from the Lycopene Cochrane review was that there is insufficient evidence to either support, or refute, the use of lycopene for the prevention of prostate cancer. This is due to only three RCTs being included in this systematic review and the high risk of bias in two of the three studies. Similarly, there was no robust evidence from RCTs to identify the impact of lycopene consumption upon the incidence of prostate cancer, prostate symptoms, PSA levels or adverse events. While the focus of the review was on prostate cancer, there was a reference to the effect of lycopene on BPH in the Mohanty 2005 study, which reported that there was no significant difference in the incidence of BPH between study participants with lycopene supplementation (RR 1.33, 95% CI 0.34 to 5.31).

Overall, the Cochrane reviews do not seem to support either *Serenoa repens* or lycopene in reducing the incidence of BPH symptoms.

EMA assessment reports (sourced by evaluator)

The evaluator sourced EMA herbal monograph assessment reports for all active ingredients except for lycopene (none found) (see Table 6, below). In general, these active ingredients were only indicated for traditional use, and not well-established scientific use, for the relief of lower urinary tract symptoms related to BPH after serious conditions have been excluded by a medical doctor.

Only the hexane extract of the fruit of *Serenoa repens* was considered to be supported by sufficient evidence to grant a well-established use as a medicinal product with recognised efficacy and acceptable safety for the symptomatic treatment of BPH. ProstateEze Max uses a CO_2 extract of the seed of *Serenoa repens*, for which the EMA concluded that: 'taking account of the limited studies, the information is not considered sufficient to support the use of the supercritical CO_2 extract as a well-established medicinal product with recognised efficacy and acceptable safety'.

Table 6. Summary of the EMA Assessment reports and monographs for the active ingredients

Ingredient	Assessment report/Monograph	Comments - report and monograph	Relevance to application
Prunus africana	Assessment report: 12 Jul 2016 EMA/HMPC/321095/2012 Monograph: 12 Jul 2016 EMA/HMPC/680626/2013	The bark and herbal preparation [soft extract (DER 114-222:1), extraction solvent: chloroform; (stabilised by 1.2% of ethanol >99.9%)] has been in medicinal use for at least 30 years in France with at least 15 years in the EU. There are no sufficient data from well-designed clinical trials to support well-established use for this indication. Therefore the medicinal use of *Pygeum africanum* bark has to be regarded as **traditional** in the sense of Directive 2004/24/EC. However, the outcome of the clinical trials supports the plausibility in the proposed indication. Indication (traditional): relief of lower urinary tract symptoms related to BPH after serious conditions have been excluded by a medical doctor. Posology: Adults and elderly - Single dose 50 mg / Daily dose 100 mg Safety: Regarded as safe. Adverse effects such as digestive disorders (nausea, constipation or diarrhoea) have been reported in rare occasions. Precaution: Warning statements to exclude serious conditions by a medical doctor and to see a doctor if symptoms worsen is recommended.	ProstateEze Max utilises a different extract (dichloromethane); at a lower dose (75 mg/d vs 100 mg/d); and for scientific, not traditional, indications.
Cucurbita pepo	Assessment report: 20 Nov 2012	Seeds of *Cucurbita pepo* and herbal preparations thereof have been in medicinal use for at least 30 years with at least 15 years in the EU.	ProstateEze Max utilises a much lower dose of pumpkin seed oil (160 mg/d vs 3-4 g/d);

Ingredient	Assessment report/Monograph	Comments - report and monograph	Relevance to application
	EMA/HMPC/136022/2010 Monograph: 20 Nov 2012 EMA/HMPC/136024/2010	The long-standing medicinal use as well pharmacological data make the use in the proposed indication plausible. There are no sufficient data from well-designed clinical trials to support a well-established use in this indication. Therefore the medicinal use of pumpkin seed and preparations thereof has to be regarded as **traditional** in the sense of Directive 2004/24/EC. The outcome of the clinical trials supports the plausibility in the proposed indication. Indication (traditional): relief of lower urinary tract symptoms related to benign prostatic hyperplasia or related to an overactive bladder, after serious conditions have been excluded by a medical doctor. Herbal substance: Whole, ripe and dried seeds Herbal preparations: a) Comminuted herbal substance b) Soft extract (DER 15-25:1), extraction solvent ethanol 92% m/m c) Dry extract (DER 15-30:1) extraction solvent ethanol 60% v/v d) Fatty oil Posology: Herbal substance Single dose: 2.5 – 7.5 g, 2 times daily. Herbal preparations	and for scientific, not traditional, indications.

Ingredient	Assessment report/Monograph	Comments - report and monograph	Relevance to application
		a) Comminuted herbal substance Single dose: 2.5 – 7.5 g, 2 times daily. b) Soft extract Single dose: 500 mg, 2 times daily. c) Dry extract Single dose: 105 mg, 3 times daily or 152 mg, 2 times daily d) Fatty oil Single dose: 1 - 1.2 g, 3 times daily Daily dose: 3 – 4 g Safety: There were no registered AEs in clinical studies but allergic reactions have been documented (e.g. gastrointestinal complaints, urticaria, asthma, facial and oral oedema, anaphylactic reaction). Precautions: Pumpkin seeds can be only used in conditions which are controlled by a doctor with regular medical checks.	
Serenoa repens	Assessment report: 24 Nov 2015 EMA/HMPC/137250/2013 Monograph: 24 Nov 2015 EMA/HMPC/280079/2013	First reports of use in urinary complaints date from beginning of 20th century. Main interest focused on its use in the treatment of symptoms of BPH, in particular, grade I to III (Vahlensieck). Used to alleviate micturition disorders such as, dysuria, pollakisuria, nocturia and urine retention. Extracts of the fruits are mainly prepared with hexane, ethanol or supercritical CO_2. Indications:	ProstateEze Max utilises an extract (CO_2 extract) for which there was insufficient information for well-established use. The dose of saw palmetto extract in ProstateEze Max (44 mg/d) is much lower than the dose recommended for the hexane extract (320 mg/d, well-established use) or the ethanol extract (320 mg/d, traditional use). The indications for

Ingredient	Assessment report/Monograph	Comments - report and monograph	Relevance to application
		Well-established use: For the symptomatic treatment of benign prostatic hyperplasia Traditional use: For the relief of lower urinary tract symptoms related to benign prostatic hyperplasia, after serious conditions have been excluded by a doctor. Efficacy: Support the use of the **hexane extract** [soft extract (DER 7-11:1)] of the fruit of *Serenoa repens* as a well-established medicinal product with recognised efficacy and acceptable safety. Ethanolic extract [soft extract (DER 7.5-14.3:1), extraction solvent: ethanol 90% to 96% m/m] is not supported for well-established use but is supported for traditional use. Insufficient information to support the use of the supercritical CO_2 extract as a well-established medicinal product with recognised efficacy and acceptable safety. Posology: Well-established use: 320 mg once daily or 160 mg twice daily. Traditional use: 320 mg once daily. Safety: Reported side effects include: Pyrosis and gastric pain when taken on an empty stomach. Nausea, eructation diarrhoea and pyrosis (rare). Reversible gynecomastia. Allergic reactions (frequency unknown) Rise in blood pressure (uncommon) Intra-operative floppy iris syndrome (frequency unknown)	ProstateEze Max are scientific, not traditional.

Ingredient	Assessment report/Monograph	Comments - report and monograph	Relevance to application
		Headache (common) Precaution: Regular control by doctor required (special warning in Czech Republic marketed products).	
Epilobium angustifolium L. and/or *Epilobium parviflorum* Schreb.,	Assessment report: 24 Nov 2015 EMA/HMPC/712510/2014 Monograph: 24 Nov 2015 EMA/HMPC/712511/2014	Comminuted herbal substances of *Epilobium angustifolium* and *Epilobium parviflorum* were used as an herbal tea for oral use at least since 1982 in considerable amounts in the treatment of benign prostatic hyperplasia as well as bladder and kidney disorders within the European Union. Thus the requirements for the period of medicinal use according to Directive 2001/83/EC as amended with respect to "traditional use" are regarded fulfilled. Posology: Herbal tea: 1.5-2.0 g of the comminuted herbal substance in 250 ml of boiling water as an herbal infusion 2 times daily. Indication (traditional): relief of lower urinary tract symptoms related to benign prostatic hyperplasia, after serious conditions have been excluded by a medical doctor. Safety: So far adverse events, serious adverse events and deaths as well as drug interactions from clinical trials or case studies have not been reported. Furthermore, no concerns arise from the few available data from toxicity studies. Due to the widespread traditional medicinal use for more than 30 years the safety of *Epilobium angustifolium* and *Epilobium parviflorum* can be assumed. Contraindications:	ProstateEze Max utilises a different preparation (aqueous extract in a capsule vs herbal tea); and for scientific, not traditional, indications.

Ingredient	Assessment report/Monograph	Comments - report and monograph	Relevance to application
		Hypersensitivity to the active substance. <u>Special Warnings and precautions for use:</u> If complaints worsen or if symptoms such as fever, spasms or blood in the urine, painful urination, or urinary retention occur during the use of the medicinal product, a doctor should be consulted.	
Lycopene	NA	NA	NA

6.6. Evaluator's conclusions on clinical efficacy

The proposed intermediate indications for ProstateEZE Max are:

1. May assist in the management of symptoms of medically diagnosed benign prostatic hypertrophy.
2. For the symptomatic relief of medically diagnosed benign prostatic hypertrophy.
3. Pygeum Africana may provide support for the symptomatic relief [of] nocturia, nocturnal frequency, weak stream, after-dribbling, hesitation and interruption of flow when such symptoms are associated with medically diagnosed benign prostatic hypertrophy.

s47 [redacted]

The sponsor has submitted one pivotal study on the finished product (Coulson et al., 2013). The rest of the references are considered secondary supporting information as these were based on individual active ingredients and not the proposed product. These were a mixture of primary clinical trial studies, a Cochrane review, a non-systematic review, monographs, bioavailability studies, and excerpts from textbooks.

Efficacy based on finished product

In the pivotal study by Coulson et al., the total prostate function as measured by the total IPSS median score at 3 months was significantly different compared to the placebo group ($p < 0.05$). In terms of individual BPH symptoms, the results require further clarification before a conclusive statement can be made. There is a significant reduction in urinary frequency during day-time and night-time. However, for the day-time results, the baseline day-time urinary frequencies are mismatched between the active/treatment and placebo groups such that the validity of the overall analysis (of impact of treatment on day-time frequency relative to placebo) may be uncertain. There was also no measure of clinical impact such as QoL scores or responder analysis thus it is unclear if there is a significant clinical impact.

As acknowledged by the sponsor, the pivotal study has some limitations, such as relatively small sample size, and the study only conducted a questionnaire survey and did not perform flow rate measurements. Also, there are no other studies that investigated this herbal combination for comparison and the mechanism of action of the combination of these ingredients is unknown. In addition, there was no dose response study using this finished product hence the optimisation of the current dose is unclear.

Overall, on face value, there is some support for the indications relating to the management of symptoms and providing symptomatic relief of medically diagnosed BPH, with the evidence for reduction of urinary night-time frequency being significantly stronger than other symptoms. Once the sponsor provides the response to the s31 RFI, the evaluator will re-assess the study for all the symptoms examined in the IPSS survey.

As the proposed product is a combination of herbal ingredients and the indications relate to the purpose or health benefit of the finished product (i.e. therapeutic use of the medicine), the wording of indication referring to efficacy of an active ingredient (*Pygeum africana*) is not

appropriate. Furthermore, the pivotal trial was conducted with the product, therefore this evidence carries greater weight than non-pivotal supporting evidence e.g. studies on individual active ingredients. The reference to *Pygeum africana* in the third indication should be removed.

Furthermore, the pivotal trial does not support the efficacy of ProstateEze Max for relieving symptoms of weak stream, after-dribbling, and hesitation and interruption of flow associated with medically diagnosed BPH as none of these symptoms showed a statistically significant difference between groups at 3 months. The pivotal trial was conducted with the product, therefore evidence carries greater weight than non-pivotal supporting evidence e.g. for individual active ingredients such as Pygeum africana. Therefore, reference to these symptoms should be removed.

Efficacy of individual active ingredients based on secondary supporting evidence

The sponsor noted in Table 5 (Module 2.5.4, page 54) of their submission the evidence supporting each of the low-level indications. The evaluator has assessed the literature provided and a summary of the evaluation is provided in Table 7 below.

Table 7. Evaluation of supporting evidence provided to support low-level indications.

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Several internationally recognised monographs and reference texts are available that may be relevant to the secondary (low level) indications. Only sources that include scientific/clinical information are appropriate to support secondary scientific indications.

Secondary (low level) indications relating to general health and wellbeing can be supported by monographs however it should be noted that the monographs are sourced from Health Canada, Physicians Desk Reference and also Natural Medicines Professional Monograph, which are not recognised/recommended sources in the TGA Assessed Listed Medicines Evidence Guidelines. The evaluator sourced other monographs/reports from the EMA and WHO for some of the active ingredients. It is unclear why the sponsor did not provide EMA assessment reports as supporting evidence as these reports are internationally recognised and recommended in the Assessed Listed Medicines application guidelines.

The evaluator used the EMA assessment reports for each individual active ingredients to determine if a general conclusion can be made for the proposed low level indications (Table 8). Overall, these reports supports traditional use only (based on EMA definitions) for prostate related indications (including urinary frequency) and only nonclinical evidence was available for indications relating to reducing free radicals effect in the body. There were no assessment reports available for lycopene.

Table 8. Summary of EMA assessment reports on the support for individual active ingredients in ProstateEZE Max in relation to low-level indications*.

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s47 [redacted]

Only two of the active ingredients in the finished product were reported in the WHO Monographs on selected medicinal plants - *Serenoa repens* and *Cucurbita pepo*. The uses that were supported by clinical data for both ingredients were in symptomatic relief of BPH. For *Serenoa repens*, the dosage form reported was crude drug, lipidosterolic extracts (n-hexane, 90% ethanol or fluid [carbon dioxide] supercritical extracts standardized to contain 70–95% free fatty acids and corresponding ethyl esters), and preparations thereof. The daily dosage was 1–2 g crude drug or 320 mg (as a single dose or 160mg twice daily) of a lipidosterolic extract. This is different from the 660mg dry seed extract in the product. For *Cucurbita pepo*, the dosage form is crude drug and extracts with an oral daily dose of 10g of seed or its equivalent. This dosage form and amount is different from the product, which is 160mg of fixed oil.

s47 [redacted]

Comments on clinical safety observed in the pivotal trial

As this is an Assessed listed medicine application, only efficacy is pre-market assessed. The following comments relate to available safety information on the product.

s47 [redacted]

7. First round benefit-risk assessment

7.1. First round assessment of benefits

At this stage, there are uncertainties around the presentation of results for the pivotal study. The sponsor is requested to clarify these via a section 31 Request for Information notice. Until the issues are addressed, it is not possible to complete the assessment of benefit.

7.2. First round assessment of risks

As this is an Assessed listed medicine application, only efficacy and the label are pre-market assessed by the TGA. Detailed information relating to clinical safety has not been provided for assessment and consequently for consideration in the assessment of risk and benefit-risk balance. The evaluator has noted that there were no adverse events observed in the pivotal trial with the finished product, and only one non-serious adverse event has been reported to the TGA for the currently listed medicine.

At this stage, there are outstanding issues relating to the results of the pivotal study, and the sponsor is requested to clarify these matters via a section 31 Request for Information notice. Until the issues are clarified, it is not possible to complete the assessment of risks.

7.3. First round assessment of benefit-risk balance

Given the outstanding issues to be addressed by the sponsor, it is not possible to complete the assessment of benefit-risk balance.

8. First round recommendations

Given the outstanding issues to be addressed by the sponsor (information on pivotal trial), the evaluator is deferring making a recommendation on listing of the product.

9. First round comments on label/product information

Given the outstanding issues relating to pivotal trial, the draft label has not been assessed for compliance with TGO 92 or presentation at this stage.

10. Questions

10.1. Clinical questions (First round s31 RFI)

Pivotal trial conducted with ProstateEZE Max (Coulson et al., 2013)

The TGA has identified some issues during the evaluation of the pivotal trial conducted with ProstateEZE Max (Coulson et al., 2013). We note that the published paper states that the funding and study medication for the trial was provided by the clinical trial sponsor, therefore information from the trial might be available to you or it might be possible for you to obtain information from the study authors. Please provide the requested information if it is available to

you or you can obtain the information from the study authors if that is possible. If the information cannot be provided, please provide comment on the identified issues.

1. GCP

   The Assessed listed medicines evidence guidelines state in section 5.4.2 that all studies should be conducted according to Good Clinical Practice (GCP) principles and have appropriate ethical certification. GCP is about ensuring good assurance and record-keeping practices, which allow for accurate reporting, interpretation and verification. The paper advises that the trial was granted ethical approval by the Endeavour College of Natural Wellness Ethics Committee, however neither the published paper nor the information in Modules 2 and 5 indicates whether the trial was conducted to GCP.

   Please clarify if the trial was conducted to GCP, and if so, please provide the supporting evidence.

   Alternatively, **please comment** on how the trial maintained good assurance and record-keeping practices to allow for accurate reporting, interpretation and verification.

2. Plant part used for *Serenoa repens* extract (p 174)

   The study states that the investigational product, ProstateEZE Max contains *Serenoa repens* (equivalent to 660 mg of dry leaf per capsule). Module 2.5.4 states that the clinical study (Coulson et al., 2013) was performed on the actual finished product. The plant part used for the *S. repens* extract in the proposed product is listed as 'seed' in the application form (module 1.2.1b) and the draft label (Module 1.3.3b). The Assessed listed medicines evidence guidelines state in section 6.1 that there must be high level of concordance between the product formulation used in the clinical trial and that intended for listing. Specifically, in the case of biological substances like herbs/herbal extracts the species, sub-species, strain, **parts**, quantity of active component and preparation should be identical.

   Please clarify this discrepancy (*S. repens*, leaf vs seed) and **comment** on what impact this may have on the extrapolation of the outcomes of the clinical trial to the proposed product.

   Please also confirm whether the extract in the proposed product is from 'fruit' or 'seed'.

3. Participant demographics (p 174)

   Results were provided for participant demographics at baseline. It was stated that there were no significant differences between the active and placebo groups in age, weight, body mass index and PSA score. It was also stated that there were no significant correlations between symptom severity and these demographic parameters in the active and placebo groups. However, it is not clear what statistical tests were conducted to reach these conclusions, as the 'Statistics' section of the paper does not mention baseline analysis.

   Please clarify what statistical tests were used for these baseline analyses **and provide** the results (if available), so that the significance of the results can be ascertained.

4. Total prostate function results (p 174 & 175)

   On page 174 of the paper it is stated that "The total IPSS median (25th, 75th percentiles) scores were not significantly different at baseline between the active and placebo groups 3 (1, 4) and 3.5 (1.25, 4.75) respectively (Table 1)". These values appear to be incorrect,

as the results in Table 1 for the active and placebo groups are 19.5 and 18, respectively, not 3 and 3.5.

Please provide the correct values for the total IPPS median (25th, 75th percentiles) scores at baseline and the statistical result.

5. Individual BPH symptoms (p 174-175)

   With respect to individual BPH symptom scores (as measured by the IPSS), the paper states that "The results for the active group showed a significant percentage decrease in mean severity for all questions, except weak urinary stream after 1 month of treatment. There was a significant improvement in urinary stream by month 2 and all symptoms remained significant at month 3". The paper also states "Of interest was that observation that, the placebo group experienced significant reduction in night-time urinary frequency at month 1 but reverted to baseline levels by month 2 and 3". There were no statistical results (p-values) presented highlighting the significant decrease for all symptoms in the active group.

   Please provide the statistical results (p-values) for all the individual BPH symptom analyses, including those that were not statistically significant.

   Please clarify whether the stated correlations between less night-time urinary frequency and 'pushing and straining' and 'stopping and starting' were statistical correlations, and if so, **provide details** of the statistical tests.

6. Baseline symptom score for nocturia (p 175)

   In Table 1 of the paper, the baseline symptom score for nocturia for the active treatment group is missing in the first column of results (printing error?); the 1-month, 2-month and 3-month results are provided.

   Please provide the baseline value so that the baseline severity of nocturia for the active treatment group can be ascertained.

7. Baseline day-time urinary frequency (p 176)

   The paper states that the average day-time urinary frequencies at baseline were similar for active and placebo groups, however p-values were not provided to support this statement. In Figure 1A the day-time urinary frequencies at time 0 do not appear similar.

   Please comment on the apparent difference in the baseline day-time urinary frequencies between groups in Figure 1A.

   Please provide the between group statistical results (p-values) for baseline day-time urinary frequency if tested, so that similarity at baseline can be ascertained.

8. Baseline night-time urinary frequency (p 176)

   The average baseline night-time urinary frequencies for the active and placebo groups were provided, however it is unclear whether these were statistically analysed.

   Please provide the between group statistical results (p-values) for baseline night-time urinary frequency, if tested, so that similarity at baseline can be ascertained.

9. Missing urinary frequency statistical results for months 1 to 3 (p 176)

   No statistical results (p-values) have been provided for paired *t*-tests conducted for day-time urinary frequency in the placebo group for months 1, 2 and 3; for night-time urinary frequency in the placebo group for months 1, 2 and 3; and for the active group for night-time urinary frequency at 3 months.

Please provide the p-values from these paired *t*-tests, so that the statistical significance can be ascertained.

10. Day-time and night-time urinary frequencies ANOVA (p 172 & 176)

    Day-time and night-time urinary frequencies were also statistically analysed using a mixed design repeated-measures analysis of variance (ANOVA), which confirmed a statistically significant trend that active treatment significantly reduced frequencies over placebo. The F statistic and p-values were provided, however it was not clear which effects were included in the model and to which effect(s) these statistics relate to. For example, the model may have assessed group, time and time x group effects.

    Please confirm which effects were assessed and provide the results, so that the effects of treatment can be confirmed.

11. Clinical significance of reduction in nocturia (p 176)

    The published trial states "…the reduction in nocturia from 2.9 times to 1.8 times was also a clinically significant outcome".

    Please comment on this conclusion, as the criteria for determining clinical significance were not mentioned in the 'Materials and Methods' section therefore it is unclear on what basis clinical significance has been determined (e.g. whether it is based on documented clinical practice information/evidence), so that the clinical significance of this outcome can be ascertained.

10.2. Additional expert input required

No additional expert input required.

11. Second round evaluation

The sponsor responded to the comments and questions raised post the first round evaluation, which were sent by TGA as an s31 Request for information dated 28th October 2020 (D20-3629809). Refer to D20-3950275 for the sponsor's complete response.

Questions relating to efficacy (Module 2 and 5):

Pivotal trial conducted with ProstateEZE Max (Coulson et al., 2013)

The TGA has identified some issues during the evaluation of the pivotal trial conducted with ProstateEZE Max (Coulson et al., 2013). We note that the published paper states that the funding and study medication for the trial was provided by the clinical trial sponsor, therefore information from the trial might be available to you or it might be possible for you to obtain information from the study authors. Please provide the requested information if it is available to you or you can obtain the information from the study authors if that is possible. If the information cannot be provided, please provide comment on the identified issues.

1. GCP

   The Assessed listed medicines evidence guidelines state in section 5.4.2 that all studies should be conducted according to Good Clinical Practice (GCP) principles and have appropriate ethical certification. GCP is about ensuring good assurance and record-keeping practices, which allow for accurate reporting, interpretation and verification. The paper advises that the trial was granted ethical approval by the Endeavour College of Natural Wellness Ethics Committee, however neither the published paper nor the information in Modules 2 and 5 indicates whether the trial was conducted to GCP.

Please clarify if the trial was conducted to GCP, and if so, please provide the supporting evidence.

Alternatively, **please comment** on how the trial maintained good assurance and record-keeping practices to allow for accurate reporting, interpretation and verification.

s47

Evaluator's response:

The sponsor has provided a statement that the trial was conducted to GCP and provided statements on the record-keeping and trial conduct.

The evaluator notes that the sponsor did not provide supporting evidence. A clinical study report for the pivotal trial or GCP certificate could be used as evidence to support the statements made by the sponsor. The sponsor will need to provide the supporting evidence if possible, e.g. certificate of GCP training.

2. Plant part used for *Serenoa repens* extract (p 174)

   The study states that the investigational product, ProstateEZE Max contains *Serenoa repens* (equivalent to 660 mg of dry leaf per capsule). Module 2.5.4 states that the clinical study (Coulson et al., 2013) was performed on the actual finished product. The plant part used for the *S. repens* extract in the proposed product is listed as 'seed' in the application form (module 1.2.1b) and the draft label (Module 1.3.3b). The Assessed listed medicines evidence guidelines state in section 6.1 that there must be high level of concordance between the product formulation used in the clinical trial and that intended for listing. Specifically, in the case of biological substances like herbs/herbal extracts the species, sub-species, strain, **parts**, quantity of active component and preparation should be identical.

   Please clarify this discrepancy (*S. repens*, leaf vs seed) and **comment** on what impact this may have on the extrapolation of the outcomes of the clinical trial to the proposed product.

   Please also confirm whether the extract in the proposed product is from 'fruit' or 'seed'.

Sponsor's response:

s47 [redacted]

Evaluator's response:

The Attachment A provided by the sponsor was for the cancelled product AUST L 148287, which could be the product used in the trial given that it was listed until 16/05/2011 and the trial was conducted in 2010 (registered 19/2/2010) and noted to be completed on 5/8/2011 based on the clinical trial entry in the ANZCTR register.

The part of *Serenoa repens* noted in the AUST L 148287 product is seed at the same concentration of 44 mg as the currently listed product and this was also confirmed through checking the formulation details in eBS.

It should be noted that there were minor differences in the type of excipients between the two products, namely AUST L 148287 was missing colloidal anhydrous silica, patent blue V and purified water, and had two additional colouring agents.

Some excipients were present in the same amount in both products (e.g. ascorbic acid, alpha-tocopherol, lecithin, maize oil, maltodextrin) while there were minor differences in the quantities of other excipients present in AUST L 148287.

The evaluator is satisfied that the *Serenoa repens* extract used is the seed in both the clinical trials and also in the proposed product and that the variations in excipients are minor.

3. Participant demographics (p 174)

   Results were provided for participant demographics at baseline. It was stated that there were no significant differences between the active and placebo groups in age, weight, body mass index and PSA score. It was also stated that there were no significant correlations between symptom severity and these demographic parameters in the active and placebo groups. However, it is not clear what statistical tests were conducted to reach these conclusions, as the 'Statistics' section of the paper does not mention baseline analysis.

   Please clarify what statistical tests were used for these baseline analyses **and provide** the results (if available), so that the significance of the results can be ascertained.

Sponsor's response:

s47 [redacted]

s47 [redacted]

Evaluator's response:

The evaluator is satisfied that the results show that no statistically significant difference as the statistical significance cut-off is $p<0.05$.

4. Total prostate function results (p 174 & 175)

   On page 174 of the paper it is stated that "The total IPSS median (25th, 75th percentiles) scores were not significantly different at baseline between the active and placebo groups 3 (1,4) and 3.5 (1.25, 4.75) respectively (Table 1)". These values appear to be incorrect, as the results in Table 1 for the active and placebo groups are 19.5 and 18, respectively, not 3 and 3.5.

   Please provide the correct values for the total IPPS median (25th, 75th percentiles) scores at baseline and the statistical result.

Sponsor's response:

s47 [redacted]

Evaluator's response:

The evaluator is not convinced that the text was in error as the title of the section was "Total prostate function", which is indicated by the total IPSS score. Question 1 of the IPSS refers to one of the individual BPH symptoms that was addressed in the following section in the text.

The sponsor noted that the total score of 19.5 and 18 is correct and provided the 25th and 75th percentiles of the total IPPS median scores at baseline.

The evaluator notes that there is some misreporting but as the sponsor has provided the requested statistical results, the evaluator can refer to these for their interpretation.

5. Individual BPH symptoms (p 174-175)

   With respect to individual BPH symptom scores (as measured by the IPSS), the paper states that "The results for the active group showed a significant percentage decrease in mean severity for all questions, except weak urinary stream after 1 month of treatment. There was a significant improvement in urinary stream by month 2 and all symptoms remained significant at month 3". The paper also states "Of interest was that observation that, the placebo group experienced significant reduction in night-time urinary frequency

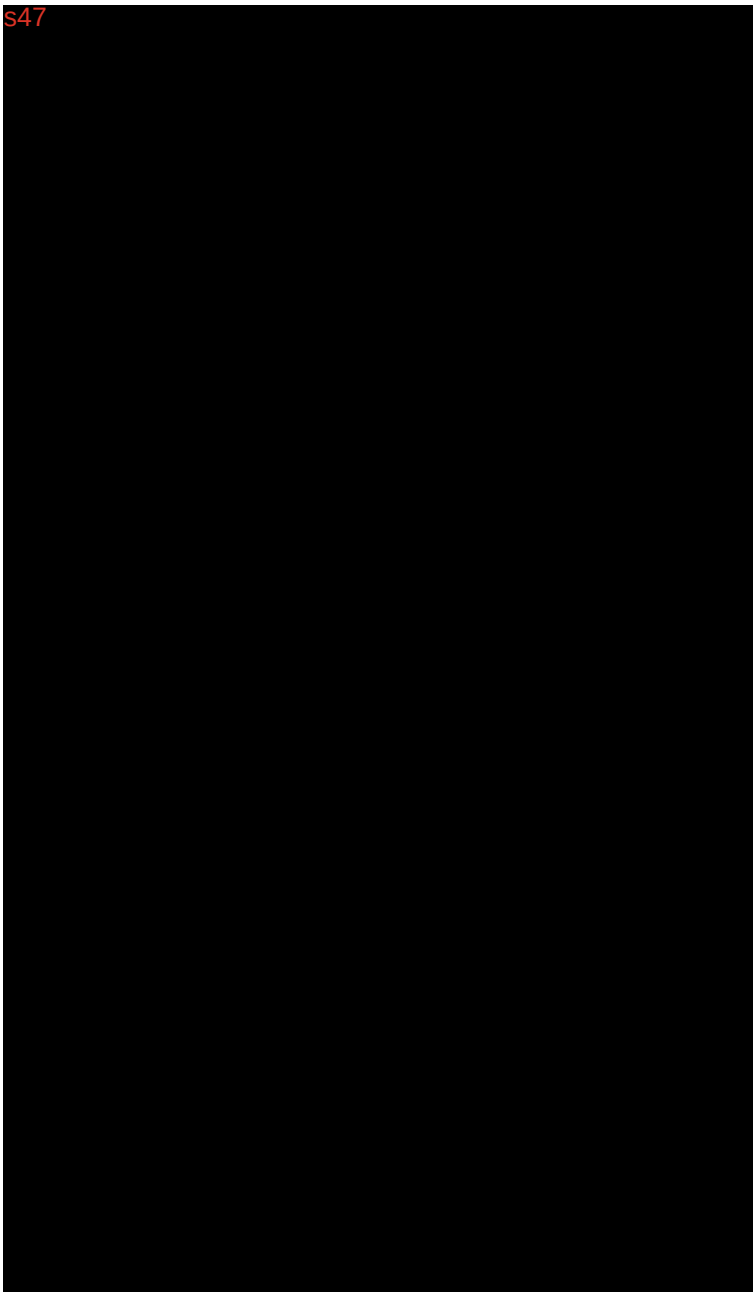
at month 1 but reverted to baseline levels by month 2 and 3". There were no statistical results (p-values) presented highlighting the significant decrease for all symptoms in the active group.

Please provide the statistical results (p-values) for all the individual BPH symptom analyses, including those that were not statistically significant.

Please clarify whether the stated correlations between less night-time urinary frequency and 'pushing and straining' and 'stopping and starting' were statistical correlations, and if so, **provide details** of the statistical tests.

Sponsor's response:

s47



Evaluator's response:

The evaluator notes that the statistical results presented would be for the active treatment group and hence supports the main text.

The sponsor did not address the second part of the request, which required the sponsor to provide a response to clarify the statement "The most positive improvements were observed in the questions relating to pushing and straining and stopping and starting that were correlated with less night-time urinary frequency." The evaluator surmised that this was perhaps due to the reduction from baseline to month 3 seen in:

a. Question 6 (pushing and straining), which showed a drop from 2 to 1
b. Question 3 (stopping and starting), which showed a reduction from 2 to 1
c. Question 7 (nocturia), which showed a reduction from 3 to 2

However, if this was based on the scores then Question 1 (incomplete emptying) would show the biggest difference from 3 to 1.5 and Question 2 (urinary frequency) showed a similar change from 4 to 3.

It is unclear how the statement came about.

6. Baseline symptom score for nocturia (p 175)

   In Table 1 of the paper, the baseline symptom score for nocturia for the active treatment group is missing in the first column of results (printing error?); the 1-month, 2-month and 3-month results are provided.

   Please provide the baseline value so that the baseline severity of nocturia for the active treatment group can be ascertained.

Sponsor's response:

The sponsor noted that the baseline symptom score for IPSS in table 1 appears to be a printing error and that the value is "3".

Evaluator's response:

The evaluator accepts the response.

7. Baseline day-time urinary frequency (p 176)

   The paper states that the average day-time urinary frequencies at baseline were similar for active and placebo groups, however p-values were not provided to support this statement. In Figure 1A the day-time urinary frequencies at time 0 do not appear similar.

   Please comment on the apparent difference in the baseline day-time urinary frequencies between groups in Figure 1A.

   Please provide the between group statistical results (p-values) for baseline day-time urinary frequency if tested, so that similarity at baseline can be ascertained.

Sponsor's response:

The sponsor noted that the daytime urinary frequencies at baseline appear to show a difference as the axis is only from 5.8 to 7. The p-value for difference between groups at baseline is as per question 3 and calculated using a 2-tail t-test s47 [redacted]

Evaluator's response:

The evaluator notes that the axis does not start from zero. Based on the reported values in the table under Figure 1, the mean baseline for placebo was 6.2 while for the active treatment it was

7.1. This is a difference of 0.9 times, which the sponsor noted as not statistically different based on the p-value.

The evaluator accepts the response.

8. Baseline night-time urinary frequency (p 176)

   The average baseline night-time urinary frequencies for the active and placebo groups were provided, however it is unclear whether these were statistically analysed.

   Please provide the between group statistical results (p-values) for baseline night-time urinary frequency, if tested, so that similarity at baseline can be ascertained.

Sponsor's response:

s47 [redacted]

Evaluator's response:

The evaluator accepts the response.

9. Missing urinary frequency statistical results for months 1 to 3 (p 176)

   No statistical results (p-values) have been provided for paired *t*-tests conducted for day-time urinary frequency in the placebo group for months 1, 2 and 3; for night-time urinary frequency in the placebo group for months 1, 2 and 3; and for the active group for night-time urinary frequency at 3 months.

   Please provide the p-values from these paired *t*-tests, so that the statistical significance can be ascertained.

Sponsor's response:

s47 [redacted]

Evaluator's response:

The evaluator notes the p-values provided and that only baseline compared with 1 month for night-time urinary frequency is significantly different in the placebo group.

The evaluator notes that the night-time frequency for the active treatment p-value is highly statistically different with $p<0.0001$.

10. Day-time and night-time urinary frequencies ANOVA (p 172 & 176)

    Day-time and night-time urinary frequencies were also statistically analysed using a mixed design repeated-measures analysis of variance (ANOVA), which confirmed a statistically significant trend that active treatment significantly reduced frequencies over placebo. The F statistic and p-values were provided, however it was not clear which effects were included in the model and to which effect(s) these statistics relate to. For example, the model may have assessed group, time and time x group effects.

    Please confirm which effects were assessed and provide the results, so that the effects of treatment can be confirmed.

Sponsor's response:

s47 [redacted] the ANOVA assessed a time, treatment and time vs treatment effect.

Evaluator's response:

The data provided by the sponsor in Appendix 1 details the ANOVA results of the IPSS score, Day-time and Night-time urinary frequency output. The results compared the test group with the placebo group over the 4 time points measured (Baseline, Month 1, Month 2 and Month 3). To test the sphericity of the results, a Mauchly's Test of Sphericity was used. The Tests of Within-Subjects Effects was provided for time and time by treatment. The p-value for the Mauchly's test was highlighted and the results for time by treatment with sphericity assumed was highlighted.

The evaluator notes that the highlighted data is not the data that should be used to show that the active treatment significantly reduced the factors examined.

Firstly, the Mauchly's test is significant for all 3 factors measured, which indicates that the variances of the differences are not equal (i.e. sphericity has been violated). This means that the data has not met one of the assumptions for the mixed measure ANOVA. Violations of sphericity could be corrected by using either the Greenhouse-Geisser or Huynh-Feldt corrections depending on the Epsilon value of Greenhouse-Geisser.

For the IPSS, as Epsilon is > .75 the Huynh-Feldt correction should be used. As the results for this treatment were significant across the different correction methods, the p-value for the time by treatment effect is the same ($P<0.000$[1]).

For the Day-time urinary frequency, as Epsilon is < .75 the Greenhouse-Geisser correction should be used. This gives a p-value of 0.049[2] for the time by treatment effect, which is considered statistically significant as the significance cut-off is $P<0.05$.

For the Night-time urinary frequency, as Epsilon is < .75 the Greenhouse-Geisser correction should be used. This gives a p-value of 0.009[3] for the time by treatment effect, which is considered statistically significant as the significance cut-off is $P<0.05$.

[1] Value provided by the sponsor in Appendix 1.
[2] Value provided by the sponsor in Appendix 1.
[3] Value provided by the sponsor in Appendix 1.

Although some of the P values have changed using the Greenhouse-Geisser corrections, the results are still statistically significant, therefore there is no material effect on the conclusions.

However, the results were all for the Tests of Within-subjects effects. As the sponsor is making a conclusion comparing the active treatment and placebo group, a test of between-subjects effects should be conducted to support the conclusion that the active treatment significantly reduced urinary frequency over placebo during day-time and night-time.

The sponsor needs to provide the results of the Tests of Between-subjects effects.

11. Clinical significance of reduction in nocturia (p 176)

    The published trial states "…the reduction in nocturia from 2.9 times to 1.8 times was also a clinically significant outcome".

    Please comment on this conclusion, as the criteria for determining clinical significance were not mentioned in the 'Materials and Methods' section therefore it is unclear on what basis clinical significance has been determined (e.g. whether it is based on documented clinical practice information/evidence), so that the clinical significance of this outcome can be ascertained.

Sponsor's response:

s47 [redacted]

Evaluator's response:

The evaluator notes that the sponsor is basing the clinical significance on the American Urological Association Guidelines with the urinary frequency of more than 2 times per night as being abnormal.

The evaluator accepts the sponsor's response.

Summary of second round evaluation

Upon examining the additional information provided by the sponsor in response to the s31 Request for information, there are still some uncertainties regarding the data quality and integrity.

As the pivotal trial provided (Coulson et al., 2013) is the only clinical trial performed on the finished product, the quality and robustness of the results of this trial are critical. The sponsor has provided most of the results requested as part of the section 31 RFI, however, there is still missing information that would be required to validate the results provided.

One of the key conclusions made was that "a repeated measures analysis with a mixed design ANOVA confirmed the statistically significant trend that the active treatment significantly reduced urinary frequency over placebo during the day-time ($F = 3.052$, $p < 0.03$) and night-time ($F = 4.601$, $p < 0.004$)" (p176 of Coulson et al., 2013). Based on the Appendix 1 data provided, the results reported were for Tests of Within-subjects effects, which is a time or time by treatment effect and not a treatment effect. In order to make a conclusion comparing the active treatment and placebo groups, a test of between-subjects effects should be conducted to support the conclusion that the active treatment significantly reduced urinary frequency over placebo during

day-time and night-time. The sponsor needs to provide the results of the Tests of Between-subjects effects to substantiate this conclusion.

If the ANOVA test of between-subjects effects is statistically significant, a post-hoc test such as a paired t-test could be conducted at each time point to determine at which time point(s) the difference in urinary frequency was significantly different. The sponsor should provide this data, if available.

From Table 1 of the Coulson study, it is noted that Wilcoxon signed ranks test was used to perform a statistical analysis to show significance between groups at 3 months. However, the Wilcoxon signed ranks test is only used for dependent samples i.e. within subjects and so it is not the appropriate test to use in this situation. The evaluator notes that there is the Wilcoxon rank sum test which can be used for independent samples. The sponsor should clarify the statistical test used to determine the statistical significance between groups at 3 months.

The sponsor has provided a statement that the trial was conducted to GCP guidelines and commented on how the trial was conducted. It would have been preferable to see evidence of GCP either in the form of a clinical audit report, the clinical study report, or GCP training certificate. The sponsor should provide the supporting evidence if possible.

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

After consideration of the responses to questions, the benefits of ProstateEZE Max for the proposed indications are outlined below:

Intermediate indications – 1. May assist in the management of symptoms of medically diagnosed benign prostatic hypertrophy. 2. For the symptomatic relief of medically diagnosed benign prostatic hypertrophy.	
Benefits	***Strengths and Uncertainties***
Coulson et al., 2013 Statistically significant difference in total IPSS median score in active group at 3 months compared to placebo ($p<0.05$). The individual IPSS symptom severity score for Nocturia (Q7) was significantly different in active group compared to placebo ($p<0.05$). The active treatment significantly reduced urinary frequency over placebo during day-time and night-time (values to be confirmed).	**Strengths** Pivotal study conducted with the proposed formulation at the recommended dose. Pivotal study was performed in Australia, thus it is relevant to the Australian population. Study was done in the target population Validated questionnaires to identify the baseline BPH symptoms and to measure the study outcomes. Randomised, double-blinded, placebo-controlled study. There was a high adherence rate (95%) with use of the study medications reported.

	3 month study (as per EMA guidelines for urinary incontinence) Response was clinically significant based on a reduction in nocturia to below 2 times per night at 3 months. **Weaknesses and uncertainties** Inclusion/exclusion criteria - No upper limit of baseline IPSS scores Unclear if the statistics used were correct in reporting IPSS median scores (Wilcoxon signed ranks test reportedly used for between groups instead of Wilcoxon rank sum test) No significant differences for other individual IPSS symptoms apart from nocturia. No treatment effect ANOVA results (between subjects test) provided. No urodynamic studies, only measurement of symptoms (EMA GL: symptoms are secondary endpoint measures) No dose-response studies (EMA GL: several doses would be preferable) No effect size or responder analysis to assess clinical relevance

Intermediate indications –	
3. Pygeum Africana may provide support for the symptomatic relief [of] nocturia, nocturnal frequency, weak stream, after-dribbling, hesitation and interruption of flow when such symptoms are associated with medically diagnosed benign prostatic hypertrophy.	
Benefits	***Strengths and Uncertainties***
Wilt et al., 2011 The overall standardized effect size and the summary improvement in global symptoms, nocturia, peak urine flow and residual urine volume suggests that *Pygeum africanum* is effective in men with symptomatic benign prostatic hyperplasia. This benefit is of modest size and appears to be clinically significant.	**Strengths** Meta-analysis was performed with rigor. Moderate to large effect size improvements for nocturia and peak urine flow. Reputable source (Cochrane review). **Weaknesses and uncertainties** No study examined in this review was done with the proposed formulation at the recommended dose. Only examined Pygeum effects on BPH. Small number of pooled studies. Placebo-controlled studies did not use standardized, validated symptom scales for

Intermediate indications –	
3. Pygeum Africana may provide support for the symptomatic relief [of] nocturia, nocturnal frequency, weak stream, after-dribbling, hesitation and interruption of flow when such symptoms are associated with medically diagnosed benign prostatic hypertrophy.	
Benefits	***Strengths and Uncertainties***
	the outcome measures of greatest clinical significance. Short treatment duration (30-122 days) in trials. No study was conducted in Australia.

s47 [redacted]	
Benefits	***Strengths and Uncertainties***
Improvement of BPH symptoms supported by: 1. Pivotal trial (Coulson et al., 2013) 2. Textbook and monographs for Pygeum, Cucurbita and Lycopene. 3. EMA assessment reports for: • Pygeum • Serenoa (only hexane extract for well-established use)Epilobium • Cucurbita	**Strengths** Pivotal study showed that PSA levels remain in healthy range before and after treatment. **Weaknesses and uncertainties** Secondary references provided referred to the same studies as pivotal study and meta-analysis (Wilt 2011) for support. Recommended dose ranges from the references are higher. The EMA reports did not examine prostate health specifically (e.g. PSA levels), and the evidence was for different extracts and/or for traditional use only. Although pivotal study showed that PSA levels were in healthy range before and after treatment, there was no significant improvement. Also, no other tests e.g. imaging or palpation were conducted to investigate prostate health. No evidence provided to support health of prostate for the functions it performs i.e. secreting enzymes, lipids, amines and metal ions essential for the normal function of spermatozoa, and metabolising testosterone, only for urinary symptoms of BPH.
Secondary permitted indications –	
• Relieves urinary frequency.	

Benefits	*Strengths and Uncertainties*
Supported by the pivotal study (Coulson, 2013) for urinary frequency. Supported by the EMA assessment reports for: • Pygeum • Serenoa (only hexane extract for well-established use) • Epilobium • Cucurbita	**Strengths** Same as for Intermediate Indications 1 and 2. **Weaknesses and uncertainties** Same as for Intermediate Indications 1 and 2. The EMA evidence was for different extracts and/or for traditional use only.
s47 [redacted]	
Benefits	*Strengths and Uncertainties*
Epilobium is suggested to have antioxidant effects contributing to beneficial effects in BPH (*in vitro* study, Hevesi, 2009). Antioxidant effects was reported in the EMA assessment reports for: • Pygeum (nonclinical - *in vitro* PD study) • Epilobium (*in vitro* PD studies only) • Cucurbita (nonclinical - *in vitro* and *in vivo* studies) Health Canada Lycopene monograph (Ref 22) permits the statement 'Provides antioxidants for the maintenance of good health' for lycopene [all-trans)-Lycopene (USP) and psi,psi-Carotene (USP) from Solanum lycopersicum (fruit flesh) or synthetic] when given orally at a dose not to exceed 30 mg/day. Ref #23 (Story et al.) notes that lycopene can be a potent antioxidant molecule, effective at scavenging the ROS singlet oxygen.	**Strengths** Reputable sources (EMA). Dose of lycopene is consistent with Health Canada Lycopene monograph. **Weaknesses and uncertainties** Not examined using the finished product in the pivotal study. No clinical data. All are based on either nonclinical *in vitro* PD studies or *in vivo* studies. Different extracts and/or in vitro data only examined in EMA monographs for Pygeum, Epilobium and Cucurbita compared to those in the proposed product. Proposed antioxidant indication is not consistent with Health Canada Lycopene monograph indication. Ref #23 (Story et al.) does not provide a dose – relevance to proposed product is not known.

12.2. Second round assessment of risks

After consideration of the responses to questions, the risks of ProstateEZE Max for the proposed use are outlined below:

Intermediate indications –
1. May assist in the management of symptoms of medically diagnosed benign prostatic hypertrophy. 2. For the symptomatic relief of medically diagnosed benign prostatic hypertrophy.

Risks	***Strengths and Uncertainties***
Coulson et al., 2013 Lack of efficacy – especially inefficacy for symptoms other than urinary frequency. Potential adverse effects, including allergic reactions.	**Strengths** No reported adverse effects in the pivotal study. Has been on the market since 2014 with only one recorded adverse event (rash) in Australia. Warning statements provided on the product label: • Keep out of reach of children. • Use only as directed. • If symptoms persist see your Healthcare Professional. • Contains Soya Oil and sulfites. • Phenylketonurics - this product contains phenylalanine. The condition (BPH) requires regular monitoring by a medical practitioner once diagnosed, which provides opportunity for the patient to discuss use and experience of the product. **Uncertainties** No safety data beyond 3 months Potential interactions with food and drug with a combination herbal product that has not been investigated.

Intermediate indications –
3. Pygeum Africana may provide support for the symptomatic relief [of] nocturia, nocturnal frequency, weak stream, after-dribbling, hesitation and interruption of flow when such symptoms are associated with medically diagnosed benign prostatic hypertrophy.

Risks	***Strengths and Uncertainties***
Wilt et al., 2011 Lack of efficacy Potential adverse effects	**Strengths** Mild adverse events (mainly GI), comparable to placebo. Warning statements provided on the product label: • Keep out of reach of children. • Use only as directed.

	• If symptoms persist see your Healthcare Professional. • Contains Soya Oil and sulfites. • Phenylketonurics - this product contains phenylalanine. The condition (BPH) requires regular monitoring by a medical practitioner once diagnosed, which provides opportunity for the patient to discuss use and experience of the product. **Weaknesses and uncertainties** Only effects of Pygeum examined, not the final product. Proposed indication refers to therapeutic use of an active ingredient, not the product. No long-term use data (treatment duration only 30 to 122 days).
s47 [redacted]	
Risks	***Strengths and Uncertainties***
Lack of efficacy – especially inefficacy for indications other than urinary frequency. Potential adverse effects.	**Strengths** Warning statements • Keep out of reach of children • Use only as directed. • If symptoms persist see your Healthcare Professional. • Contains Soya Oil and sulfites. • Phenylketonurics - this product contains phenylalanine. **Weaknesses and uncertainties** Insufficient evidence provided to support efficacy for prostate health/function and free radicals indications, which could mislead consumers with respect to the expected health benefits of the product. No safety data beyond 3 months. Potential interactions with food and drug with a combination herbal product that has not been investigated.

12.3. Second round assessment of benefit-risk balance

Intermediate indications

On face value, there were benefits shown in the pivotal trial on the proposed product, which showed an improvement in symptoms related to BPH based on the total IPSS score. Not all symptoms showed an improvement, the main symptom with a clear difference was nocturia, which was statistically significant as an individual question in the IPSS questionnaire and also in the daily record of urinary frequency. The day-time urinary frequency was also reported as showing a significant difference between treatment groups according to the ANOVA analysis.

The overall quality of reporting in this study was mediocre, as there were missing values, inconsistencies and uncertainty regarding reporting of some of the statistical tests and results. The sponsor has provided the required response to the first section 31, however there are still a few uncertainties with the statistics provided. Firstly, the ANOVA analysis provided to show the difference between active and placebo group in urinary frequency was a within-subjects test (i.e. time and time x group effects), when it should have been a between-subjects test. Furthermore, if the between-subjects test was statistically significant, the statistical results for a post-hoc analysis showing a difference between these treatment groups at each time point, if available, were not provided. In addition, the Wilcoxon signed ranks test was reportedly used to show a significance between groups at 3 months for the IPSS total score and subscores, but this test is only for use in dependent samples i.e. within subjects. The between-subjects statistical test that should have been used is the Wilcoxon rank sum test. The sponsor will need to clarify these points prior to the evaluator being able to making a conclusive statement on the symptoms that showed improvement with treatment.

The sponsor also proposed an intermediate indication that is specific to Pygeum. As the indications relate to the purpose or health benefit of the finished product (i.e. therapeutic use of the medicine), the wording of an indication referring to efficacy of an active ingredient (*Pygeum africana*) is not appropriate. Furthermore, the pivotal trial was conducted with the product, therefore this evidence carries greater weight than non-pivotal supporting evidence e.g. studies on individual active ingredients. The reference to *Pygeum africana* in the third indication should be removed. This leaves an indication referring to relief of nocturia, nocturnal frequency, weak stream, after-dribbling, hesitation and interruption of flow associated with medically diagnosed BPH. Of these symptoms, only nocturia showed a statistically significant difference in the IPSS subscores in the pivotal trial.

The main risk associated with this product is lack of efficacy. Given that this is a medically diagnosed condition, the consumer will need to have regular checks with a medical practitioner to ensure that the condition has not progressed. This provides a safeguard should the product be ineffective in an individual, and provides an opportunity for the patient to discuss their use and experience of the product with their doctor. A warning statement such as “If symptoms persist see your Healthcare Professional” could manage the risks associated with inefficacy however the term “Healthcare Professional” needs to be replaced with “Medical Practitioner”, as this condition requires the management of a medical practitioner (doctor) rather other healthcare professionals such as pharmacists or naturopaths.

Overall, the benefit-risk balance of ProstateEze Max for the relief of nocturia associated with medically diagnosed benign prostatic hypertrophy is potentially favourable, pending further clarifying information from sponsor.

Secondary (low level) indications

s47 [redacted]

s47 [redacted]

The secondary indications relating to prostate health are non-specific indications making general health maintenance or improvement claims, in which the defined health benefit is related to normal physiological effects of substances in growth, development and normal functions of the body.

The prostate performs a number of functions including secreting enzymes, lipids, amines and metal ions essential for the normal function of spermatozoa, and metabolising testosterone. Prostate health can be ascertained by several means including, but not limited to, determining size via imaging, digital rectal examination (size and regularity) and PSA test. While the pivotal trial with the product measured PSA test results, there were no other tests e.g. imaging or palpation conducted to investigate prostate health. The PSA test results were reported to be within normal levels at baseline, which did not improve upon treatment with the product. Furthermore, the subjects were suffering from BPH thus the PSA results do not support the enhancement/promotion or maintenance/support of prostate health.

In Table 4 (Module 2), Ref #10 (Braun & Cohen, textbook) is provided as evidence of phytosterols inhibiting the production of prostaglandins in the prostate, which suppresses the inflammatory symptoms of BPH. However, the primary (cited) reference was not provided and the dose for this effect was not reported in the textbook, therefore its relevance to ProstateEze Max is unknown.

Ref #22 (Health Canada monograph for lycopene) permits the statement 'Helps to support prostate health' for lycopene [all-trans)-Lycopene (USP) and psi,psi-Carotene (USP) from Solanum lycopersicum (fruit flesh) or synthetic] when given orally at a dose of 6.5-30 mg/day. ProstateEze Max provides 2.1 mg/day of lycopene, which is below this range. Therefore, this evidence does not support the proposed indications.

The remaining evidence provided in Table 4 (Module 2) to support these indications relates to the improvement in urinary symptoms of BPH. Evidence of improvement in urinary symptoms of BPH alone is insufficient to support the broader indication relating to prostate function or health.

The above secondary indications for prostate health and function are not supported by the evidence, therefore the benefit-risk assessment for these indications is not favourable.

s47 [redacted]

The secondary indication relating to urinary frequency is supported by the day-time and night-time urinary frequency results in the pivotal study and also the Health Canada Monograph for Pygeum. The pivotal trial carries greater weight than the secondary supporting evidence, therefore the acceptability of this indication is dependent on satisfactory resolution of the issues relating to the urinary frequency results in the pivotal trial.

s47 [redacted]

The evidence provided is insufficient, for the following reasons, to show that either the finished product or any of the ingredients administered at the proposed dose rate reduce free radicals formed in the body or reduce/decrease free radical damage to body cells.

Ref #1 (pivotal trial with ProstateEze Max) did not investigate free radical formation in the body or damage to body cells, therefore no evidence is available from this study to support these indications for the finished product.

Ref #22 (Health Canada monograph for lycopene) permits the statement 'Provides antioxidants for the maintenance of good health' for lycopene [all-trans)-Lycopene (USP) and psi,psi-

Carotene (USP) from Solanum lycopersicum (fruit flesh) or synthetic] when given orally at a dose not to exceed 30 mg/day. ProstateEze Max provides 2.1 mg/day of lycopene, which is within this range. However, the statement permitted by the Health Canada monograph 'Provides antioxidants for the maintenance of good health' is not the same as the proposed indications, therefore it does not support the proposed indications.

Ref #23 (Story et al.) notes that lycopene can be a potent antioxidant molecule, effective at scavenging the ROS singlet oxygen. However, a dose is not provided, therefore its relevance to these indications for this product is unknown.

Ref #9 (Natural medicines monograph – lycopene) reports under 'Antineoplastic effects' that lycopene has antioxidant effects and might reduce cancer risk by scavenging free radicals and quenching singlet oxygen, which prevents oxidative damage to DNA. A dose is not reported, although Table 4 (Module 2) states that 6 mg/day has been used. ProstateEze Max provides 2.1 mg/day, which is below the reported amount. Furthermore, the presented effect in the monograph is in relation to cancer, which is not relevant or appropriate for this product.

Ref #8 (Hevesi et al.) describes an in vitro study investigating the anti-oxidant and anti-inflammatory effects of Epilobium parviflorum. The aqueous acetone extract of E. parviflorum showed higher antioxidant effect in the DPPH assay than well-known antioxidants; inhibited the lipid peroxidation determined by the TBA assay; and possessed a protective effect against oxidative damage, generated in fibroblast cells. In the COX inhibition assay, E. parviflorum decreased the PGE2 release, so showing inhibition of the COX-enzyme. Although this study provides some support for anti-inflammatory and antioxidant effects of E. parviflorum, and reduction in free radical damage to the cells used in the assays, the dose required to be administered orally to produce these effects in people in vivo is not reported. Therefore, the relevance of these results to these indications for this product are unknown. Furthermore, the study used an aqueous acetone extract, while the eBS details for this product indicate an aqueous extract.

As these secondary indications for free radical formation or damage are not supported by the evidence, the benefit-risk assessment for these indications is not favourable.

13. Second round recommendations

The evaluator has assessed the responses provided for the s31 RFI1 questions. The proposed recommendations are as follows:

<u>Intermediate indications</u>

The following two intermediate indications are similar

- May assist in the management of symptoms of medically diagnosed benign prostatic hypertrophy.
- For the symptomatic relief of medically diagnosed benign prostatic hypertrophy.

and could be merged into one indication, which should be modified to refer to relief of urinary frequency i.e.

- For the relief of urinary frequency associated with medically diagnosed benign prostatic hypertrophy

The acceptability of this modified indication is dependent on satisfactory resolution of issues relating to the urinary frequency results in the pivotal trial and changes to the label warnings

The following proposed intermediate indication is not supported:

- Pygeum Africana may provide support for the symptomatic relief [of] nocturia, nocturnal frequency, weak stream, after-dribbling, hesitation and interruption of flow when such symptoms are associated with medically diagnosed benign prostatic hypertrophy.

Low level permitted indications

The acceptability of the following proposed permitted indication is dependent on satisfactory resolution of issues relating to the urinary frequency results in the pivotal trial:

s47 [redacted]

The following proposed permitted indications are not supported:

s47 [redacted]

14. Second round comments on label/product information

The labels have been assessed in accordance with the new labelling requirements as per TGO 92 – Standard for labels of non-prescription medicines. Please see D21-2125566, for further information.

Relevant guidelines include:

Therapeutic Goods Order No. **92** – Standard for labels of non-prescription medicines

Medicines label: Guidance on TGO 92

TGA-assessed claim for assessed listed and registered complementary medicines

Labelling requirements

The label for the product has been assessed and there are moderate deficiencies that need to be addressed:

s47 [redacted]

Please advise of your preferred name for the product.
Please provide an amended label with the name presented consistently.

2. The quantity or proportion of active ingredients needs to be expressed as outlined in TGO 92 guidance. Example:

Prunus africana (Pygeum) dry stem bark extract.....15g

Standardised to contain sitosterol and sitosterol glycosides calculated as sitosterol 9.75 mg

Sereno repens (Saw palmetto) dry seed extract.....660mg

Standardised to contain Fatty Acids 39.6 mg

Epilobium parviflorum dry herb extract.....500mg

Cucurbita pepo seed oil fixed.....160mg

Lycopene.....2.1mg

Please amend the label as required.

3. Indications – please amend the indications on the label to be consistent with the outcomes presented in Questions 5 to 9, above i.e.
   - The intermediate indication on the label should reflect the amended indication: 'For the relief of nocturia (night-time urinary frequency) associated with medically diagnosed benign prostatic hypertrophy'.
   - Remove the indication relating to *Pygeum africana*.

4. The label says 'Contains Soya Oil and sulfites'. The source of sulphites is unclear, as it is not listed as an individual ingredient.

   Please **clarify** the source of sulfites..

5. Benign prostatic hypertrophy is a medically diagnosed condition that requires ongoing monitoring from the medical practitioner. The proposed warning statement 'If symptoms persist see your Healthcare Professional' may not communicate this accurately.

   Please change the above warning statement to "If symptoms persist see your Medical Practitioner" or words to that effect e.g. '… see your doctor'.

6. As TGO 92 requires the active ingredients to be included on the main label, except where the medicine contains multiple active ingredients and is in a medium, small or very small container, the sole phrase 'CONTAINS 15,000MG PYGEUM' on the main label is capable of being misleading or confusing as to the content in the medicine, i.e. this phrase could mislead or confuse consumers to think that the only active ingredient in this product is Pygeum, when it is a combination of multiple active ingredients.

   Please remove the phrase "CONTAINS 15,000MG PYGEUM" from the main label. Please note that if space permits, you could include <u>all</u> the active constituents on the main label instead of the side panel.

7. The mock-up label provided with the application includes the current AUSTL number.

   Please provide an amended label with the AUSTL number replaced by 'AUST L(A) XXXX'.

8. The mock-up label provided with the application appears to be a bottle label, however the listed product appears to be supplied as a bottle in a carton (outer pack/primary pack).

   Please confirm the packaging for this product e.g. bottle, carton, enclosed leaflet. **Please provide** all components of the packaging that will be supplied with the product for label approval.

9. The mock-up of the label provided with the submission does not show the measurements/size of the label. When providing the amended labels for approval, **please confirm** that the mock-up label is the actual size at 100% magnification if measurements will not be included on the artwork mock-up.

15. Clinical Questions (Second RFI)

As there are still outstanding issues that need to be addressed by the sponsor, a second request for information was sent on 12th February 2021 (D21-2212766). The questions related to the literature search strategy, the pivotal trial and the label. The sponsor was also provided with an opportunity to comment on the interim outcome of assessment. Please refer to Section 14 above for the labelling questions, and to Section 16 below for the remaining questions.

16. Third round evaluation

The sponsor has responded to the comments and questions raised after the second round evaluation, which were sent by TGA as an s31 Request for information dated 12th February 2021 (D21-2212766). Refer to D21-2395526 and D21-2463293 for the sponsor's complete response.

Questions relating to efficacy (Module 2 and 5) and the label

Literature search strategy

1. The literature search strategy appears unclear and incomplete.

   Please comment on the literature search strategy and **please address** the identified inconsistencies.

Sponsor's response:

s47 [redacted]

Evaluator's response:

In the updated Module 1.5.1, the search strategy included searching the Cochrane database, which was not in the initial submission.

The exclusion criteria provided by the sponsor are:

- Not relevant to subject
- Animal studies, in vitro/in vivo (specifically wanted human clinicals) *(sic)*
- Irrelevant dosage forms
- Review articles were noted down as potentially supportive articles but not considered primary sources as per TGA Evidence guidelines
- Studies which looked at Cancer as this is a restricted representation

- Articles not in English

The search results in Table 5 are different between the initial submission and the one provided in this RFI response. The point of difference is in the number of references retrieved for specific search terms and also the references retrieved. Although the sponsor clarified the search strategy used and it appears that the publication date range chosen is the same, it is unclear why the search results are different. The evaluator notes from Table 5a that the search filter is different based on the ingredient, which may have contributed to the difference.

The evaluator is still uncertain about the reliability of the search strategy and results. However, this will not be pursued further, as the pivotal trial was conducted with the final product and carries greater weight than the results of the literature search, which provide secondary evidence for the individual active ingredients. Furthermore, the evaluator has also sourced the EMA monograph assessment reports for four of the five ingredients for additional comparison of secondary information.

Pivotal trial conducted with ProstateEZE Max (Coulson et al., 2013)

The TGA has identified some issues during the evaluation of the pivotal trial conducted with ProstateEZE Max (Coulson et al., 2013). We note that the published paper states that the funding and study medication for the trial was provided by the clinical trial sponsor, therefore information from the trial might be available to you or it might be possible for you to obtain information from the study authors. Please provide the requested information if it is available to you or you can obtain the information from the study authors. If the information cannot be provided, please provide comment on the identified issues.

2. Pivotal trial – IPPS scores (p 174-175)

   Please clarify which Wilcoxon statistical test was used to determine the statistical significance between groups at 3 months.

   Also, **please provide** the absolute p-values for the results that were statistically significant.

Sponsor's response:

s47

Evaluator's response:

The Wilcoxon test reportedly used in the paper was incorrect based on the sponsor's response though no clarification was given as to the possible error in reporting.

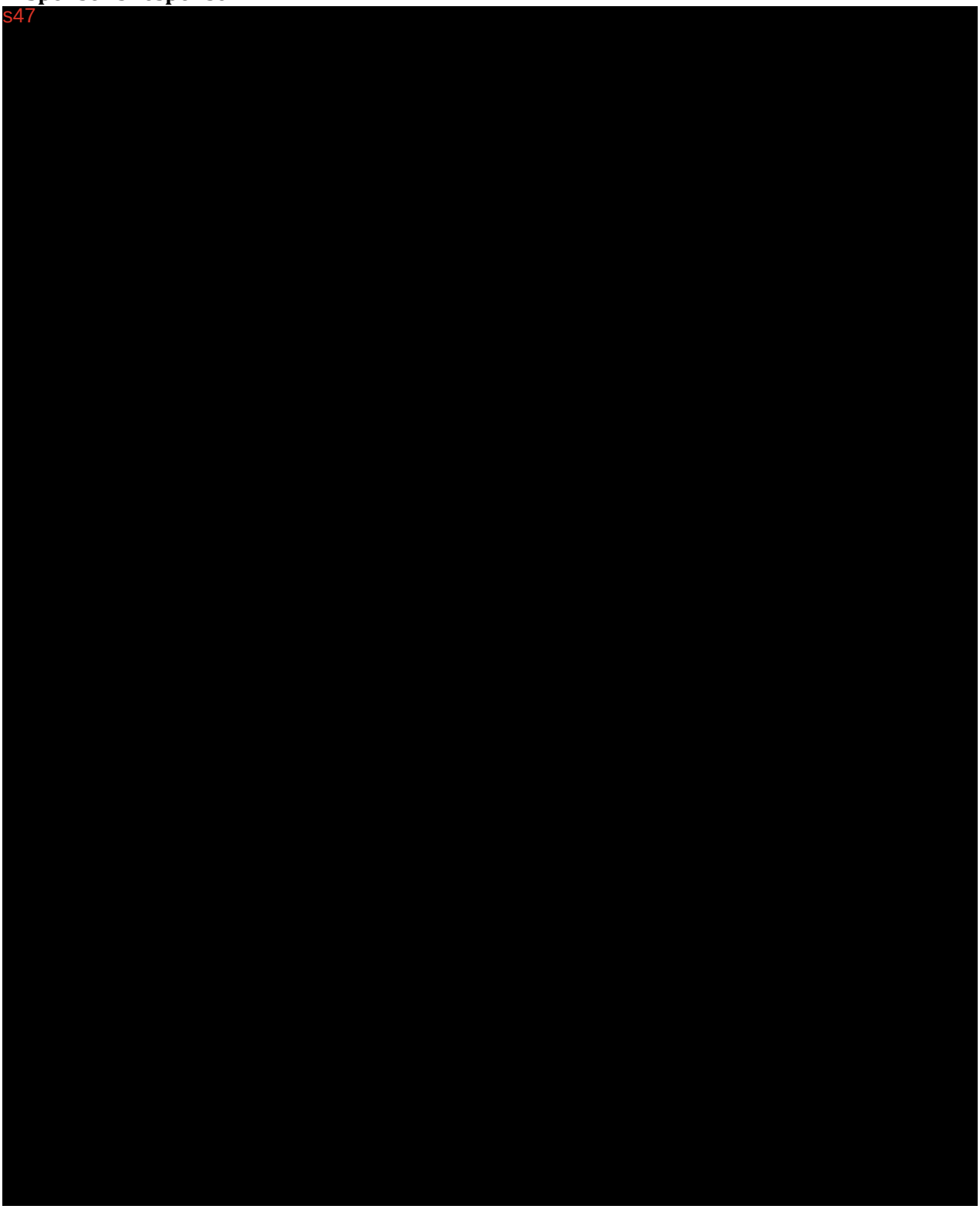
The evaluator accepts the provided p-values.

3. Pivotal trial – Day-time and night-time urinary frequencies ANOVA (p 172 & 176)

Please provide the data on the Tests of Between-subjects effects for the ANOVA analysis, and any other post-hoc analysis that might have been conducted if this was significant e.g. tests for significance between groups at each time point.

Sponsor's response:

s47



s47 [redacted]

Evaluator's response:

Based on the ANOVA results, there was no statistically significant difference between treatments for day-time urinary frequency (p=0.106), however there was a statistically significant difference between treatments for night-time urinary frequency (p=0.014).

The post-hoc analysis for night-time urinary frequency showed a significant difference between groups at 3 months (p=0.016), which is consistent with the results seen for night-time urinary frequency in the IPPS questionnaire (p=0.017, Wilcoxon rank sum test). The post-hoc analysis for night-time urinary frequency also showed a significant difference between groups for change from baseline at 2 months (p=0.002) and 3 months (p=0.002).

The post-hoc analyses for day-time urinary frequency did not show a significant difference between groups at any individual time point. There was a significant difference between groups in change from baseline at 3 months (p=0.032), however this statistical result is not relevant as overall there was no significant difference between groups for the ANOVA test of between-subject effects for day-time urinary frequency.

The results presented show that by 3 months, the product improved night-time urinary frequency, but not day-time urinary frequency, compared to placebo.

Thus, in terms of efficacy for relief of urinary frequency, only relief of night-time urinary frequency is supported and the indication should be modified to:

For the relief of nocturia (night-time urinary frequency) associated with medically diagnosed benign prostatic hypertrophy

4. GCP

   Thank you for clarifying in your previous response to the first round section 31 Request for Information that the trial was conducted to GCP guidelines and that all researchers are trained and aware of GCP guidelines. As requested in the first round section 31 Request for Information, **please provide** the supporting evidence if possible, e.g. certificate of GCP training.

Sponsor's response:

s47 [redacted]

Evaluator's response:

The ICH E6 Good Clinical Practice Consolidated Guidance states under Section 4.1.3 that "the investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements." Awareness and knowledge of GCP would ordinarily be acquired through a GCP training course. A good practice of maintaining GCP knowledge is a GCP refresher course every 3 years. According to the University of Queensland website, the current mandated practice in UQ[4] since 2020 is GCP training requirements evidenced by a certificate of completion in GCP training that is current.

The sponsor has indicated that as the study was conducted in 2011/12 there is no supporting evidence for GCP certificates relevant to this period. The evaluator considers there might be other evidence that could have been provided (e.g. induction checklist sign-off for having GCP training, or a page within a clinical study report stating that the study was performed to GCP guidelines). Though no satisfactory evidence was provided, the sponsor has stated that the trial was conducted to TGA GCP guidelines in the first response to the RFI (see D20-3950275) and the evaluator will not pursue this further.

Indications – interim outcome of assessment

Please comment on the individual interim outcomes and/or **please advise** of any errors of omission or fact. Please note that additional data is not being requested at this stage of evaluation.

Intermediate indications

May assist in the management of symptoms of medically diagnosed benign prostatic hypertrophy.

For the symptomatic relief of medically diagnosed benign prostatic hypertrophy.

5. In the pivotal trial with ProstateEze Max, only one of the IPSS subscores for symptoms (night time urinary frequency) was statistically significant between groups at 3 months. As such, it would be misleading to refer to this product relieving or managing **symptoms** (plural) of BPH. As the pivotal trial was conducted with the product, this evidence carries greater weight than non-pivotal supporting evidence e.g. for individual active ingredients such as *Pygeum africana*.

   Interim outcome: Indications 1 and 2 above are similar and can be merged into one indication, which refers to relief of urinary frequency (currently night-time and day-time) i.e. *'For the relief of urinary frequency associated with medically diagnosed benign prostatic hypertrophy'*.

Sponsor's response:

s47 [redacted]

[4] https://research.uq.edu.au/research-support/ethics-integrity-and-compliance/human-ethics/clinical-trials

s47 [redacted]

Evaluator's response:

The evaluator has considered the sponsor's request and concludes as follows:

- Ref. 16, a now out-of-date and withdrawn Cochrane review and meta-analysis on Pygeum (also discussed in Section 6.4), concluded that the results suggest that Pygeum treatment is effective in men with symptomatic BPH and led to an improvement in global symptoms, nocturia, peak urine flow and residual urine volume, hence it provides secondary supporting evidence. The majority of the studies utilised a standardised extract (standardisation details not specified in the review), with doses ranging from 75 to 200 mg/day (1 study with 75 mg/day, 7 studies with 100 mg/day, 4 studies with 200 mg/day, 1 study with dose not specified). Prostate Eze Max utilises a standardised extract at a dose of 75 mg Pygeum extract/day, which is at the lowest point of the range and represented by only one study in the review and meta-analysis.
- Ref. 20 and 21 were both uncontrolled studies (hence less robust study design) utilising a dose of 100 mg Pygeum per day, which is higher than Prostate Eze Max (75 mg/day). In addition, details of the extracts were not provided, other than the tradename 'Tadenan' for Ref. 21.
- Ref. 10 (textbook) referenced Ref. 16 and the pivotal Prostate Eze Max trial (Ref. 1). It also referenced an observational study comparing treatment with either P. africanum, Serenoa repens, finasteride or alpha-blocker drugs (tamsulosin etc.) to untreated men. Follow-up was at 1 year, with significant improvement (IPSS change >4) seen in all categories for the treatments: P. africanum 43.3%, S. repens 42.7%, finasteride 57% and alpha-blockers 68%, when compared to untreated men (Hutchison et al 2007). The dose(s) of Pygeum and extract(s) used in this study were not reported in Ref. 10.
- The evidence presented in Ref. 14 and 15, both of which are scientific monographs, cite similar supporting references, some of which have been assessed in this application (e.g. Refs. 1, 16, 20, 21). As such, these monographs are not entirely independent sources of information for evaluation of this application. The monograph(s) cite 75-200 mg/day of Pygeum extract, standardised to 12-14% of phytosterols, for reducing urologic symptoms (urinary frequency, peak urine flow and incomplete voiding) associated with BPH.
- Ref. 26 (Physician's desk reference) lists Pygeum africanum as a remedy for prostate enlargement, utilising a standardised extract containing 13% beta-sitosterol, and a typical dose of 50 to 100 mg extract twice a day. The recommended dose of Pygeum extract is higher than for Prostate Eze Max (75 mg/day). No references were cited to support this information.
- The EMA Assessment report on Prunus africana (2016; sourced by TGA) concluded that there were no sufficient data from well-designed clinical trials to support well-established use of the herbal preparation (Soft extract; DER 114-222:1 extraction solvent: chloroform; stabilised by 1.2% of ethanol >99.9%) for relief of lower urinary tract symptoms related to BPH. Prostate Eze Max utilises a different extract (dichloromethane extract).

Although some of this information might suggest plausibility for Pygeum eliciting a positive effect on incomplete voiding or weak urinary flow, in most cases the extracts and/or doses

cannot be reliably extrapolated to Prostate Eze Max. Even if plausibility could be reliably extrapolated to Prostate Eze Max, this outcome was not borne out in the results of the pivotal trial conducted with the product, where efficacy was not demonstrated for these symptoms. The pivotal trial did not show a statistically significant difference (P>0.05) between treatment and placebo in the IPSS sub-scores examining these symptoms (question 1 for incomplete voiding and question 5 for weak urinary flow).

As the evidence from the pivotal trial was negative/did not support efficacy for these symptoms for the product, the proposed new indication relating to incomplete voiding and weak urine flow is not supported for the product.

Pygeum africana may provide support for the symptomatic relief [of] nocturia, nocturnal frequency, weak stream, after-dribbling, hesitation and interruption of flow when such symptoms are associated with medically diagnosed benign prostatic hypertrophy.

6. As indications relate to the purpose or health benefit of the finished product (i.e. therapeutic use of the medicine), the wording of Indication 3 referring to efficacy of an active ingredient (*Pygeum africana*) is not appropriate. The reference to *Pygeum africana* in the third indication should be removed.

   Furthermore, the pivotal trial does not support the efficacy of ProstateEze Max for relieving symptoms of weak stream, after-dribbling, and hesitation and interruption of flow associated with medically diagnosed BPH as none of these symptoms showed a statistically significant difference between groups at 3 months. As noted in Question 5 above, the pivotal trial was conducted with the product, therefore this evidence carries greater weight than non-pivotal supporting evidence e.g. for individual active ingredients such as *Pygeum africana*. Therefore, reference to these symptoms should be removed.

   Interim outcome: As the only remaining symptom in this indication is nocturia/nocturnal frequency, the outcome for this indication is captured by the revised first indication above (Question 5).

Sponsor's response:

s47 [redacted]

Evaluator's response:

Please see the evaluator's response for Question 5. The indication is not supported.

<u>Secondary indications</u>

s47 [redacted]

7. Insufficient evidence has been provided to support these three indications.

   The prostate performs a number of functions including secreting enzymes, lipids, amines and metal ions essential for the normal function of spermatozoa, and metabolising testosterone. No evidence has been provided to support ProstateEze Max in maintaining or supporting these healthy functions, as these parameters were not measured in the pivotal trial.

Prostate health can be ascertained by several means including, but not limited to, determining size via imaging, digital rectal examination (size and regularity) and PSA test. In the pivotal trial with ProstateEze Max there was no difference in PSA test results, which were reported to remain within normal levels. As the subjects were suffering from BPH, these PSA results do not support enhancement/promotion or maintenance/support of prostate health. No other tests e.g. imaging or palpation were conducted to investigate prostate health.

In Table 4 (Module 2), Ref #10 (Braun & Cohen, textbook) is provided as evidence of phytosterols inhibiting the production of prostaglandins in the prostate, which suppresses the inflammatory symptoms of BPH. However, the primary (cited) reference was not provided and the dose for this effect was not reported in the textbook, therefore its relevance to ProstateEze Max is unknown.

Ref #22 (Health Canada monograph for lycopene) permits the statement 'Helps to support prostate health' for lycopene [all-trans)-Lycopene (USP) and psi,psi-Carotene (USP) from Solanum lycopersicum (fruit flesh) or synthetic] when given orally at a dose of 6.5-30 mg/day. ProstateEze Max provides 2.1 mg/day of lycopene, which is below this range. Therefore, this evidence does not support the proposed indications.

The remaining evidence provided in Table 4 (Module 2) to support these indications relates to the improvement in urinary symptoms of BPH. Evidence of improvement in urinary symptoms of BPH alone is insufficient to support the broader indication relating to prostate function or health.

Interim outcome: The above secondary indications for prostate health and function are not supported.

Sponsor's response:

s47 [redacted]

Evaluator's response:

Adding the target population qualifier of men with medically diagnosed benign prostatic hypertrophy, which is a restricted representation, makes this indication an intermediate indication. However, this does not change the (lack of) evidence provided to support prostate health for this formulated product. As noted in the second round RFI, only the PSA levels were examined in the pivotal study, which did not show a difference with treatment, and no other tests were conducted to investigate prostate health. Evidence for improvement in urinary symptoms of BPH alone is not sufficient to support a broader indication relating to prostate health or function, irrespective of a target population qualifier.

The proposed modified indication is not supported.

s47 [redacted]

8. This indication is supported by the night-time and day-time urinary frequency results in the pivotal trial.

Interim outcome: The acceptability of this indication is dependent on satisfactory resolution of issues relating to the urinary frequency results in the pivotal trial (Questions 2 and 3, above).

Sponsor's response:

The sponsor noted that there were no further comments as answers have been provided above for questions 2 and 3.

Evaluator's response:

The evaluator notes the response.

The statistical results provided in the response to the second round RFI show that only night-time urinary frequency was significantly different between treatment and placebo; day-time urinary frequency was not significantly different between treatment and placebo. Therefore, an indication referring broadly to 'urinary frequency' is not supported.

In spite of the TGA's previous advice in the second round RFI for this indication, the evaluator now notes the corresponding low level permitted indication in the Therapeutic Goods (Permissible Indications) Determination is s47 ', not s47 '. The indication was proposed as a low level permitted indication for the product, therefore it appears that the sponsor has made an error in the wording of the indication. It is also unclear what could be meant by 'symptoms of urinary frequency', given that urinary frequency is a symptom itself, and no evidence of efficacy has been provided for 's47 ', only for 's47 '.

Based on the outcomes of the assessment for questions 2 and 3, only a reduction in night-time urinary frequency is supported, therefore the broader low level permitted indication of 'Relieve urinary frequency' is not supported. Although this indication could be made more definitive by specifying 'night-time', as the supporting evidence is for urinary frequency associated with BPH, this is already covered by the modified intermediate indication suggested by the evaluator: *'For the relief of urinary frequency associated with medically diagnosed benign prostatic hypertrophy'.*

The indication 'Relieve symptoms of urinary frequency' is not supported.

s47

9. The evidence provided is insufficient to show that either the finished product or any of the ingredients administered at the proposed dose rate reduce free radicals formed in the body or reduce/decrease free radical damage to body cells.

   - Ref #1 (pivotal trial with ProstateEze Max) did not investigate free radical formation in the body or damage to body cells, therefore no evidence is available from this study to support these indications for the finished product.
   - Ref #22 (Health Canada monograph for lycopene) permits the statement 'Provides antioxidants for the maintenance of good health' for lycopene [all-trans)-Lycopene (USP) and psi,psi-Carotene (USP) from Solanum lycopersicum (fruit flesh) or synthetic] when given orally at a dose not to exceed 30 mg/day. ProstateEze Max provides 2.1 mg/day of lycopene, which is within this range. However, the statement permitted by the Health Canada monograph 'Provides antioxidants for

the maintenance of good health' is not the same as the proposed indications, therefore it does not support the proposed indications.

- Ref #23 (Story et al.) notes that lycopene can be a potent antioxidant molecule, effective at scavenging the ROS singlet oxygen. However, a dose is not provided, therefore its relevance to these indications for this product is unknown.
- Ref #9 (Natural medicines monograph – lycopene) reports under 'Antineoplastic effects' that lycopene has antioxidant effects and might reduce cancer risk by scavenging free radicals and quenching singlet oxygen, which prevents oxidative damage to DNA. A dose is not reported, although Table 4 (Module 2) states that 6 mg/day has been used. ProstateEze Max provides 2.1 mg/day, which is below the reported amount. Furthermore, the presented effect in the monograph is in relation to cancer, which is not relevant or appropriate for this product.
- Ref #8 (Hevesi et al.) describes an *in vitro* study investigating the anti-oxidant and anti-inflammatory effects of Epilobium parviflorum. The aqueous acetone extract of E. parviflorum showed higher antioxidant effect in the DPPH assay than well-known antioxidants; inhibited the lipid peroxidation determined by the TBA assay; and possessed a protective effect against oxidative damage, generated in fibroblast cells. In the COX inhibition assay, E. parviflorum decreased the PGE2 release, so showing inhibition of the COX-enzyme. Although this study provides some support for anti-inflammatory and antioxidant effects of E. parviflorum, and reduction in free radical damage to the cells used in the assays, the dose required to be administered orally to produce these effects in people in vivo is not reported. Therefore, the relevance of these results to these indications for this product are unknown. Furthermore, the study used an aqueous acetone extract, while the eBS details for this product indicate an aqueous extract.

Interim outcome: The above secondary indications relating to a reduction and/or decrease in free radical formation or damage are not supported.

Sponsor's response:

s47 [redacted]

Evaluator's response:

From the references provided in the submission, antioxidant effects were reported for lycopene and Epilobium, although the information for Epilobium was for a different extract (aqueous acetone extract in study vs aqueous extract in product) therefore its relevance to the product is unknown. The EMA monograph assessment report for Epilobium (sourced by the evaluator) refers to aqueous extracts of Epilobium having antioxidant activity. The evaluator also notes that the EMA monograph assessment reports sourced by the evaluator for Pygeum and Cucurbita reported antioxidant effects for these ingredients, however the extracts mentioned were different from those used in the product.

Although the claim s47 [redacted] ' is factually correct, as it is presented on the label of a medicine indicated for relief of nocturia associated with benign prostatic hypertrophy, and with the name 'Prostate Eze Max', this presentation would imply that a) the antioxidants provided would have an effect in the body of the consumer, and b) this antioxidant effect is likely to be related to the indication for benign prostatic hypertrophy and/or be beneficial for the prostate.

As noted in the second section 31 Request for Information, the proposed low level indications were not supported due to insufficient evidence being provided to show that

either the finished product or any of the ingredients administered at the proposed dose rate have an antioxidant effect in the body (in vivo). In addition, the EFSA Scientific Opinion on the substantiation of health claims related to lycopene and protection of DNA, proteins and lipids from oxidative damage, protection of the skin from UV-induced (including photo-oxidative) damage, contribution to normal cardiac function, and maintenance of normal vision (2011; sourced by the evaluator) concluded that a cause and effect relationship has not been established between the consumption of lycopene and protection of DNA, proteins and lipids from oxidative damage.

Therefore, the implication that the antioxidants provided in the product would have an antioxidant effect in the body, including the prostate, is not supported by the evidence, and consumers could be misled by the claim 'contains antioxidants', resulting in an unacceptable presentation of the product.

This claim is not supported.

Summary of third round evaluation

Literature search strategy

Upon examining the additional information provided by the sponsor in response to the s31 Request for information, there are still some uncertainties regarding the literature search strategy. However, this will not be pursued further, as the pivotal trial was conducted with the final product while the results of the literature search only provide secondary evidence for the individual active ingredients. Furthermore, the evaluator has also sourced the EMA monograph assessment reports for four of the five ingredients for additional comparison.

Evidence of GCP

Due to the time elapsed since the pivotal trial was conducted, the sponsor advised that they were unable to provide evidence to support the assertion that the study was conducted to GCP. This will not be pursued further.

Indications – Final outcome of assessment

i. Intermediate indications

For the relief of urinary frequency associated with medically diagnosed benign prostatic hypertrophy

From the ANOVA and post-hoc analyses results provided for the pivotal trial, only relief of night-time urinary frequency is supported. Therefore, the broader indication referring to 'urinary frequency' should be made more definitive and modified to:

For the relief of nocturia (night-time urinary frequency) associated with medically diagnosed benign prostatic hypertrophy

For the relief of urinary frequency, incomplete voiding and weak urine flow associated with medically diagnosed benign prostatic hypertrophy

The sponsor proposed this amended indication in lieu of three indications that were not supported in the second round RFI: 'May assist in the management of symptoms of medically diagnosed benign prostatic hypertrophy', 'For the symptomatic relief of medically diagnosed

benign prostatic hypertrophy' and 'Pygeum Africana may provide support for the symptomatic relief [of] nocturia, nocturnal frequency, weak stream, after-dribbling, hesitation and interruption of flow when such symptoms are associated with medically diagnosed benign prostatic hypertrophy'. The sponsor acknowledged the TGA's position that the pivotal trial evidence, which was conducted with the product, carried greater weight than the secondary supporting evidence on individual active ingredients. However, the sponsor felt that the secondary supporting evidence relating to urologic symptoms (such as weak urine flow, incomplete voiding, frequent daytime and night-time urination) should not be discounted in supporting the indications.

The evaluator has considered the sponsor's request and concludes that although some of the secondary information might suggest plausibility for Pygeum eliciting a positive effect on incomplete voiding or weak urinary flow, in most cases the extracts and/or doses cannot be reliably extrapolated to Prostate Eze Max. Even if plausibility could be reliably extrapolated to Prostate Eze Max, this outcome was not borne out in the results of the pivotal trial conducted with the product, where efficacy was not demonstrated for these symptoms.

As the evidence from the pivotal trial was negative/did not support efficacy for these symptoms for the product, the proposed new indication relating to incomplete voiding and weak urine flow is not supported for the product.

Helps support prostate health for men with medically diagnosed benign prostatic hypertrophy

The sponsor suggested adding the qualifier 'for men with medically diagnosed benign prostatic hypertrophy' to the low level indication 'Helps support prostate health', as the low level indication on its own was not supported. Adding the target population qualifier of 'men with medically diagnosed benign prostatic hypertrophy', which is a restricted representation, makes this indication an intermediate indication. However, adding this target population qualifier does not change the (lack of) evidence provided to support prostate health for this product. Evidence for improvement in urinary symptoms of BPH alone is not sufficient to support a broader indication relating to prostate health or function, irrespective of a target population qualifier.

The proposed modified indication is not supported.

ii. Secondary (low-level) indications

s47 [redacted]

The statistical results provided in the response to the second round RFI show that only night-time urinary frequency was significantly different between treatment and placebo; day-time urinary frequency was not significantly different between treatment and placebo. Therefore, an indication referring broadly to 'urinary frequency' is not supported.

Although this indication could be made more definitive by specifying 'night-time', as the supporting evidence is for urinary frequency associated with BPH, this is already covered by the modified intermediate indication suggested by the evaluator: *'For the relief of urinary frequency associated with medically diagnosed benign prostatic hypertrophy'.*

Furthermore, the evaluator now notes that the corresponding low level permitted indication in the Therapeutic Goods (Permissible Indications) Determination is s47 [redacted]', not 's47 [redacted]', therefore it appears that the sponsor has made an error in the wording of the indication. It is also unclear what could be meant by 'symptoms of urinary frequency', given that urinary frequency is a symptom itself, and no evidence of efficacy

has been provided for 's47 ', only for 's47 '.

The indication 's47 ' is not supported.

Pygeum has been included specifically in the Caruso' PROSTATE EZE MAX formula to relieve symptoms of urinary frequency **[on label side panel]**

This information, which is included on the side panel of the label, refers to a therapeutic use and is therefore an indication.

This indication attributes efficacy to the active ingredient, Pygeum. The sponsor was advised previously in the second round RFI for another Pygeum-related indication that, as indications relate to the purpose or health benefit of the finished product (i.e. therapeutic use of the medicine), the wording of an indication referring to efficacy of an active ingredient (Pygeum africana) is not appropriate and the reference to Pygeum should be removed.

Removing reference to Pygeum in this case results in an indication for relief of symptoms of urinary frequency, which as already noted above, is not supported.

This information/indication is not supported.

Claims

s47

The sponsor proposed replacing the unsupported low level indications relating to free radical formation or free radical damage with the claim 's47 ", and noted that lycopene is a known antioxidant.

Although the claim is factually correct, as it is presented on the label of a medicine indicated for relief of nocturia associated with benign prostatic hypertrophy, and with the name 'Prostate Eze Max', this presentation would imply that: a) the antioxidants provided would have an effect in the body of the consumer, and b) this antioxidant effect is likely to be related to the indication for benign prostatic hypertrophy and/or be beneficial for the prostate.

The implication that the antioxidants provided in the product would have an antioxidant effect in the body, including the prostate, is not supported by the evidence, and consumers could be misled by the claim 's47 ', resulting in an unacceptable presentation of the product.

This claim is not supported.

17. Third round benefit-risk assessment

17.1. Third round assessment of benefits

After consideration of the responses to the questions, only one modified indication is supported: *For the relief of nocturia (night-time urinary frequency) associated with medically diagnosed benign prostatic hypertrophy.*

The benefits of ProstateEZE Max for this modified indication are outlined below:

Intermediate indications – 1. *For the relief of nocturia (night-time urinary frequency) associated with medically diagnosed benign prostatic hypertrophy*	
Benefits	***Strengths and Uncertainties***
Coulson et al., 2013 *Reduction in nocturia in treatment group:* Statistically significant difference in total IPSS median score in active group at 3 months compared to placebo (p=0.033, Wilcoxon rank sum test). The individual IPSS symptom severity score for Nocturia (Q7) was significantly different in active group compared to placebo at 3 months (p=0.017, Wilcoxon rank sum test). There was a significant difference between active group and placebo in night-time urinary frequency over the period of the trial (p=0.014, ANOVA). There was a significant difference between active group and placebo at 3 months for night-time urinary frequency (p=0.016, post-hoc t-test). There was a significant difference between active group and placebo in night-time urinary frequency with respect to change from baseline at 2 and 3 months (both p=0.002, post-hoc t-test).	**Strengths** Pivotal study conducted with the proposed formulation at the recommended dose. Pivotal study was performed in Australia, thus it is relevant to the Australian population. Study was done in the target population. Validated questionnaires to identify the baseline BPH symptoms and to measure the study outcomes. Randomised, double-blinded, placebo-controlled study. There was a high adherence rate (95%) with use of the study medications reported. 3 month study (as per EMA guidelines for urinary incontinence) Response was clinically significant based on a reduction in nocturia to below 2 times per night at 3 months. **Weaknesses and uncertainties** Inclusion/exclusion criteria - No upper limit for baseline IPSS scores No urodynamic studies, only measurement of symptoms (EMA GL: symptoms are secondary endpoint measures) No dose-response studies (EMA GL: several doses would be preferable) No effect size or responder analysis to assess clinical relevance

The following indications are not supported due to either insufficient evidence, or the evidence does not demonstrate efficacy, or the indication (and hence efficacy) is attributed to an active ingredient and not the product:

For the relief of urinary frequency, incomplete voiding and weak urine flow associated with medically diagnosed benign prostatic hypertrophy.

Helps support prostate health for men with medically diagnosed benign prostatic hypertrophy.

Relieve symptoms of urinary frequency.

Pygeum has been included specifically in the Caruso' PROSTATE EZE MAX formula to relieve symptoms of urinary frequency.

As efficacy has not been satisfactorily demonstrated for these indications for the product, there are no benefits of ProstateEZE Max for these indications.

17.2. Third round assessment of risks

After consideration of the responses to questions, the risks of ProstateEZE Max for the supported modified use are outlined below:

Intermediate indications – 1. *For the relief of nocturia (night-time urinary frequency) associated with medically diagnosed benign prostatic hypertrophy*	
Risks	***Strengths and Uncertainties***
Coulson et al., 2013 Lack of efficacy Potential adverse effects, including allergic reactions.	**Strengths** No reported adverse effects in the pivotal study. Has been on the market since 2014 with only one recorded adverse event (rash) in Australia. Warning statements provided on the label to manage risks: • KEEP OUT OF REACH OF CHILDREN • Use only as directed. • If symptoms persist see your Medical Professional. • Contains Soya Oil and sulfites. • Phenylketonurics - this product contains phenylalanine. • If you have not had your symptoms diagnosed or if you experience an increase in symptoms, see a health professional. • Free from: sugar, lactose, yeast, gluten, salt and preservatives. The condition (BPH) requires regular monitoring by a medical practitioner once diagnosed, which provides opportunity for the patient to discuss use and experience of the product. **Uncertainties** No safety data beyond 3 months Unknown potential for interactions with food or other drugs.

	Label warnings need to refer to a 'medical practitioner' or 'doctor', not 'medical professional' (definition unknown) or 'health professional' (not necessarily a doctor). Free from statement is inaccurate: Sugar and Salt are present in the product. 'Contains soya oil' warning needs to be amended to 'Contains soya bean products', as this product also contains lecithin derived from soybean and soy product residual, in addition to soya oil.

An additional risk relates to the presentation of the product. ***Presentation***, in relation to therapeutic goods, means the way in which the goods are presented for supply, and includes matters relating to the name of the goods, the labelling and packaging of the goods and any advertising or other informational material associated with the goods. The presentation of therapeutic goods is unacceptable if it is capable of being misleading or confusing as to the content or proper use or identification of the goods.

The proposed name of this assessed listed medicine, 'Caruso's Prostate Eze Max', is very similar to the currently listed medicine, 'Caruso's ProstateEze Max' (AUST L 231578), and the label presentation is also very similar. The indications for the two products are, however, different. This can be potentially misleading or confusing for the consumer with respect to the proper use and/or identification of the therapeutic goods, and also taking into consideration that the proposed assessed listed medicine has been pre-market assessed for efficacy by the TGA while the 'standard' listed medicine has not. Hence, both medicines should not be supplied at the same time, unless the proposed assessed listed medicine is adequately differentiated from the 'standard' listed medicine.

The sponsor should be requested to advise of their intention for the currently listed 'Caruso's ProstateEze Max' (AUST L 231578), if the proposed assessed listed medicine is approved. If the two products will be co-marketed, they must be adequately differentiated with respect to the presentation (name and label) e.g. amended name, amended label, which better differentiates the two medicines.

17.3. Third round assessment of benefit-risk balance

The only benefit that is supported by the results in the pivotal trial with the finished product is an improvement in night-time urinary frequency associated with medically diagnosed benign prostatic hypertrophy.

The efficacy and safety risks of the product can be managed adequately by label warnings, which include advice to consult a medical practitioner. Consultation with a medical practitioner after the initial medical diagnosis is likely to occur on a regular basis due to the ongoing nature of this condition (BPH), even if some symptoms can be relieved or improved by this or another product. The label warnings need to be amended to refer to a 'medical practitioner' or 'doctor', rather than a 'health professional' (which may not be a doctor) or a 'medical professional' (definition uncertain), in order to manage the risks. The 'free from' advice on the label also needs to be corrected to manage the risks to consumers for whom salt and sugar intake is a concern. And the 'Contains soya oil' warning needs to be amended to 'Contains soya bean products', as this product also contains lecithin derived from soybean and soy product residual, in addition to soya oil.

The risks relating to similar presentation of this medicine to the 'standard' listed medicine, Caruso's ProstateEze Max (AUST L 231578) need to be raised with the sponsor and satisfactorily resolved, so that consumers are not misled or confused by the two medicines.

Overall, the benefit-risk balance of ProstateEze Max for the relief of nocturia (night-time urinary frequency) associated with medically diagnosed benign prostatic hypertrophy is favourable, provided the indication(s)/claim(s) are restricted to the one modified indication that is supported; the label changes identified here and in section 19 'Third round comments on label' are made; and the issue of similar presentation to the 'standard' listed medicine, Caruso's ProstateEze Max (AUST L 231578), is satisfactorily resolved.

18. Third round recommendations

The evaluator makes the following recommendations after assessing the information provided with this application, including the responses provided for the s31 RFI1 and RFI2 questions, and other information sourced by the evaluator:

1. The information provided **supports** an indication for this product that relates to relief of nocturia associated with medically diagnosed benign prostatic hypertrophy. The evaluator proposes the following wording for the indication:

   For the relief of nocturia (night-time urinary frequency) associated with medically diagnosed benign prostatic hypertrophy.

2. The following indications are **not supported,** either due to insufficient evidence, or the evidence does not demonstrate efficacy, or the indication (and hence efficacy) is attributed to an active ingredient and not the product:

   For the relief of urinary frequency associated with medically diagnosed benign prostatic hypertrophy.

   For the relief of urinary frequency, incomplete voiding and weak urine flow associated with medically diagnosed benign prostatic hypertrophy.

   Helps support prostate health for men with medically diagnosed benign prostatic hypertrophy.

   Relieve symptoms of urinary frequency.

   Pygeum has been included specifically in the Caruso' PROSTATE EZE MAX formula to relieve symptoms of urinary frequency.

3. The following claim is **not supported**, due to the potential to mislead consumers by implying that the antioxidants provided in the product would have an antioxidant effect in the body, including the prostate, which is not supported by the evidence:

   s47 [redacted]

19. Third round comments on label/product information

The sponsor provided an updated label in response to the second round s31 request for information. Refer to D21-2395526 and D21-2463293 for the sponsor's complete response.

Carton label (second round s31 RFI – Attachment D, 16 March 2021)

Blister pack (second round s31 RFI – Attachment A, 29 March 2021)

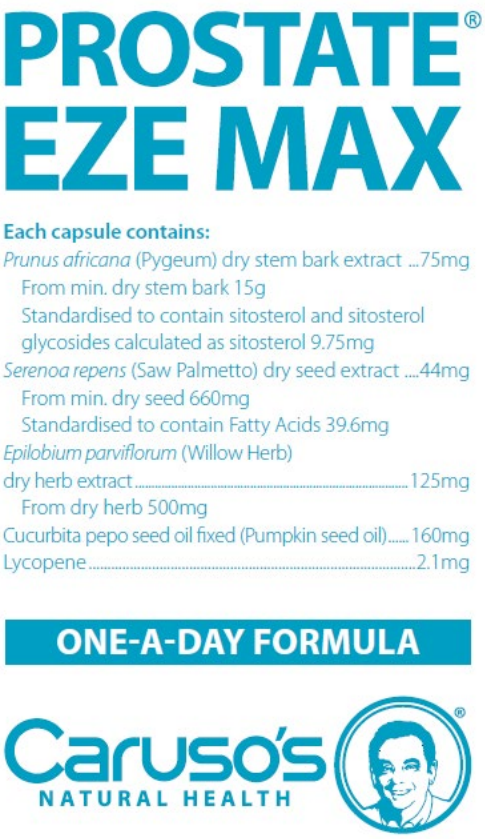


Table of label changes provided in response to second round RFI

Change requested	Sponsor's response	Evaluator's response
Preferred name for the product.	Preferred name is 'Caruso's Prostate Eze Max' Provided updated artwork with new name for carton and blister components of the label.	New name is acceptable Consistent name on carton. The name on the blister is not consistent (missing 'Caruso's'). **Sponsor to provide corrected blister label.**
Quantity or proportion of active ingredients needs to be expressed as outlined in TGO 92 guidance.	Provided updated artwork for carton and blister components with active ingredients quantity/proportion presented in line with TGO92 requirements.	Acceptable.
Amend the indications on the label to be consistent with the outcomes presented in Questions 5 to 9.	Provided updated artwork (Attachment D) with amended indications: • For the relief of nocturia (night-time urinary frequency)	Satisfactory response, however the indications require further amendment in light of the statistical results

	associated with medically diagnosed benign prostatic hypertrophy • Relieves symptoms of urinary frequency. (Although the sponsor would like to continue discussions on possible amendments to unsupported indications).	provided in this second round RFI response.
Clarify the source of sulfites.	s47 [redacted]	Acceptable.
Replace warning statement for 'healthcare professional' with 'If symptoms persist see your Medical Practitioner' or words to that effect e.g. '… see your doctor'.	Provided updated artwork (Attachment D) which has been amended to read: If symptoms persist see your Medical Professional. If you have not had your symptoms diagnosed or if you experience an increase in symptoms, see a health professional.	The terms "medical professional" and "health professional" are not appropriate for use in this product. The term "medical professional" is not defined in the Act and could be open to interpretation. As BPH requires a medical diagnosis by a qualified medical doctor, the term "medical practitioner" or "doctor" should be used. **Sponsor to update label with the correct terminology.**
Remove the phrase "CONTAINS 15,000MG PYGEUM" from the main label.	Provided updated artwork (Attachment D) which has the phrase removed from the main label.	Acceptable.
Replace AUSTL number with 'AUST L(A) XXXX'.	Provided updated artwork (Attachment D) which has the has AUST L(A) XXXX instead.	Acceptable.
Confirm the packaging for this product and provide all components of the packaging that will be supplied with the product for label approval.	Amended the packaging to be a blister in an inner *(sic)* carton and noted that there is no bottle label or enclosed leaflet required. Provided the carton and blister artwork.	Acceptable
Confirm that the mock-up label is the actual size at 100% magnification if measurements	Included measurements in the carton mock up with	

will not be included on the artwork mock-up.	measurements of LxWxD: 68 x 58 x 117.14mm. No measurements provided for the blister label	

Labelling requirements

The new carton and blister labels for the product have been assessed and there are moderate deficiencies that need to be addressed:

Carton label

Carton – Left panel (panel 1)

1. s47 [redacted]

Please delete this section of information.

2. s47 [redacted]

Please delete this claim.

3. s47 [redacted]

Please delete this claim, or alternatively, **please amend** this claim to:
'Caruso's PROSTATE EZE MAX contains herbal extracts and has been shown to provide relief of nocturia associated with medically diagnosed benign prostatic hypertrophy.'

4. s47 [redacted]

Please delete this therapeutic claim.

5. s47 [redacted]

Please delete this therapeutic claim.

6. s47 [redacted]

Please delete this statement/claim.

Carton – Main panel (panel 2)

s47 [redacted]

s47

Carton – Panel 3

s47

Carton – Right panel (panel 4)

s47

s47

[redacted]

s47 

20. Clinical Questions (Third s31 RFI)

The evaluation of efficacy is now complete and no further additional data or information is being requested at this stage, other than the requirement identified here regarding the presentation of the medicine, and the labelling requirements identified in section 19 'Third round comments on the label'.

Question:

Presentation, in relation to therapeutic goods, means the way in which the goods are presented for supply, and includes matters relating to the name of the goods, the labelling and packaging of the goods and any advertising or other informational material associated with the goods. The presentation of therapeutic goods is unacceptable if it is capable of being misleading or confusing as to the content or proper use or identification of the goods.

The proposed name of this assessed listed medicine, 'Caruso's Prostate Eze Max', is very similar to the currently listed medicine, 'Caruso's ProstateEze Max' (AUST L 231578), and the label presentation is also very similar. The indications for the two products are, however, different. This can be potentially misleading or confusing for the consumer with respect to the proper use and/or identification of the therapeutic goods, and also taking into consideration that the proposed assessed listed medicine has been pre-market assessed for efficacy by the TGA while the 'standard' listed medicine has not. Hence, both medicines should not be supplied at the same time, unless the proposed assessed listed medicine is adequately differentiated from the 'standard' listed medicine.

Please advise of your intention for the currently listed 'Caruso's ProstateEze Max' (AUST L 231578), if the proposed assessed listed medicine is approved.

If you do not intend to co-market the two products, **please provide** an assurance that the assessed listed medicine will replace the 'standard' listed medicine and that the two products will not be supplied concurrently.

If you do intend to co-market these products i.e. if the assessed listed medicine will not replace the 'standard' listed medicine in the market, then the name and label presentation of the assessed listed medicine are not appropriate, due to the similar presentation to the 'standard' listed medicine. To co-market these products you must adequately differentiate the proposed 'Caruso's Prostate Eze Max' assessed listed medicine from the 'Caruso's ProstateEze Max' listed medicine with respect to the presentation (name and label). Therefore, **please provide** the amended information e.g. amended name, amended label, which better differentiates the two medicines.

The sponsor was sent a third request for information on 16th April 2021 (D21-2546121) with the above requirement and labelling requirements, as well as the opportunity to comment on the final outcome of assessment.

21. Fourth round evaluation and recommendations

The sponsor has responded to the comments and questions raised after the third round evaluation, which were sent by TGA as an s31 Request for information dated 16th April 2021 (D21-2546131). Refer to D21-2634640 for the sponsor's complete response.

The sponsor acknowledged the final outcome of evaluation for the indications and agreed to move forward with the indication "For the relief of nocturia (night-time urinary frequency) associated with medically diagnosed benign prostatic hypertrophy".

s47 [redacted]

The evaluator accepts the sponsor's response and notes that there are minor labelling issues to be resolved (outlined in section 22 below).

The listing of Caruso's Prostate Eze Max is recommended, with the following indication:

For the relief of nocturia (night-time urinary frequency) associated with medically diagnosed benign prostatic hypertrophy.

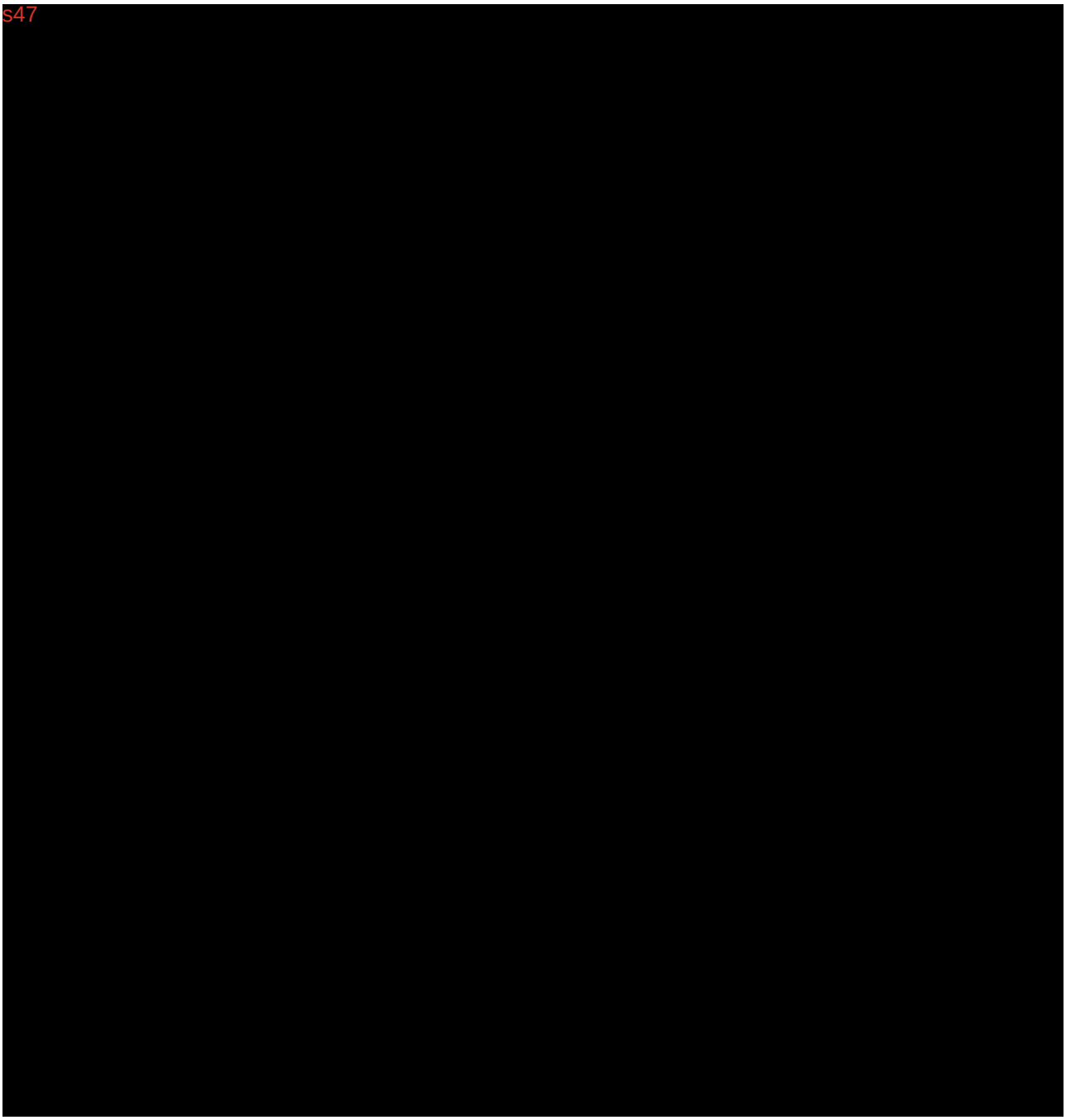
s47 [redacted]

22. Fourth round comments on label/product information

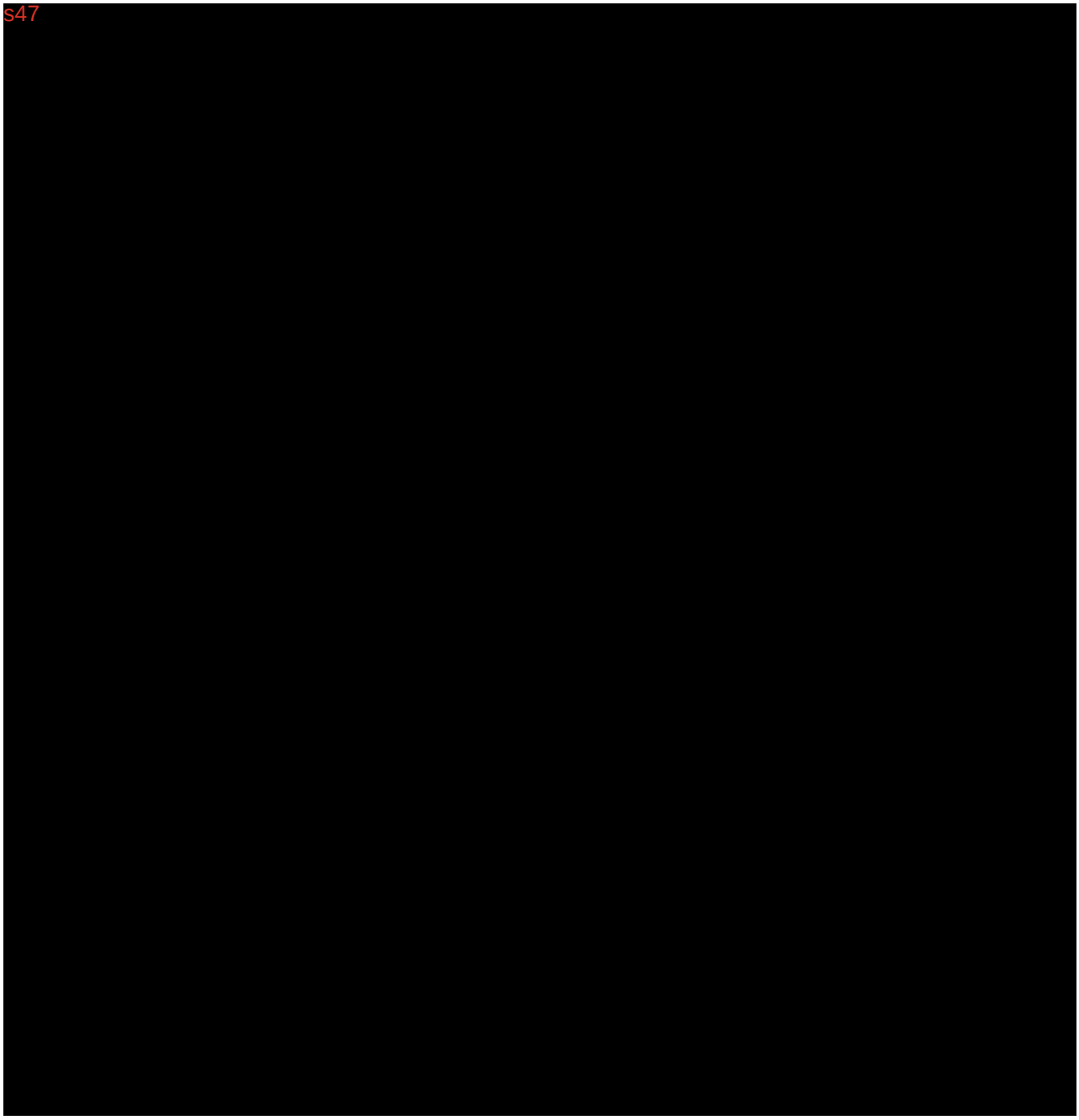
In response to the third round s31 request for information, the sponsor accepted all label update recommendations and provided the annotated and clean mock-up labels for the carton label for 60 capsules and the blister pack. They also provided the carton label for both 30 and 90 capsule

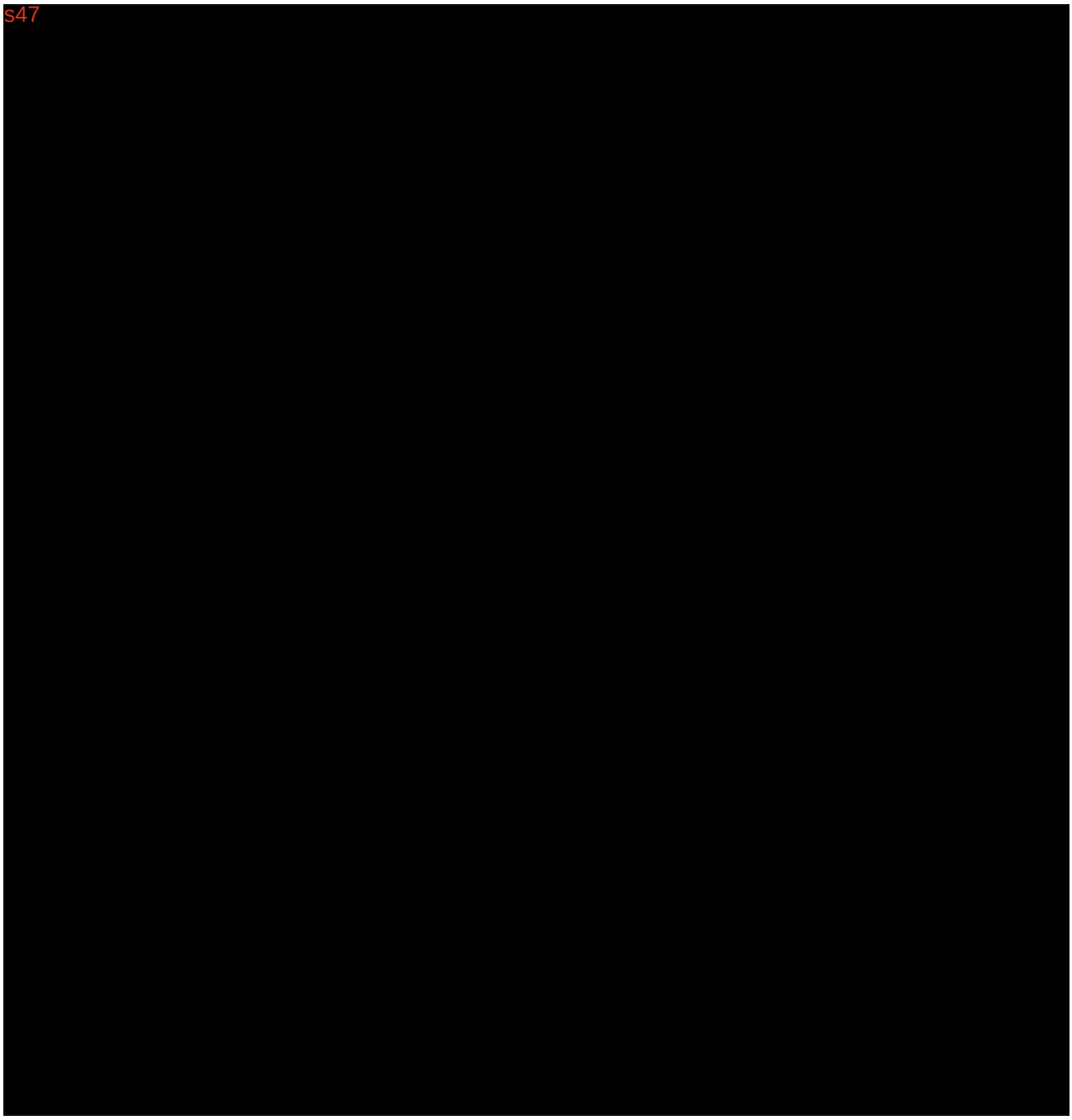
pack size. They confirmed that they intend to apply for a section 14/14A exemption with regards to the name of the medicine on the main label, as it does not comply with TGO92. This situation is similar to their other listed medicine for which they have received a section 14/14A exemption. Refer to D21-2634640 for the sponsor's complete response.

s47



s47




s47

s47

Labelling requirements

The new carton and blister labels for the product have been assessed and there are minor deficiencies that need to be addressed:

Carton label (for all pack sizes)

Carton – Left panel (panel 1)

1. The text "Caruso's PROSTATE EZE® MAX contains Saw Palmetto and Lycopene" and "Caruso's PROSTATE EZE® MAX also contains Epilobium and Pumpkin seed oil" is duplication of information presented in paragraph 2 of the same panel.

   Please delete these statements from the label.

Carton – Main panel (panel 2)

2. The 'TGA assessed' claim is not in a TGA-approved format.

   'TGA assessed' symbol
   The 'TGA assessed' symbol you have included on the front panel of the carton does not appear to be the approved TGA .eps file (please refer to page 6 of the Guidelines for using the TGA assessed claim on medicine labels).

   The approved TGA assessed symbol is being provided to you in the covering e-mail with this Notice (please see .eps file attached to the email) for you to use.

   Also, the font size in the symbol does not comply with the requirements in the Guidelines for using the TGA assessed claim on medicine labels, as it is larger than the

font size of the active ingredients, warnings or other essential information included on the medicine label.

With respect to the font size, please follow these requirements when using the TGA assessed symbol:

a. Text size: The letters in the word 'assessed' must be a minimum of 1.5 mm, inclusive of the ascender. The overall size of the symbol must be a minimum of 4.7mm high and 9mm wide (see example below).

The text for the word 'assessed', inclusive of the ascender, must not be larger than the active ingredients, warnings or other essential information included on the medicine label (see dotted red lines in the example below).

b. Font style and colour: The TGA assessed symbol must be presented in black ink on a white background and surrounded by a black outline (as provided in the '.eps' file attached to this email).

Please replace the TGA assessed symbol on the label with the file provided (.eps file attached to the email) and ensure all the requirements of use are met, as per the Guidelines for using the TGA assessed claim on medicine labels.

'TGA assessed' statement

The Guidelines for using the TGA assessed claim on medicine labels also state that if the symbol is used, a statement authorised by the TGA must also be used (page 4).

The compliant statement to use is "Evidence for the approved indications has been assessed by the TGA." You can choose the text size, font style and colour but it must follow these requirements:

a. Text size: The minimum text size is 1.5 millimetres. The maximum text size for the TGA assessed statement is no more than the text size for the names and amounts of active ingredients, warnings or other essential information included on the medicine label.
b. Font style and colour: Must be presented in a colour that contrasts strongly with the background it is printed on; and be consistent with the font style, colour and prominence of the surrounding label text, warnings or other essential information.

The sentence must be written in lower case, with the exception of the first letter of the sentence and TGA, as shown below:

> Evidence for the approved indications has been assessed by the TGA.

Please include the statement "Evidence for the approved indications has been assessed by the TGA." on the label in the correct format.

Blister label

3. **Presentation of dosage units**

   Thank you for your response received 12 May 2021, in which you advised for Question 23 that: 'Each blister tray contains 2 rows of 5 pockets that can be extracted individually'.

   It is not clear from your response whether each dosage unit is readily detachable e.g. whether there are perforations in the blister tray that allow the dosage units to be separated from each other. It is noted that no perforations have been included on the blister label.

   Please confirm whether each dosage unit is readily detachable e.g. if there are perforations in the blister tray to allow the individual segments to be readily detached.

   If each dosage unit is not readily detachable, then no changes will need to be made to the blister label already provided.

   If each dosage unit is readily detachable, **please indicate** the perforations on the blister label. **Please also ensure** that the blister label you provide is compliant with TGO 92 labelling requirements for blister labels where individual segments containing the dosage unit can be readily detached (TGO 92, Section 10, Part 9(c)).

23. Fifth round comments on label/product information

In response to the fourth round s31 request for information, the sponsor accepted all label update recommendations and provided the annotated and clean mock-up labels for the carton label for the 30, 60 and 90 capsules pack size and the blister pack. They confirmed that there are no perforations for individual dosage units on the blister pack. Refer to D21-2650050 for the sponsor's complete response. The TGA also noted that the storage statement on the current draft labels for Prostate Eze Max labels, 'Store at 25°C in a cool, dry place', is incorrect. The correct wording should be 'Store below 25°C in a cool, dry place'. The sponsor was requested to update the labels with the correct wording and the updated labels were provided by email (D21-2651056).

Carton label for 30 capsules (fourth round s31 RFI – Attachment D, 18 May 2021)

s47

s47

s47

Further labelling requirements

The new carton labels for the product have been assessed and there are minor deficiencies that still need to be addressed:

Carton label (for all pack sizes)

1. It is noted that the presentation of the active ingredients in latest version of the label has been changed. The current presentation of the active ingredients is unacceptable as it is potentially confusing to the consumer.

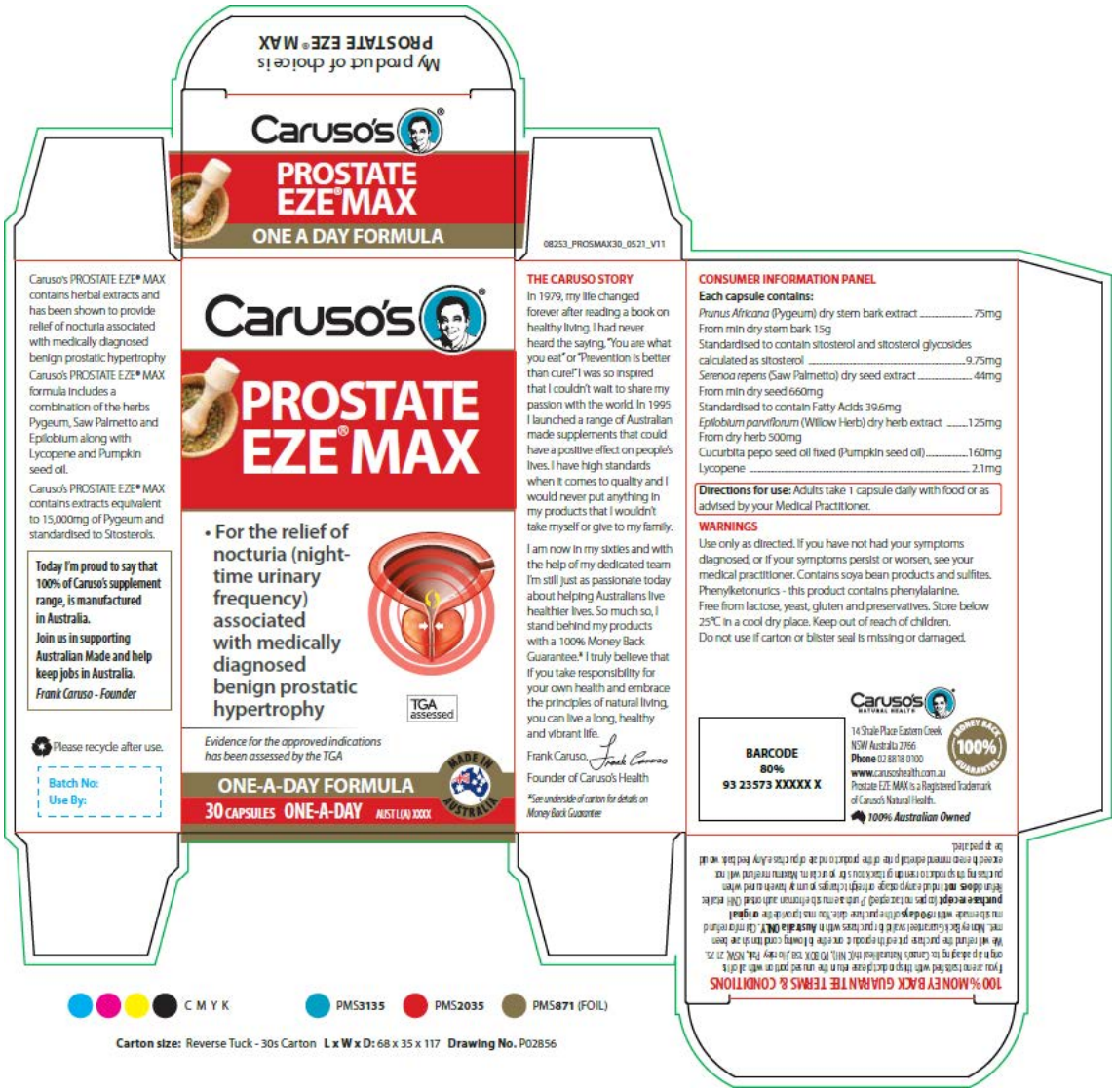
   The sponsor has agreed to revert back to the previous label format for the active ingredients (Round 3 s31) and this is acceptable.

2. As the font size of the active ingredients is likely to change, please ensure that the TGA Assessed statement and symbol font size is no larger than the font size of the active ingredient.

The sponsor provided the following updated labels (D21-2654475) with the requested changes.

The labels are acceptable.

Carton label for 30 capsules (fourth round s31 RFI – Attachment D updated, 18 May 2021)



Carton label for 60 capsules (fourth round s31 RFI – Attachment E updated, 18 May 2021)

Carton label for 90 capsules (fourth round s31 RFI – Attachment F updated, 18 May 2021)

24. References

24.1. References provided for assessment

Braun, L. & Cohen, M (2014a)., Herbs & Natural Supplements: An Evidence-based Guide: Volume 2, Pygeum, *Churchill Livingstone.*

Braun, L. & Cohen, M (2014b)., Herbs & Natural Supplements: An Evidence-based Guide: Volume 2, Saw palmetto – liposterolic extract, *Churchill Livingstone.*

Breza, J., Dzurny, O., Borowka, A., Hanus, T., Petrik, R., Blane, G., Chadha-Boreham, H. (1998)., Efficacy and acceptablility of tandenan (Pygeum africanum extract) in the treatment of benign prostatic hyperplasia (BPH): a multicentre trial in central Europe. *Current Medical Research and Opinion*, Vol 14(3), pp 127-139.

Chatelain, C., Autet, W., Brackman, F. (1999)., Comparison of once and twice daily dosage forms of Pygeum africanum extract in patients with benign prostatic hyperplasia: a randomized, double blind study with long term open label extension. *Urology*, Vol 54, pp 473-478.

Coulson, S., Rao, A., Beck, SL., Steels, E., Gramotnev, H. & Vitetta, L (2013)., A phase II randomised double blind placebo-controlled clinical trial investigating the efficacy and safety of ProstateEZE Max: A herbal medicine preparation for the management of symptoms of benign prostatic hypertrophy. *Complementary Therapies in Medicine,* Vol 21 pp172-179.

Emara, LH., El-Menshawi, B. & Estefan, MY. (1999). Bioavailability of Beta-sitosterol from pygeum africanum extract in Humans. *Pharmaceutical and Pharmacological Letters*, Vol 9(2), pp 80-83.

Frick, J. & Aulitzky, W (1991). Physiology of the prostate. *Infection*, Vol 19(S3), pp S115-S118. DOI: 10.1007/bf01643679.

Health Canada Monographs – Pygeum – Prunus Africana (2019 viewed in 2020).

Health Canada Monographs – Saw Palmetto – liposterolic extract (2019 viewed in 2020).

Health Canada Monographs – Lycopene (2019 viewed in 2020).

Hevesi, BT., Houghton, PJ., Habtemariam, S. & Kery, A (2009)., Antioxidant and anti-inflammatory effect of Epilobium parviflorumSchreb. *Phytotherapy Research*, Vol 23(5) pp 719-724.

Kumar, VL. & Majumder, PK (1995). Prostate gland: Structure, functions and regulation. *International Urology and Nephrology*, Vol 27(3) pp 231-243. DOI: 10.1007/bf02564756.

Montvale, NJ. (2007). PDR for Herbal Medicines, Epilobium Thompsons Healthcare.

Montvale, NJ. (2007). PDR for Herbal Medicines, Saw palmetto Thompsons Healthcare.

Montvale, NJ. (2007). PDR for Herbal Medicines, Pumpkin, Thompsons Healthcare.

Natural Medicines Professional Monograph (2019a) – Database – Pumpkin.

Natural Medicines Professional Monograph (2019b) – Database – Lycopene.

Natural Medicines Professional Monograph (2019c) – Database – Pygeum.

Natural Medicines Professional Monograph (2019d) – Database – Saw Palmetto.

PDR – Physicians Desk Reference (2005), Online Database, Pygeum.

Ross, AB., Vuong, LT., Ruckle, J., Synal, HA., Schulze-Koing, T., Wertz, K., Rumbeli, R., Liberman, RG., Skipper, PL., Tannenbaum, SR., Bourgeois, A., Guy, PA., Enslen, M., Nielsen, ILF., Kochhar, S., Richelle, M., Fay, LB., Williamson, G. (2011). Lycopene bioavailability and metabolism in humans: an accelerator mass spectrometry study. American Journal of Clinical Nutrition, Vol 93, pp 1263-73.

Saladin, KS (2007). Anatomy & Physiology: The unity of form and function, McGraw Hill, Fourth Edition.

Simoes, GF., Sakuramoto, P., Santos, CB., dos, Furlan, NKC. & Augusto, TM (2018). An Overview on Prostate Pathophysiology: New Insights into Prostate Cancer Clinical Diagnosis. Pathophysiology – Altered Physiological States, Chapter 10, pp 183-202. DOI: 10.5772/intechopen.74269.

Skinder, D., Zacharia, I., Studin, J. & Covino, J (2016). Benign prostatic hyperplasia. Journal of the American Academy of Physician Assistants, Vol 29(8) pp19-23. DOI: 10.1097/01.jaa0000488689.58176.0a.

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TGA Advertising Code (No. 2), 2018.

Wilt, TJ., Ishani, A. (2011). Pygeum africanum for benign prostatic hyperplasia (Review). The Cochrane Collaboration, The Cochrane Library 9.

24.2. References sourced by the evaluator

EMA Assessment reports and herbal monographs

Assessment report on *Prunus africana* (Hook f.) Kalkm., cortex

Assessment report on *Serenoa repens* (W. Bartram) Small, fructus

Assessment report on *Epilobium angustifolium* L. and/or *Epilobium parviflorum* Schreb., herba

Assessment report on *Cucurbita pepo* L., semen

Community herbal monograph on *Cucurbita pepo* L., semen

European Union herbal monograph on *Epilobium angustifolium* L. and/or *Epilobium parviflorum* Schreb., herba

Cochrane Reviews

Ilic D, Forbes KM, Hassed C. (2011). Lycopene for the prevention of prostate cancer. *Cochrane Database of Systematic Reviews.*

Tacklind J, MacDonald R, Rutks I, Stanke JU, Wilt TJ. (2012). *Serenoa repens* for benign prostatic hyperplasia. *Cochrane Database of Systematic Reviews.*

Other

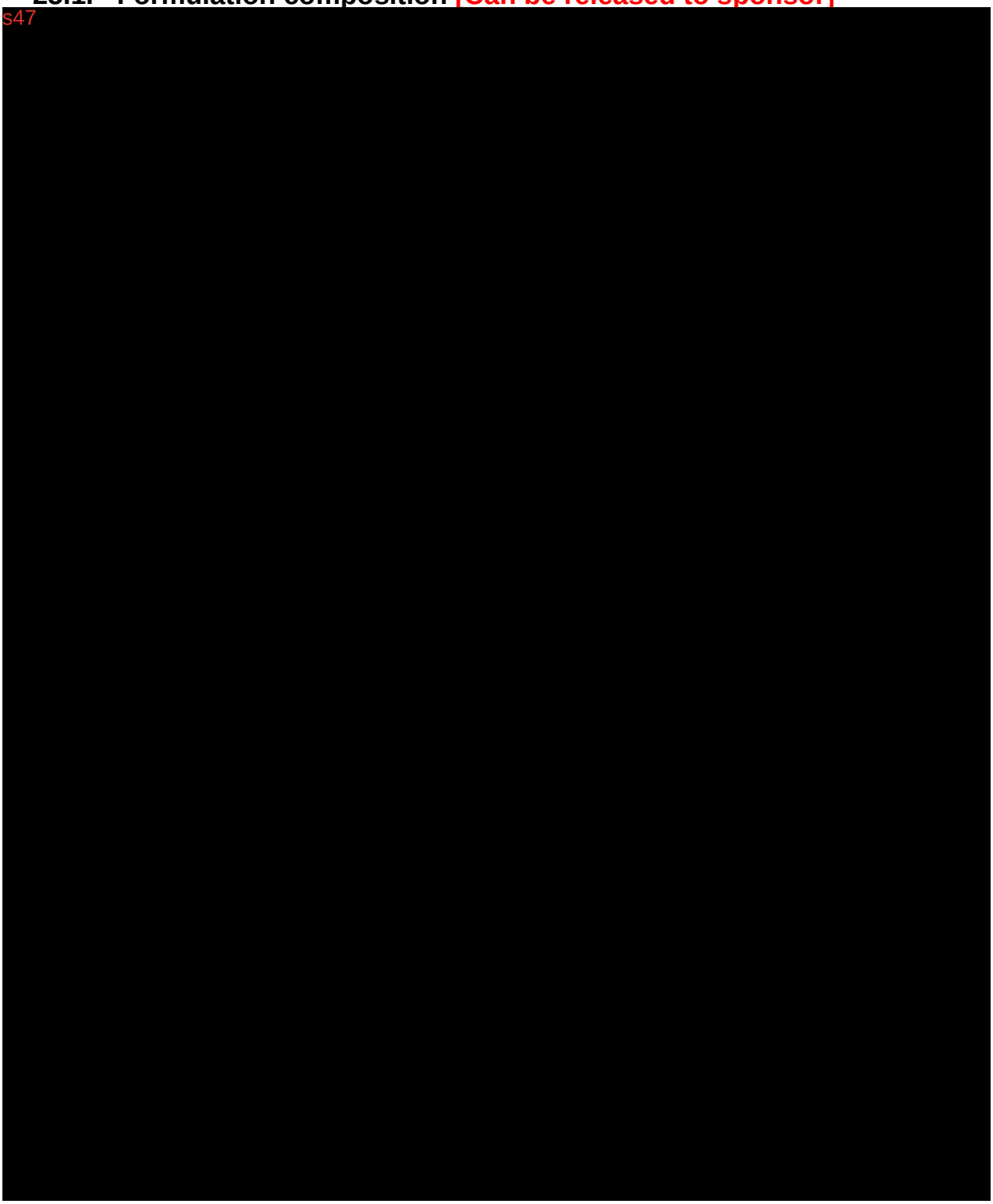
EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). (2011). Scientific Opinion on the substantiation of health claims related to lycopene and protection of DNA, proteins and lipids from oxidative damage (ID 1608, 1609, 1611, 1662, 1663, 1664, 1899, 1942, 2081, 2082, 2142, 2374), protection of the skin from UV-induced (including photo-oxidative) damage (ID

1259, 1607, 1665, 2143, 2262, 2373), contribution to normal cardiac function (ID 1610, 2372), and maintenance of normal vision (ID 1827) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2011;9(4):2031

25. Confidential information

25.1. Formulation composition [Can be released to sponsor]

s47



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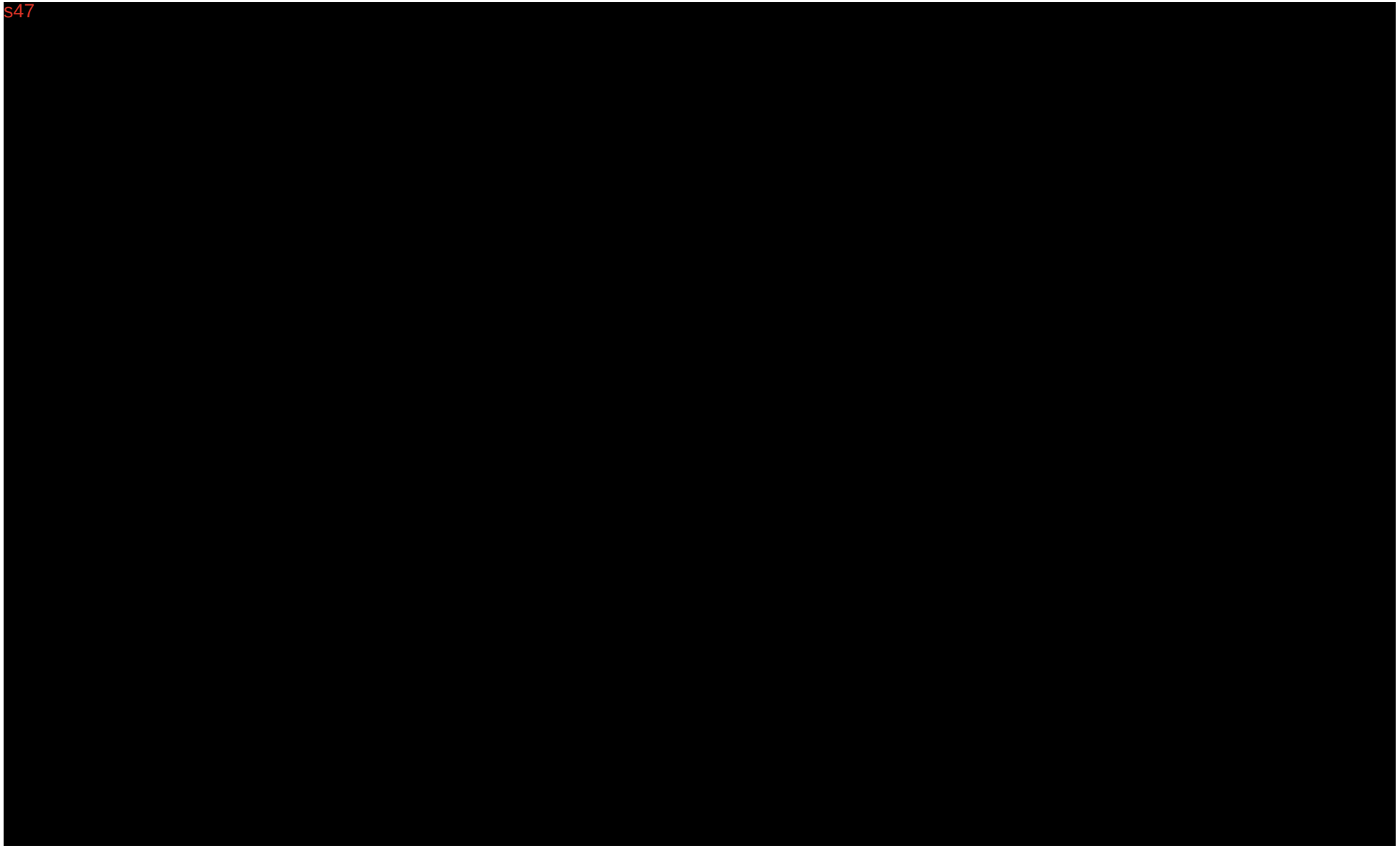
26. APPENDIX

26.1. APPENDIX I: Evidence Table for ProstateEZE Max capsule provided by sponsor

s47



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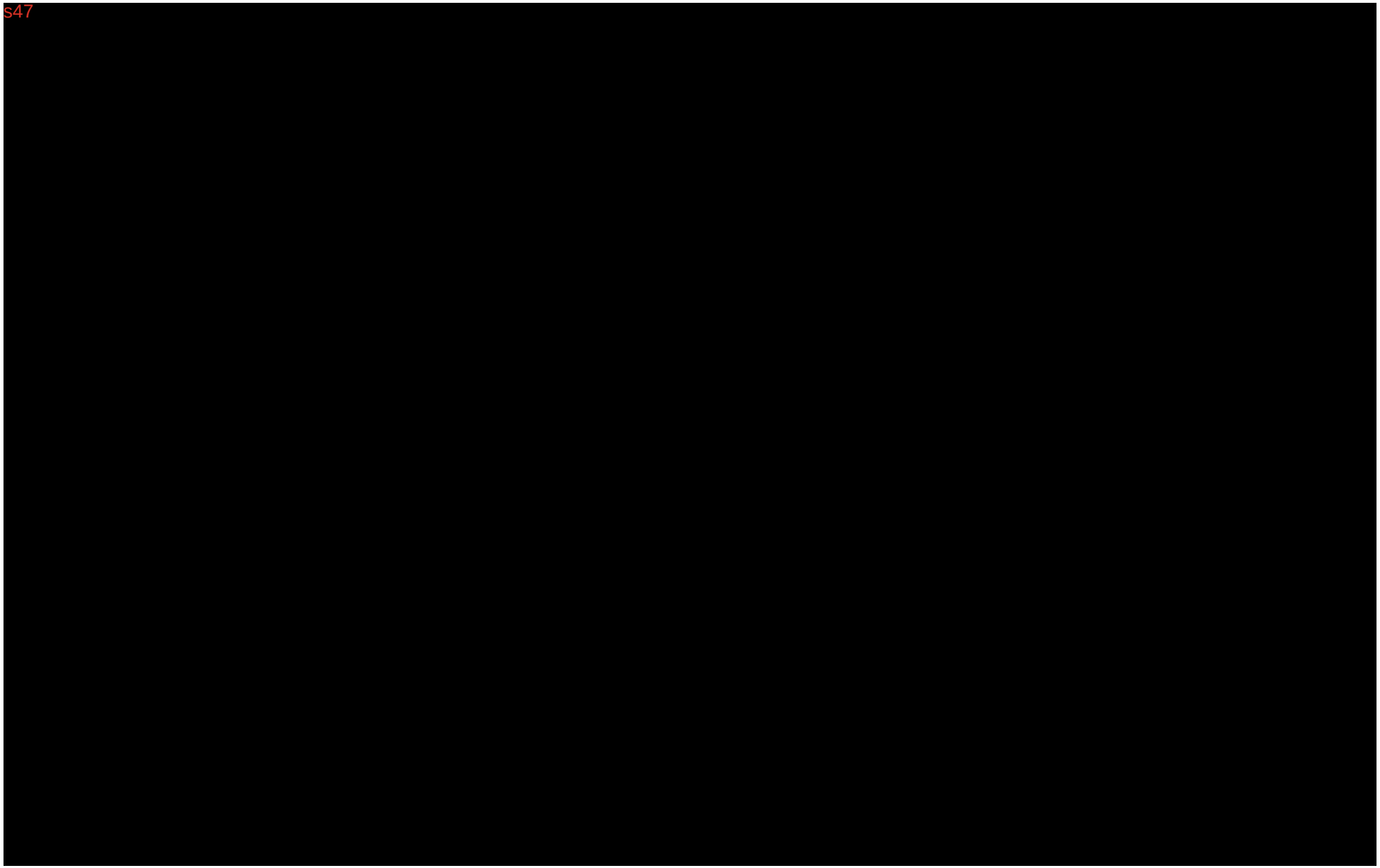

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s47

Complementary & OTC Medicines Branch, Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: complementary.medicines@health.gov.au Phone: 1800 020 653
https://www.tga.gov.au

Caruso's NATURAL HEALTH

Submission ID: **LM-2020-01113-1**
TGA Reference: **D20-3605878**
Revised due date for response 17 December 2020
(as per email correspondence with s22 [redacted] 17.11.2020)

Senior Evaluator, CMES
Delegate of the Secretary
Complementary & OTC Medicines Branch

Attention: s22 [redacted]

I refer to the recent Notice under Section 31 of the Therapeutic Goods Act 1989 requiring further information for the AUSTL(A) application for Caruso's ProstateEZE Max (AUSTL 231578). Attachment A of the notice raised 11 questions. Please see the responses to each of the questions below.

Question 1. GCP

The Assessed listed medicines evidence guidelines state in section 5.4.2 that all studies should be conducted according to Good Clinical Practice (GCP) principles and have appropriate ethical certification. GCP is about ensuring good assurance and record-keeping practices, which allow for accurate reporting, interpretation and verification s47 [redacted]

Please clarify if the trial was conducted to GCP, and if so, please provide the supporting evidence.
Alternatively, **please comment** on how the trial maintained good assurance and record-keeping practices to allow for accurate reporting, interpretation and verification

Answer

s47 [redacted]

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Question 2. Plant part used for *Serenoa repens* extract (p174)

The study states that the investigational product, ProstateEZE Max contains **Serenoa repens** (equivalent to 660 mg of dry leaf per capsule). Module 2.5.4 states that the clinical study (Coulson et al., 2013) was performed on the actual finished product. The plant part used for the **S. repens** extract in the proposed product is listed as 'seed' in the application form (module 1.2.1b) and the draft label (Module 1.3.3b). The Assessed listed medicines evidence guidelines state in section 6.1 that there must be high level of concordance between the product formulation used in the clinical trial and that intended for listing. Specifically, in the case of biological substances like herbs/herbal extracts the species, sub-species, strain, **parts**, quantity of active component and preparation should be identical.

Please clarify this discrepancy (**S. repens**, leaf vs seed) and **comment** on what impact this may have on the extrapolation of the outcomes of the clinical trial to the proposed product.

Please also confirm whether the extract in the proposed product is from 'fruit' or 'seed

Answer

This was addressed initially in Module 1.2.5 and Appendix E of our submission. The TGA also looked at this discrepancy when the previous restricted representation was applied for and approved in 2015.

There was an error in the clinical paper relating to the plant part used in the study. The actual plant part used in the formula was the seed. I have attached the specification for the product used in the trial as attachment A to this email.

The extract in the proposed product is identical to that used in the clinical trial.

Question 3. Participant demographics (p 174)

Results were provided for participant demographics at baseline. It was stated that there were no significant differences between the active and placebo groups in age, weight, body mass index and PSA score. It was also stated that there were no significant correlations between symptom severity and these demographic parameters in the active and placebo groups. However, it is not clear what statistical tests were conducted to reach these conclusions, as the 'Statistics' section of the paper does not mention baseline analysis.

Please clarify what statistical tests were used for these baseline analyses **and provide** the results (if available), so that the significance of the results can be ascertained.

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Answer

s47

Question 4. Total prostate function results (p 174 & 175)

On page 174 of the paper it is stated that "The total IPSS median (25th, 75th percentiles) scores were not significantly different at baseline between the active and placebo groups 3 (1,4) and 3.5 (1.25, 4.75) respectively (Table 1)". These values appear to be incorrect, as the results in Table 1 for the active and placebo groups are 19.5 and 18, respectively, not 3 and 3.5.

Please provide the correct values for the total IPPS median (25th, 75th percentiles) scores at baseline and the statistical result.

Answer

There is an error in the text in the paper, instead of referring to total IPSS it is referring to Question 1 results "had a sensation of not emptying your bladder completely after urination"

Table 1 total score is the correct data 19.5 and 18

Question 5. Individual BPH symptoms (p 174-175)

With respect to individual BPH symptom scores (as measured by the IPSS), the paper states that "The results for the active group showed a significant percentage decrease in mean severity for all questions, except weak urinary stream after 1 month of treatment. There was a significant improvement in urinary stream by month 2 and all symptoms remained significant at month 3". The paper also states "Of interest was that observation that, the placebo group experienced significant reduction in night-time urinary frequency at month 1 but reverted to baseline levels by month 2 and 3". There were no statistical results (p-values) presented highlighting the significant decrease for all symptoms in the active group.

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Please provide the statistical results (p-values) for all the individual BPH symptom analyses, including those that were not statistically significant.
Please clarify whether the stated correlations between less night-time urinary frequency and 'pushing and straining' and 'stopping and starting' were statistical correlations, and if so, **provide details** of the statistical tests.

Answer

s47

[redacted]

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Question 6. Baseline symptom score for nocturia (p 175)

In Table 1 of the paper, the baseline symptom score for nocturia for the active treatment group is missing in the first column of results (printing error?); the 1-month, 2-month and 3-month results are provided.

Please provide the baseline value so that the baseline severity of nocturia for the active treatment group can be ascertained.

Answer

Baseline symptom score for IPSS in table 1 appears to be a printing error. The value is "3"

Question 7. Baseline day-time urinary frequency (p 176)

The paper states that the average day-time urinary frequencies at baseline were similar for active and placebo groups, however p-values were not provided to support this statement. In Figure 1A the day-time urinary frequencies at time 0 do not appear similar.

Please comment on the apparent difference in the baseline day-time urinary frequencies between groups in Figure 1A.

Please provide the between group statistical results (p-values) for baseline daytime urinary frequency if tested, so that similarity at baseline can be ascertained

Answer

The daytime urinary frequencies are provided in the table below Figure 1. The graph looks like there is a difference as the axis is only from 5.8 to 7. The p-value for difference between groups at baseline is as per question 3 and calculated using a 2-tail t-test s47 [redacted].

Question 8. Baseline night-time urinary frequency (p 176)

The average baseline night-time urinary frequencies for the active and placebo groups were provided, however it is unclear whether these were statistically analysed.

Please provide the between group statistical results (p-values) for baseline night time urinary frequency, if tested, so that similarity at baseline can be ascertained.

Answer

s47 [redacted]

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Question 9. Missing urinary frequency statistical results for months 1 to 3 (p 176)

No statistical results (p-values) have been provided for paired *t*-tests conducted for day-time urinary frequency in the placebo group for months 1, 2 and 3; for night-time urinary frequency in the placebo group for months 1, 2 and 3; and for the active group for night-time urinary frequency at 3 months.

Please provide the p-values from these paired **t**-tests, so that the statistical significance can be ascertained

Answer

s47

Question 10. Day-time and night-time urinary frequencies ANOVA (p 172 & 176)

Day-time and night-time urinary frequencies were also statistically analysed using a mixed design repeated-measures analysis of variance (ANOVA), which confirmed a statistically significant trend that active treatment significantly reduced frequencies over placebo. The F statistic and p-values were provided, however it was not clear which effects were included in the model and to which effect(s) these statistics relate to. For example, the model may have assessed group, time and time x group effects.

Please confirm which effects were assessed and provide the results, so that the effects of treatment can be confirmed

Answer

The ANOVA assessed a time, treatment and time vs treatment effect

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Question 11. Clinical significance of reduction in nocturia (p 176)

The published trial states "…the reduction in nocturia from 2.9 times to 1.8 times was also a clinically significant outcome".

Please comment on this conclusion, as the criteria for determining clinical significance were not mentioned in the 'Materials and Methods' section therefore it is unclear on what basis clinical significance has been determined (e.g. whether it is based on documented clinical practice information/evidence), so that the clinical significance of this outcome can be ascertained

Answer

s47 [redacted]

Please do not hesitate to contact me should you require any further information.

Kind regards,

s22 [redacted]
s22 [redacted]
Caruso's Natural Health

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