SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

MYTRICON 150 mg/ml suspension for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 150 mg medroxyprogesterone acetate.

Preservatives: methylparaben 0,137 % *m/v*, propylparaben 0,015 % *m/v*.

Sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection.

White to off-white suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Endometriosis.
2. Contraception (ovulation suppression).
3. Endometrial Cancer: As adjunctive and/or palliative therapy ininoperable, recurrent or metastatic endometrial carcinoma.
4. Renal Cancer: As adjunctive and/or palliative therapy in recurrent and/or metastatic adenocarcinoma of the kidney.

4.2 Posology and method of administration

Posology

Endometriosis

The recommended dose of MYTRICON in this condition is 50 mg weekly or 100 mg every 2 weeks intramuscularly for at least 6 months. It should be noted that return of ovulation may be delayed following this therapy due to the depot properties of the medicine (see section 4.4).

Contraception

The recommended dose is 150 mg MYTRICON every three months administered by deep intramuscular injection. To increase assurance that the patient is not pregnant at the time of the first administration, it is recommended that this injection be given during the first 5 days after the onset of a normal menstrual period, within 5 days postpartum if not breastfeeding, or, if exclusively breastfeeding at or after the sixth week postpartum.
If the period between injections is greater than 14 weeks, the medical practitioner should determine that the patient is not pregnant before administering MYTRICON.

Switching from other methods of contraception

When switching from other contraceptive methods, MYTRICON should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods, (e.g., patients switching from oral contraceptives should have their first injection of MYTRICON within 7 days after taking their last active pill).

Endometrial and renal carcinoma

Doses of 400 mg to 1 000 mg of MYTRICON intramuscularly per week are recommended initially. If improvement is noted within a few weeks or months and the disease appears stabilised, it may be possible to maintain improvement with as little as 400 mg per month.

Special populations

Hepatic insufficiency

No clinical studies have evaluated the effect of hepatic disease on the pharmacokinetics of MYTRICON. However, MYTRICON is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe liver insufficiency (see section 4.3).

Renal insufficiency

No clinical studies have evaluated the effect of renal disease on the pharmacokinetics of MYTRICON. However, since MYTRICON is almost exclusively eliminated by hepatic metabolism, no dosage adjustment should be necessary in women with renal insufficiency.

Paediatric population:

MYTRICON is not indicated before menarche. Data are available in adolescent females (12 to 18 years), (see section 4.4). Other than concerns about loss of bone mineral density (BMD), the safety and effectiveness of MYTRICON are expected to be the same for post-menarcheal adolescent and adult females.

Method of administration:

For intramuscular injection.

The sterile aqueous suspension of MYTRICON should be vigorously shaken just before use to ensure that the dose being administered represents a uniform suspension of MYTRICON. Doses should be given by deep intramuscular injection. Care should be taken to ensure that the depot injection is given into the muscle tissue preferably the gluteus maximus, but other muscle tissue such as the deltoid may be used.

The site of injection should be cleansed using standard methods prior to administration of the

injection.

4.3 Contraindications

- Known hypersensitivity to medroxyprogesterone acetate, or to any of the excipients of MYTRICON (see section 6.1).
- Undiagnosed vaginal bleeding.
- Undiagnosed breast pathology.
- Severe impairment of liver function.
- Undiagnosed urinary tract bleeding.
- Thrombophlebitis, or a history of thrombophlebitis.
- Known or suspected pregnancy (see section 4.6).
- Known or suspected malignancy of the breast (excluding use in oncology indications).
- Depression not well controlled with treatment.
- A history of depression with the use of hormonal contraceptives.

4.4 Special warnings and precautions for use

Safe assessment of women prior to starting hormonal contraceptives (and at regular intervals thereafter) should include a personal and family medical history of each woman. Physical examination should be guided by this and by the contraindications (section 4.3) and warnings (section 4.4) for this medicine. The frequency and nature of these assessments should be based upon relevant guidelines and should be adapted to the individual woman, but should include measurement of blood pressure and, if judged appropriate by the clinician, breast, abdominal and pelvic examination including cervical cytology.

Contraception and endometriosis

Loss of Bone Mineral Density:

Use of depot medroxyprogesterone acetate intramuscular (DMPA-IM) reduces serum oestrogen levels and is associated with significant loss of BMD due to the known effect of oestrogen deficiency on the bone remodelling system. Bone loss is greater with increasing duration of use; however BMD appears to increase after DMPA-IM is discontinued and ovarian oestrogen production increases. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of DMPA-IM by younger women will reduce peak bone mass and increase the risk for fracture in later life i.e. after menopause.

A study to assess the BMD effects of DMPA-IM MYTRICON in adolescent females (12 – 18 years) showed that its use was associated with a statistically significant decline in BMD from baseline, by 1 – 3 years after discontinuing treatment. After discontinuing DMPA-IM in adolescents, return of mean BMD to baseline values required 1,2 years at the lumbar spine, 4,6 years at the total hip and at least 4,6 years at the femoral neck. However in some participants, BMD did not fully return to baseline during follow-up and the long-term outcome is not known in this group. In adolescents, MYTRICON may be used, but only after other methods of contraception have been discussed with the patients and considered to be unsuitable or unacceptable.

A large observational study of predominantly adult female contraceptive users showed that use of DMPA-IM did not increase risk for bone fractures. Importantly, this study could not determine whether use of DMPA has an effect on fracture rate later in life.

In women of all ages, careful re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than 2 years. In particular, in women with significant lifestyle and/or medical risk factors for osteoporosis, other methods of contraception should be considered prior to use of MYTRICON.

Significant risk factors for osteoporosis include:

- Alcohol abuse or tobacco use.
- Chronic use of drugs that can reduce bone mass, e.g. anticonvulsants or corticosteroids.
- Low body mass index or eating disorder, e.g. anorexia nervosa or bulimia.
- Previous low trauma fracture.
- Family history of osteoporosis.

Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

Menstrual Irregularity:

The administration of MYTRICON usually causes disruption of the normal menstrual cycle. Bleeding patterns include amenorrhoea (present in up to 30 % of women during the first 3 months and increasing to 55 % by month 12 and 68 % by month 24); irregular bleeding and spotting; prolonged (>10 days) episodes of bleeding (up to 33 % of women in the first 3 months of use decreasing to 12 % by month 12). Rarely, heavy prolonged bleeding may occur. Evidence suggests that prolonged or heavy bleeding requiring treatment may occur in 0,5 - 4 occasions per 100 women years of use. If abnormal bleeding persists or is severe, appropriate investigation should take place to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary. Excessive or prolonged bleeding can be controlled by the co-administration of oestrogen. This may be delivered either in the form of a low dose (30 micrograms oestrogen) combined oral contraceptive pill or in the form of oestrogen replacement therapy such as conjugated equine oestrogen (0,625 - 1,25 mg daily). Oestrogen therapy may need to be repeated for 1-2 cycles. Long-term co-administration of oestrogen is not recommended.

Return to Fertility:

There is no evidence that MYTRICON causes permanent infertility. Pregnancies have occurred as early as 14 weeks after a preceding injection, however, in clinical trials, the mean time to return of ovulation was 5,3 months following the preceding injection. Women should be counselled that there is a potential for delay in return to full fertility following use of the method, regardless of the duration of use, however, 83 % of women may be expected to conceive within 12 months of the first "missed" injection (i.e. 15 months after the last injection administered). The median time to conception was 10 months (range 4 - 31) after the last injection.

Cancer Risks:

Long-term case-controlled surveillance of MYTRICON users found no overall increased risk of ovarian, liver, or cervical cancer and a prolonged, protective effect of reducing the risk of endometrial cancer in the population of users.

Breast cancer is rare among women under 40 years of age whether or not they use hormonal contraceptives. Results from some epidemiological studies suggest a small difference in risk of the disease in current and recent users compared with never-users. Any excess risk in current or recent DMPA users is small in relation to the overall risk of breast cancer, particularly in young women (see below), and is not apparent after 10 years since last use. Duration of use does not seem to be important.

Possible number of additional cases of breast cancer diagnosed up to 10 years after stopping injectable progestogens*

Age at last use of DMPA	**No of cases per 10,000 women who are never users**	**Possible additional cases per 10,000 DMPA users**

20	Less than 1	Much less than 1
30	44	2 - 3
40	160	10

*based on use for 5 years"

Weight Gain:

There is a tendency for women to gain weight while on MYTRICON therapy. Studies indicate that over the first 1-2 years of use, average weight gain was 5 - 8 lbs (2,6 kg). Women completing 4-6 years of therapy gained an average of 14 - 16,5 lbs (6 - 7,48 kg). There is evidence that weight is gained as a result of increased fat and is not secondary to an anabolic effect or fluid retention.

Anaphylaxis:

Reports of anaphylactic responses (anaphylactic reactions, anaphylactic shock, anaphylactoid reactions) have been received.

Thromboembolic Disorders:

Should the patient experience pulmonary embolism, cerebrovascular disease or retinal thrombosis while receiving MYTRICON, the medicine should not be re-administered.

Ocular Disorders:

In any patient who develops an acute impairment of vision, proptosis, diplopia, or migraine headache, MYTRICON should be discontinued and the patient carefully evaluated ophthalmologically to exclude the presence of papilloedema or retinal vascular lesions before continuing medication.

Psychiatric Disorders:

Patients with a history of endogenous depression should be carefully monitored. Some patients may complain of premenstrual-type depression while on MYTRICON therapy. Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Abscess formation:

As with any intramuscular injection, especially if not administered correctly, there is a risk of abscess formation at the site of injection, which may require medical and/or surgical intervention.

Fluid retention:

Because MYTRICON may cause fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

Adrenocortical effects:

Clinical suppression of adrenocortical function has not been observed at the dose levels employed for contraception. However, at very high doses (500 mg daily or more) used in the treatment of certain cancers, corticoid-like activity has been reported. Some patients receiving MYTRICON may exhibit suppressed adrenal function. MYTRICON may decrease ACTH and hydrocortisone blood levels.

The high dose of MYTRICON used in the treatment of cancer patients may, in some cases produce Cushingoid symptoms, e.g. moon faces, fluid retention, glucose intolerance, and blood pressure elevation.

Other Precautions:

History or emergence of the following conditions require careful consideration and appropriate investigation: migraine or unusually severe headaches, acute visual disturbances of any kind, pathological changes in liver function and hormone levels.

Patients with thromboembolic or coronary vascular disease should be carefully evaluated before using MYTRICON.

A decrease in glucose tolerance has been observed in some patients treated with progestogens. The mechanism for this decrease is obscure. For this reason, diabetic patients should be carefully monitored while receiving progestogen therapy.

Rare cases of thromboembolism have been reported with use of MYTRICON, but causality has not been established.

The effects of medroxyprogesterone acetate on lipid metabolism have been studied with no clear impact demonstrated. Both increases and decreases in total cholesterol, triglycerides and low-density lipoprotein (LDL) cholesterol have been observed in studies.

The use of MYTRICON appears to be associated with a 15-20 % reduction in serum high density lipoprotein (HDL) cholesterol levels which may protect women from cardiovascular disease. The clinical consequences of this observation are unknown. The potential for an increased risk of coronary disease should be considered prior to use.

Doctors should carefully consider the use of MYTRICON in patients with recent trophoblastic disease before levels of human chorionic gonadotrophin have returned to normal.

Medical practitioners should be aware that pathologists should be informed of the patient's use of MYTRICON if endometrial or endocervical tissue is submitted for examination.

The results of certain laboratory tests may be affected by the use of MYTRICON. These include:

- gonadotrophin levels (decreased),
- plasma progesterone levels (decreased),
- urinary pregnanediol levels (decreased),
- plasma oestrogen levels (decreased),
- plasma cortisol levels (decreased),
- glucose tolerance test, liver function tests (may increase),
- metyrapone test (may increase) - the medical practitioner/laboratory should be informed that, in addition to the endocrine biomarkers listed above, the use of MYTRICON in oncology indications (endometrial and renal carcinoma) may also cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus, the ability of adrenal cortex to respond to adrenocorticotropic hormone (ACTH) should be demonstrated before metyrapone is administered,
- thyroid function tests (protein bound iodine levels may increase and T3 uptake levels may decrease). Coagulation test values for prothrombin (Factor II), and Factors VII, VIII, IX and X may increase,
- hypercalcaemia,
- sex hormone-binding-globulin.

Women should be counselled that MYTRICON does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS). Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

The benefits of contraceptive options and their risks must be evaluated individually for each woman.

If any of the conditions/risk factors mentioned is present, the benefits of MYTRICON use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her medical practitioner. The medical practitioner should then decide on whether MYTRICON use should be discontinued.

4.5 Interaction with other medicines and other forms of interaction

Aminoglutethimide administered concurrently with MYTRICON may significantly depress the bioavailability of medroxyprogesterone acetate.

Interactions with other medicines (including oral anticoagulants) have been reported. The possibility of interaction should be borne in mind in patients receiving concurrent treatment with other medicines.

The clearance of medroxyprogesterone acetate is approximately equal to the rate of hepatic blood flow. Because of this fact, it is unlikely that medicines which induce hepatic enzymes will significantly affect the kinetics of medroxyprogesterone acetate. Therefore, no dose adjustment is recommended in patients receiving medicines known to affect hepatic metabolising enzymes.

Medroxyprogesterone acetate (MPA) is metabolised *in-vitro* primarily by hydroxylation via the CYP3A4. Specific interaction studies evaluating the clinical effects with CYP3A4 inducers or inhibitors on MPA have not been conducted and therefore the clinical effects of CYP3A4 inducers or inhibitors are unknown.

4.6 Fertility, pregnancy and lactation

Pregnancy:

The use of MYTRICON during pregnancy is contraindicated (see section 4.3).

Doctors should check that patients are not pregnant before initial injection of MYTRICON, and also if administration of any subsequent injection is delayed beyond 89 days (12 weeks and five days).

MYTRICON is not recommended as a diagnostic test for pregnancy.

Some reports suggest an association between intra-uterine exposure to progestational medicines in the first trimester of pregnancy and genital abnormalities in male and female foetuses.

Infants from unintentional pregnancies that occur 1-2 months after injection of MYTRICON may be at an increased risk of low birth weight, which in turn is associated with an increased risk of neonatal death.

The attributable risk is low because pregnancies while on MYTRICON are uncommon.

If the patient becomes pregnant while using MYTRICON, the patient should be apprised of the potential hazard to the foetus.

Breastfeeding

Medroxyprogesterone acetate and/or its metabolites are secreted in breast milk. Infants exposed to medroxyprogesterone acetate via breast milk have been studied for developmental and behavioural effects to puberty.

No adverse effects have been noted. However, due to limitations of the data regarding the effects of MPA in breastfed infants less than six weeks old, MYTRICON should be given no sooner than six weeks post-partum when the infant's enzyme system is more developed.

Fertility:

MYTRICON is indicated for the prevention of pregnancy. Women may experience a delay in return to fertility (conception) following discontinuation of MYTRICON (see section 4.4).

4.7 Effects on ability to drive and use machines

MYTRICON may cause headaches and dizziness. Patients should be advised not to drive or operate machinery if affected.

4.8 Undesirable effects

a. Summary of the safety profile

Contraception:

The table below provides a listing of adverse reactions with frequency based on all-causality data from clinical studies that enrolled more than 4 200 women who received DMPA for contraception for up to 7 years. Those most frequently (> 5 %) reported adverse reactions were weight increased (69 %), weight decreased (25 %), headache (16 %), nervousness (11 %), abdominal pain or discomfort (11 %), dizziness (6 %), and decrease in libido (6 %).

The following lists of adverse reactions are listed within the organ system classes, under headings of frequency (number of patients expected to experience the reaction), using the following categories: Frequent, Less frequent and Frequency unknown (ADRs reported post-marketing).

b. Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Neoplasms benign, malignant and unspecified (including cysts	Less frequent	Breast cancer

MedDRA system organ class	Frequency	Adverse reactions
and polyps)		
Blood and lymphatic system disorders	Less frequent	Anaemia, blood disorder
Immune system disorders	Less frequent	Medicine hypersensitivity, anaphylactic reaction, anaphylactoid reaction, angioedema
Endocrine disorders	Less frequent	Prolonged anovulation
Metabolism & Nutrition Disorder	Less frequent	Increased appetite, decreased appetite
Psychiatric disorders	Frequent	Nervousness, depression, libido decreased
	Less frequent	Insomnia, anorgasmia emotional disturbance, effective disorder, irritability, anxiety
	Frequency not known	Severe depression with a higher risk of suicidal thoughts/behaviour and suicide*
Nervous system disorders	Frequent	Headache, dizziness
	Less frequent	Seizure, somnolence paraesthesia, migraine, paralysis, syncope
Ear and Labyrinth Disorder	Less frequent	Vertigo
Cardiac disorders	Less frequent	Tachycardia

MedDRA system organ class	**Frequency**	**Adverse reactions**
Vascular disorders	Less frequent	Hot flush, embolism and thrombosis, deep vein thrombosis, thrombophlebitis, hypertension, varicose veins
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea, pulmonary embolism
Gastrointestinal disorders	Frequent	Abdominal pain, abdominal discomfort, nausea, abdominal distension
	Less frequent	Diarrhoea, rectal haemorrhage, gastrointestinal disorder
Hepatobiliary disorders	Less frequent	Hepatic function abnormal, jaundice, hepatic enzyme abnormal
Skin and subcutaneous tissue disorders	Frequent	Alopecia, acne, rash
	Less frequent	Hirsutism, urticaria, pruritus, chloasma, lipodystrophy acquired*, dermatitis, ecchymosis, scleroderma, skin striae
Musculoskeletal and connective tissue disorders	Frequent	Back pain, pain in extremity
	Less frequent	Arthralgia, muscle spasms, osteoporosis, osteoporotic fractures
Reproductive system and breast disorders	Frequent	Vaginal discharge, breast tenderness, dysmenorrhea, genitourinary tract infection
	Less frequent	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), galactorrhoea, pelvic pain, dyspareunia, suppressed

MedDRA system organ class	Frequency	Adverse reactions
		lactation, vaginitis, amenorrhoea, breast pain, metrorrhagia, menometrorrhagia, menorrhagia, vulvovaginal dryness, breast atropy, ovarian cyst, premenstrual syndrome, endometrial hyperplasia, breast mass, nipple exudate bloody, vaginal cyst, breast enlargement, lack of return to fertility, sensation of pregnancy, prolonged anovulation, virilisation, feminisation
General disorders and administrative site conditions	Frequent	Oedema/ fluid retention, asthenia
	Less frequent	Chest pain, pyrexia, fatigue, injection site reaction*, injection site persistent atrophy/indentation/dimpling*, injection site nodule/lump*, injection site pain/tenderness*, thirst, dysphonia, VIIth nerve paralysis, axillary swelling
Investigation	Frequent	Weight increased, weight decreased
	Less frequent	Bone density decreased, glucose tolerance decreased, cervical smear abnormal

*ADR identified post-marketing

Oncology:

MedDRA system organ class	**Frequency**	**Adverse reactions**
Endocrine disorders	Less frequent	Moon face
Metabolism and nutrition disorders	Frequent	Weight increase
Psychiatric disorders	Frequency not known	Severe depression with a higher risk of suicidal thoughts/behaviour and suicide*
Nervous system disorders	Frequent	Tremor
Vascular disorders	Less frequent	Thrombophlebitis
Skin and subcutaneous tissue disorders	Frequent	Hyperhidrosis
	Frequency not known	Acquired lipodystrophy*
Musculoskeletal and connective tissue disorders	Frequency not known	Osteoporosis including osteoporotic fractures
Reproductive system and breast disorders	Less frequent	Dysfunctional vaginal bleeding (irregular, increased, decreased, spotting)
General disorders and administration site conditions	Frequent	Oedema/fluid retention
	Less frequent	Pyrexia
	Frequency not known	Injection site reaction*, injection site pain/tenderness*, injection site persistent atrophy/indentation/dimpling*, injection site

MedDRA system organ class	Frequency	Adverse reactions
		nodule/lump*
Investigations	Frequency not known	Abnormal liver values

*ADR identified post-marketing

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Nausea, vomiting, somnolence, lower abdominal discomfort, insomnia, fullness and tenderness of the breasts, headache have nee attributed to therapeutic doses. Treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens, ATC code: G03AC06

Category and class: A 21.8.2 Progesterone with or without oestrogens.

Medroxyprogesterone acetate exerts anti-oestrogenic, anti-androgenic and antigonadotrophic effects. DMPA (depot medroxyprogesterone acetate), when administered parenterally at the

recommended dose to women, inhibits the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation and causes thickening of cervical mucus which inhibits sperm entry into the uterus. Medoxyprogesterone acetate suppresses the Leydis cell function in the male i.e suppresses endogenous testosterone production.

The anti-cancer activity of medroxyprogesterone acetate at high doses is unexplained and may be dependent on its effect on the hypothalamic/pituitary/ gonadal axis, oestrogen receptors or the metabolism of steroids at the tissue level. At the high dose levels used in the treatment of certain cancers, corticoid-like activity may be manifested.

5.2 Pharmacokinetic properties

Parenteral medroxyprogesterone acetate (MPA) is a long acting progestational steroid. The long duration of action results from its slow absorption from the injection site. Immediately after injection of 150 mg/ml MPA, plasma levels were 1,7 ± 0,3 nmol/l.

Two weeks later, levels were 6,8 ± 0,8 nmol/l. Concentrations fell to the initial levels by the end of 12 weeks. At lower doses, plasma levels of MPA appear directly related to the dose administered. Serum accumulation over time was not demonstrated. MPA is eliminated via faecal and urinary excretion. Plasma half-life is about six weeks after a single intramuscular injection. At least 11 metabolites have been reported. All are excreted in the urine, some, but not all, conjugated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methylparaben (E218)

Polyethylene glycol 3350

Polysorbate 80

Propylparaben (E216)

Sodium chloride

Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C. Do not freeze.

6.5 Nature and contents of container

MYTRICON is available as 1 ml of suspension filled in a 2 ml clear, type I, glass vial sealed with a grey, bromobutyl rubber stopper and white, flip-off, aluminium seal. Packs of 1 or 25 single dose vials per carton.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7 HOLDER OF CERTIFICATE OF REGISTRATION

VIATRIS HEALTHCARE (PTY) LTD

4 Brewery Street

Isando

Gauteng, 1601

Republic of South Africa

8 REGISTRATION NUMBER

52/21.8.2/0991

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 November 2021

10 DATE OF REVISION OF THE TEXT

04 December 2024