1. Name of the medicinal product

VERASAFE INJECTION (Medroxyprogesterone Acetate Injectable Suspension USP 150mg/ml)

2. Qualitative and Quantitative Composition

Each ml contains:
Medroxyprogesterone Acetate USP …….150mg
Excipients ……..…….q.s
Water for Injection USP……..…….q.s.

Sr. No	Ingredients	Spec.	Quantity mg per ml	Reason for inclusion
1	Medroxyprogesterone Acetate	USP	150.0	API
2	Propylene Glycol	USP	150.0	Solvent
3	Polymeg 3350	IH	30.00	Solvent
4	Polysorbate 80	USP	2.00	Suspending Agent
5	Methyl Paraben	USP	1.50	Antimicrobial preservative.
6	Propyl Paraben	USP	0.15	Antimicrobial preservative.
7	Sodium Chloride	USP	9.00	Tonicity agent.
8	Water for Injection	USP	q.s 1.0 ml	Vehicle

3. Pharmaceutical Form

Sterile Injectable Suspension for IM use only

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Progestogen: for contraception.

Medroxyprogesterone Acetate Injectable Suspension USP is indicated for long-term female contraception. Each injection prevents ovulation and provides contraception for at least 12 weeks (+/- 5 days). However, it should be taken into consideration that the return to fertility (ovulation) may be delayed for up to one year (see section 4.4).

Medroxyprogesterone Acetate Injectable Suspension USP is suitable for use in women who have been appropriately counselled concerning the likelihood of menstrual disturbance and the potential for a delay in return to full fertility.

Medroxyprogesterone Acetate Injectable Suspension USP may also be used for short-term contraception in the following circumstances:

1) For partners of men undergoing vasectomy, for protection until the vasectomy becomes effective.

2) In women who are being immunised against rubella, to prevent pregnancy during the period of activity of the virus.

3) In women awaiting sterilisation.

Since loss of bone mineral density (BMD) may occur in females of all ages who use Medroxyprogesterone Acetate Injectable Suspension USP injection long-term (see section 4.4), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered before giving the injection of Medroxyprogesterone Acetate Injectable Suspension USP .

Paediatric population (12-18 years)

In adolescents, Medroxyprogesterone Acetate Injectable Suspension USP may be used, but **only** after other methods of contraception have been discussed with the patient and considered unsuitable or unacceptable.

It is of the greatest importance that adequate explanations of the long-term nature of the product, of its possible side-effects and of the impossibility of immediately reversing the effects of each injection are given to potential users and that every effort is made to ensure that each patient receives such counselling as to enable her to fully understand these explanations. Patient information leaflets are supplied by the manufacturer. It is recommended that the doctor uses these leaflets to aid counselling of the patient before giving the injection of Medroxyprogesterone Acetate Injectable Suspension USP.

4.2 Posology and method of administration

Route of administration:

Posology

Adults:

First injection: To provide contraceptive cover in the first cycle of use, an injection of 150 mg i.m. should be given during the first five days of a normal menstrual cycle. If the injection is carried out according to these instructions, no additional contraceptive cover is required.

Post Partum: To increase assurance that the patient is not pregnant at the time of first administration, this injection should be given within 5 days post-partum if not breast-feeding.

There is evidence that women prescribed Medroxyprogesterone Acetate Injectable Suspension in the immediate puerperium can experience prolonged and heavy bleeding. Because of this, the drug should be used with caution in the puerperium. Women who are considering use of the product immediately following delivery or termination should be advised that the risk of heavy or prolonged bleeding may be

increased. Doctors are reminded that in the non-breast-feeding, post-partum patient, ovulation may occur as early as week 4.

If the puerperal woman will be breast-feeding, the initial injection should be given no sooner than six weeks post-partum, when the infant's enzyme system is more fully developed. Further injections should be given at 12 week intervals.

Further doses: These should be given at 12 week intervals, however, as long as the injection is given no later than five days after this time, no additional contraceptive measures (e.g. barrier) are required. (N.B. For partners of men undergoing vasectomy, a second injection of 150 mg I.M. 12 weeks after the first may be necessary in a small proportion of patients where the partner's sperm count has not fallen to zero.) If the interval from the preceding injection is greater than 89 days (12 weeks and five days) for any reason, then pregnancy should be excluded before the next injection is given and the patient should use additional contraceptive measures (e.g. barrier) for fourteen days after this subsequent injection.

Elderly: Not appropriate.

Paediatric population:

Medroxyprogesterone Acetate Injectable Suspension is not indicated before menarche (see section 4.1 Therapeutic Indications)

Data in adolescent females (12-18 years) is available for IM administration of medroxyprogesterone acetate (MPA) (see Section 4.4 Special Warnings and Precautions for Use and section 5.1 Pharmacodynamic properties). Other than concerns about loss of BMD, the safety and effectiveness of Medroxyprogesterone Acetate Injectable Suspension is expected to be the same for adolescents after menarche and adult females.

Switching from other Methods of Contraception

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

Hepatic Insufficiency

The effect of hepatic disease on the pharmacokinetics of Medroxyprogesterone Acetate Injectable Suspension is unknown. As Medroxyprogesterone Acetate Injectable Suspension largely undergoes hepatic elimination it may be poorly metabolised in patients with severe liver insufficiency (see section 4.3).

Renal Insufficiency

The effect of renal disease on the pharmacokinetics of Medroxyprogesterone Acetate Injectable

Suspension is unknown. No dosage adjustment should be necessary in women with renal insufficiency, since Medroxyprogesterone Acetate Injectable Suspension is almost exclusively eliminated by hepatic metabolism.

Method of Administration

The sterile aqueous suspension of Medroxyprogesterone Acetate Injectable Suspension should be vigorously shaken just before use to ensure that the dose being given represents a uniform suspension of Medroxyprogesterone Acetate Injectable Suspension.

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:

Hypersensitivity to Medroxyprogesterone acetate or to any of excipients listed in section 6.1.

Medroxyprogesterone Acetate Injectable Suspension should not be used during pregnancy, either for diagnosis or therapy.

Medroxyprogesterone Acetate Injectable Suspension is contraindicated as a contraceptive at the above dosage in known or suspected hormone-dependent malignancy of breast or genital organs.

Medroxyprogesterone Acetate Injectable Suspension is contraindicated in patients with the presence or history of severe hepatic disease whose liver function tests have not returned to normal.

Whether administered alone or in combination with oestrogen, Medroxyprogesterone Acetate Injectable Suspension should not be employed in patients with abnormal uterine bleeding until a definite diagnosis has been established and the possibility of genital tract malignancy eliminated.

4.4 Special warnings and precautions for use

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 product. 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.

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 (Medroxyprogesterone Acetate Injectable Suspension) in adolescent females showed that its use was associated with a statistically significant decline in BMD from baseline. 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 4.6 years at the femoral neck (see section 5.1). 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, Medroxyprogesterone Acetate Injectable Suspension 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 (see section 5.1 – Relationship of fracture incidence to use of DMPA-IM by women of reproductive age).

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 Medroxyprogesterone Acetate Injectable Suspension.

Significant risk factors for osteoporosis include:

• Alcohol abuse and/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

For further information on BMD changes in both adult and adolescent females, refer to section 5.1.

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 Medroxyprogesterone Acetate Injectable Suspension 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 Medroxyprogesterone Acetate Injectable Suspension 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 Medroxyprogesterone Acetate Injectable Suspension 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.

4.5 Interaction with other medicinal products and other forms of interaction

Aminoglutethimide administered concurrently with Medroxyprogesterone Acetate Injectable Suspension may significantly depress the bioavailability of Medroxyprogesterone Acetate Injectable Suspension.

Interactions with other medicinal treatments (including oral anticoagulants) have rarely been reported, but causality has not been determined. The possibility of interaction should be borne in mind in patients receiving concurrent treatment with other drugs.

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

Medroxyprogesterone acetate (MPA) is metabolized in-vitro primarily by hydroxylation via the CYP3A4. Specific drug-drug 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

Fertility:

Medroxyprogesterone Acetate Injectable Suspension is indicated for the prevention of pregnancy.

Women may experience a delay in return to fertility (conception) following discontinuation of Medroxyprogesterone Acetate Injectable Suspension (see section 4.4).

Pregnancy:

Medroxyprogesterone Acetate Injectable Suspension is contraindicated in pregnancy.

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

Infants from accidental pregnancies that occur 1-2 months after injection of Medroxyprogesterone Acetate Injectable Suspension 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 such pregnancies are uncommon.

Children exposed to medroxyprogesterone acetate *in utero* and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

Lactation:

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, Medroxyprogesterone Acetate Injectable Suspension should be given no sooner than six weeks post-partum when the infant's enzyme system is more developed.

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive or operate machinery if affected.

4.8 Undesirable effects

The table below provides a listing of adverse drug reactions with frequency based on all-causality data from clinical studies that enrolled more than 4200 women who received DMPA for contraception for up to 7 years. Those most frequently (>5%) reported adverse drug 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:

Very common (≥1/10)

Common (≥1/100 to <1/10);

Uncommon (≥1/1000 to <1/100);

Rare (≥1/10,000 to <1/1000);

Very rare (<1/10,000);

Not known (cannot be estimated from the available data)

System Organ Class	Very Common ≥1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Rare ≥ 1/10,000 to < 1/1000
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)				Breast cancer
Blood and lymphatic system disorders				Anaemia, Blood disorder
Immune system disorders			Drug hypersensitivity	Anaphylactic reaction, Anaphylactoid reaction, Angioedema
Metabolism & Nutrition Disorder			Increased appetite, decreased appetite	
Psychiatric disorders	Nervousness	Depression, Libido decreased	Insomnia	Anorgasmia, Emotional disturbance, Effective disorder, Irritability, Anxiety
Nervous system disorders	Headache	Dizziness	Seizure, Somnolence, Paraesthesia	Migraine, Paralysis, Syncope
Ear and Labyrinth Disorder				Vertigo
Cardiac disorder				Tachycardia
Vascular disorders			Hot flush	Embolism and thrombosis, Deep vein thrombosis, Thrombophlebitis, Hypertension, Varicose veins
Respiratory, thoracic, and mediastinal disorders			Dyspnoea	Pulmonary embolism
Gastrointestinal disorders	Abdominal pain, Abdominal discomfort	Nausea, Abdominal distension		Rectal haemorrhage, Gastrointestinal disorder

Hepatobiliary disorders			Hepatic function abnormal	Jaundice, Hepatic enzyme abnormal
Skin and subcutaneous tissue disorders		Alopecia, Acne, Rash	Hirsutism, Urticaria, Pruritus, Chloasma	Lipodystrophy acquired*, Dermatitis, Ecchymosis, Scleroderma, Skin striae
Musculoskeletal and connective tissue disorders		Back pain, Pain in extremity		Arthralgia, Muscle spasms, Osteoporosis, Osteoporotic fractures
Reproductive system and breast disorders		Vaginal discharge, Breast tenderness, Dysmenorrhea, Genitourinary tract infection	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting, Galactorrhoea Pelvic pain, Dyspareunia, Suppressed 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
General disorders and administration site conditions		Oedema/Fluid retention, Asthenia	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	Weight increased, Weight decreased			Bone density decreased, Glucose tolerance decreased, Cervical smear abnormal

*ADR identified post-marketing

4.9 Overdose

No positive action is required other than cessation of therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Progestogens, ATC code: G03AC06

Medroxyprogesterone acetate exerts anti-oestrogenic, anti-androgenic and antigonadotrophic effects.

Mechanism of action

DMPA, 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.

BMD Changes in Adult Women

A study comparing changes in BMD in women using DMPA SC with women using DMPA-IM showed similar BMD loss between the two groups after two years of treatment. Mean percent changes in BMD in the DMPA-SC group are listed in Table 1.

Table 1. Mean Percent Change (with 95% Confidence Intervals) from Baseline in BMD in Adult Women Using DMPA-SC by Skeletal Site

Time on Treatment	Lumbar Spine		Total Hip		Femoral Neck	
	N	Mean % Change (95% CI)	N	Mean % Change (95% CI)	N	Mean % Change (95% CI)
1 year	166	-2.7 (-3.1 to -2.3)	166	-1.7 (-2.1 to -1.3)	166	-1.9 (-2.5 to -1.4)
2 year	106	- 4.1 (-4.6 to -3.5)	106	-3.5 (-4.2 to -2.7)	106	-3.5 (-4.3 to -2.6)

CI = Confidence Interval

In another controlled, clinical study adult women using DMPA-IM for up to 5 years showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of –2.9%, -4.1%, -4.9%, -4.9% and –5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar. Please refer to Table 2 below for further details.

After stopping use of DMPA-IM, BMD increased towards baseline values during the post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery.

In the same clinical study, a limited number of women who had used DMPA-IM for 5 years were followed-up for 2 years after stopping DMPA-IM use. BMD increased towards baseline values during the 2-year post-therapy period. Two years after stopping DMPA injections, mean BMD had increased at all 3 skeletal sites but deficits remained.

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.

5.3 Preclinical safety data

No data held

6. Pharmaceutical particulars

6.1 List of excipients

Propylene Glycol

Polymeg 3350

Polysorbate 80

Methyl Paraben

Propyl Paraben

Sodium Chloride

Water for Injection

6.2 Incompatibilities

None known.

6.3 Shelf life:

36 months from the date of manufacturing.

6.4 Special precautions for storage:

Store below 30°C. Do not freeze. Protect from light.

6.5 Nature and contents of container:

Pack Style: 2 ml transparent tubular flint vial with 13 mm plain unslotted rubber stopper & 13 mm Flip Top Royal Blue Aluminium Seal is used as primary packaging material for packing of Medroxyprogesterone Acetate Injectable Suspension USP (150 mg/ml).
Secondary Packing: One vial is packed in a carton along with pack insert.

6.6 Special precautions for disposal

None

7. Applicant / Manufacturer

SHREE VENKATESH INTERNATIONAL LIMITED

Block No. 311, Kosamba Pardi Road, Village: Nandav,

Taluka: Mangrol, Dist. Surat – 394125, Gujarat- INDIA