REACOTEN V6 Clotrimazole

Summary of Product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

REACOTEN V6 Clotrimazole Vaginal Tablets 100 mg, 100 mg per Tablet, Uncoated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Clotrimazole	B.P.	100 mg
Excipients		Q.S.

For a full list of excipients, refer section 6.1

3. PHARMACEUTICAL FORM

Uncoated Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

REACOTEN V6 Clotrimazole Vaginal Tablets is indicated for luteal support as part of an AssistedReproductive Technology (ART) treatment program for infertile women.

4.2 Posology and method of administration

Posology Adults: The dose of REACOTEN V6 Clotrimazole Vaginal Tablets is 100 mg administered vaginally three times daily starting at oocyte retrieval. The administration of REACOTEN V6 Clotrimazole Vaginal Tablets should be continued for 30 days, if pregnancy has been confirmed.
Paediatric population: There is no relevant use of Lutinus in the paediatric population.
Elderly: No clinical data have been collected in patients over age 65.
Use in special populations
There is no experience with use of REACOTEN V6 Clotrimazole Vaginal Tablets in patients with impairedliver or renal function.

Method of Administration: REACOTEN V6 Clotrimazole Vaginal Tablets is to be placed directly into thevagina by the applicator provided.

4.3 Contraindications

REACOTEN V6 Clotrimazole Vaginal Tablets should not be used in individuals with any of thefollowing conditions:

- Hypersensitivity to the active substance or to any of the excipients.
- Undiagnosed vaginal bleeding
- Known missed abortion or ectopic pregnancy
- Severe hepatic dysfunction or disease
- Known or suspected breast or genital tract cancer
- Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events
- Porphyria.

4.4 Special warnings and precautions for use

REACOTEN V6 Clotrimazole Vaginal Tablets should be discontinued if any of the following conditions are suspected:
Myocardial infarction, cerebrovascular disorders, arterial or venous thromboembolism (venous thromboembolism or pulmonary embolism), thrombophlebitis, or retinal thrombosis.
Cautious use in patients with mild to moderate hepatic dysfunction.
Patients with a history of depression need to be closely observed. Consider discontinuation if symptoms worsen.
Because progesterone may cause some degree of fluid retention, conditions that might be influenced by this factor (e.g. epilepsy, migraine, asthma, cardiac or renal dysfunction) require careful observation.
A decrease in insulin sensitivity and thereby in glucose tolerance has been observed in a small number of patients on oestrogen-progestogen combination drugs. The mechanism of this decrease is not known. For this reason, diabetic patients should be carefully observed while receiving progesterone therapy.
Sex steroid use may also increase the risk of retinal vascular lesions. To prevent these latter complications, caution is to be taken in users >35 years, in smokers, and in those with risk factors for atherosclerosis. Use should be terminated in case of transient ischemic events, appearance of sudden severe headaches, or vision impairments related to papillary edema or retinal hemorrhage.
Abrupt discontinuation of progesterone dosing may cause increased anxiety, moodiness, and increased sensibility to seizures.
Before starting treatment with REACOTEN V6 Clotrimazole Vaginal Tablets, the patient and her partner should be assessed by a doctor for causes of infertility.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs known to induce the hepatic cytochrome-P450-3A4 system (e.g. rifampicin, carbamazepine or St. John's wort (Hypericum perforatum)-containing herbal products) may increase the elimination rate and thereby decrease the bioavailability of progesterone.
In contrast ketoconazole and other inhibitors of cytochrome P450-3A4 may decrease elimination rate and thereby increase the bioavailability of progesterone.
The effect of concomitant vaginal products on the exposure of progesterone from REACOTEN V6 Clotrimazole Vaginal Tablets has not been assessed. However, REACOTEN V6 Clotrimazole Vaginal Tablets is not recommended for use with other vaginal products (such as antifungal products) as this may alter progesterone release and absorption from the vaginal tablet.

4.6 Pregnancy and lactation

Pregnancy: REACOTEN V6 Clotrimazole Vaginal Tablets vaginal tablets are only indicated during the first trimester of pregnancy for use as part of an assisted reproduction (ART) regimen.
There is yet limited and inconclusive data on the risk of congenital anomalies, including genital abnormalities in male or female infants, following intrauterine exposure during

pregnancy.

In the pivotal trial, the rate of foetal anomalies following 10-week exposure to REACOTEN V6 Clotrimazole Vaginal Tablets 100 mg TID was 4.5% in the REACOTEN V6 Clotrimazole Vaginal Tablets TID group, a total of 7 cases of foetal anomalies (i.e. oesophageal fistula, underdeveloped right ear with hypospadias, small aorta/ valvular regurgitation/ deviated septum, hand deformity, cleft palate/cleft lip, hydrocephalus and holoprosencephaly/ proboscis/ polydactylia) were seen in 404 patients. The rate of foetal anomalies observed during the clinical trial is comparable with the event rate described in the general population, although the total exposure is too low to allow conclusions to be drawn.

During the conduct of the pivotal clinical trial, the number of spontaneous abortions and ectopic pregnancies associated with the use of REACOTEN V6 Clotrimazole Vaginal Tablets100 mg TID were 5.4% and 1%, respectively.

Breast-feeding: Detectable amounts of progesterone have been identified in the milk of mothers. Therefore REACOTEN V6 Clotrimazole Vaginal Tablets should not be used during lactation.

4.7 Effects on ability to drive and use machines

REACOTEN V6 Clotrimazole Vaginal Tablets has minor or moderate influence on the ability to drive and use machines. Progesterone may cause drowsiness and/or dizziness; therefore caution is advised in drivers and users of machines.

4.8 Undesirable effects

The most frequently reported adverse drug reactions during treatment with REACOTEN V6 Clotrimazole Vaginal Tablets in IVF patients during clinical trials are headache, vulvovaginal disorders and uterine spasm, reported in 1.5%, 1.5% and 1.4% subjects, respectively. The table below displays the main adverse drug reactions in women treated with REACOTEN V6 Clotrimazole Vaginal Tablets in the clinical trial distributed by system organ classes (SOCs) and frequency.

System Organ Class (SOC)	**Common (> 1/100 and < 1/10)**	**Uncommon (> 1/1000 and < 1/100)**	**Not known*** ** (cannot be estimated from the available data)
Nervous system disorders	Headache	Dizziness,Insomnia	Fatigue
Gastrointestinal disorders	Abdominal distension, Abdominal pain Nausea	Diarrhoea,Constipation	Vomiting
Skin and subcutaneous tissue disorders		Urticaria, Rash	Hypersensitivity reactions
Reproductive system and breast disorders	Uterine spasm	Vulvovaginal disorders*, Vaginal mycosis Breast disorders**, Pruritus genital	

General disorders and administration site conditions		Oedema peripheral	

* Vulvovaginal disorders such as vulvovaginal discomfort, vaginal burning sensation, vaginal discharge, vulvovaginal dryness and vaginal haemorrhage, have been reported following use of REACOTEN V6 Clotrimazole Vaginal Tablets, with cumulative reporting frequency of 1.5%.
** Breast disorders, such as breast pain, breast swelling and breast tenderness have been reported in the clinical trial as single cases, with cumulative reporting frequency of 0.4%.
***Cases seen during post marketing experience.

4.9 Overdose

High doses of progesterone may cause drowsiness.
Treatment of over dosage consists of discontinuation of REACOTEN V6 Clotrimazole Vaginal Tablets together with institution of appropriate symptomatic and supportive care.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system; Progestogens; Pregnen-(4) derivatives
ATC code: G03DA04.
Mechanism of action: Progesterone is a naturally occurring steroid that is secreted by the ovary, placenta, and adrenal gland. In the presence of adequate estrogen, progesterone transforms a proliferative endometrium into a secretory endometrium. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy.

5.2 Pharmacokinetic properties

Absorption:
Progesterone serum concentrations increased following the administration of the REACOTEN V6 Clotrimazole Vaginal Tablets vaginal tablets in 12 healthy premenopausal females. On day 1 of treatment, the mean Cmax 19.8 ± 2.9 ng/mL with a Tmax of 17.3 ± 3.0 hours after administration of REACOTEN V6 Clotrimazole Vaginal Tablets three times daily 8 hours apart.
On multiple dosing, steady state concentrations were attained within approximately 1 day after initiation of treatment with REACOTEN V6 Clotrimazole Vaginal Tablets. Trough values of
10.9 ± 2.7 ng/mL were observed with an AUC0-24 of 436 ± 43 ng*hr/mL on Day 5.
Distribution:
Progesterone is approximately 96 % to 99 % bound to serum proteins, primarily to serum albumin and corticosteroid binding globulin.
Biotransformation
Progesterone is metabolized primarily by the liver largely to pregnanediols and pregnanolones. Pregnanediols and pregnanolones are conjugated in the liver to glucuronide and sulfate metabolites. Progesterone metabolites that are excreted in the bile may be deconjugated and may be further metabolized in the gut via reduction, dehydroxylation, and epimerization.

Elimination:
Progesterone undergoes renal and biliary elimination.

Following injection of labelled progesterone, 50-60% of the excretion of metabolites occurs via the kidney; approximately 10% occurs via the bile and faeces. Overall recovery of the labelled material accounts for 70% of an administered dose. Only a small portion of unchanged progesterone is excreted in the bile.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of repeated dose toxicity, genotoxicity and carcinogenicity.
Clotrimazole was not teratogenic in reproductive toxicity studies in mice, rats and rabbits. In rats high oral doses were associated with maternal toxicity, embryotoxicity, reduced fetal weights and decreased pup survival.

In rats clotrimazole and/or its metabolites were secreted into milk at levels higher than in plasma by a factor of 10 to 20 at 4 hrs after administration, followed by a decline to a factor of 0.4 by 24 hrs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose phosphate
Lactose
Hydroxy propyl methyl cellulose
Polyvinyl pyrrolidone (PVP K – 30)
Sodium Starch Glycolate
Magnesium Stearate
Purified Talc
Sodium Bicarbonate
Citric Acid Monohydrate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a dark, dry place, not exceeding 30ºC temp.
Keep out of the reach and sight of children.

6.5 Nature and contents of container

6 Tablets Packed in Jar.

6.6 Special precautions for disposal and other handling

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/MANUFACTURER

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