

New Zealand Datasheet

1 PRODUCT NAME

SITERONE

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Cyproterone acetate tablets 50 mg, 100 mg

3 PHARMACEUTICAL FORM

SITERONE 50 mg tablets are white, round, flat, 8.50mm diameter, blank on one side and scored on the other.

SITERONE 100 mg tablets are white, capsule shaped, unscored, 15 mm long, 4.6 mm wide, plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indications in the man

- Antiandrogen treatment in inoperable carcinoma of the prostate
- Reduction of drive in sexual deviations

Indications in the woman

- Severe signs of androgenization, e.g. very severe hirsutism in the female, severe androgenetic alopecia, often attended by severe forms of acne and/or seborrhoea.

4.2 Dose and method of administration

Dosage in the man

Antiandrogen treatment in inoperable carcinoma of the prostate

To eliminate the effect of adrenocortical androgens after orchiectomy: one SITERONE 100 mg tablet once or twice daily (100-200 mg). Without orchiectomy: one SITERONE 100 mg tablet twice to three times daily (200-300 mg).

The tablets are to be taken with some liquid after meals. Treatment should not be interrupted nor the dosage reduced after improvement or remissions have occurred. To reduce the initial increase of male sex hormones in treatment with LH-RH agonists: Initially one SITERONE 100 mg tablet twice daily (200 mg) alone for 5 - 7 days followed by one SITERONE 100 mg tablet twice daily (200 mg) for 3 - 4 weeks together with an LH-RH agonist in the dosage recommended by the manufacturer.

To eliminate the effect of adrenocortical androgens in treatment with LH-RH agonists: Continuation of the antiandrogen therapy with one SITERONE 100 mg tablet once to twice daily (100 – 200 mg).

Reduction of drive in pathologically altered or increased sexuality

Generally, the treatment is started with one 50 mg tablet twice daily. It may be necessary to increase the dose to two 50 mg tablets twice daily or even two 50 mg tablets three times daily for a short period of time. When a satisfactory result is achieved, an attempt should be made to maintain the therapeutic effect with the lowest possible dose. Quite often 1/2 a 50 mg tablet twice daily is sufficient. When establishing the maintenance dose or when discontinuing the preparation, one should not reduce the dosage abruptly, but gradually. To

this end, the daily dose should be reduced by one 50 mg tablet or, better, 1/2 a 50 mg tablet, at intervals of several weeks.

To stabilise the therapeutic effect, it is necessary to take SITERONE over a protracted period of time, if possible, with the simultaneous use of psychotherapeutic measures.

Dosage in the Woman

Pregnant women must not take SITERONE. Therefore, pregnancy must be excluded before the start of therapy.

In women of childbearing age, the treatment is commenced on the 1st day of the cycle. Only women with amenorrhoea can start the treatment immediately. In this case, the first day of treatment is to be regarded as the 1st day of the cycle and the following recommendations then observed as normal.

One tablet of SITERONE 100 mg is to be taken daily with some liquid after a meal from the 1st to the 10th day of the cycle (for 10 days). In addition, these women receive a progestogen-oestrogen preparation, e.g. from the 1st to the 21st day of the cycle, to provide the necessary contraceptive protection and to stabilise the cycle.

Women receiving the cyclical combined therapy should keep to a particular time of the day for tablet taking. If more than 12 hours elapse from this time, contraceptive protection in this cycle may be reduced. The use of SITERONE and the progestogen-oestrogen preparation should nevertheless be continued according to the instructions, ignoring the missed tablet or tablets, in order to avoid premature bleeding in this cycle. However, a non-hormonal method of contraception (with the exception of the rhythm and temperature methods) is to be employed additionally for the rest of the cycle.

A 7-day tablet-free interval is observed after 21 days during which time withdrawal bleeding occurs. Exactly 4 weeks after the first course was started i.e. on the same day of the week, the next cyclical course of combined treatment is started, regardless of whether bleeding has stopped or not. If no bleeding occurs, the treatment must be interrupted and pregnancy must be excluded before tablet taking is resumed.

Following clinical improvement, the daily dose of SITERONE during the first 10 days of the combined treatment with the progestogen-oestrogen preparation can be reduced to one or ½ 50 mg tablet. Perhaps the progestogen-oestrogen preparation alone will be sufficient.

In postmenopausal or hysterectomised patients, SITERONE may be administered alone. According to the severity of the complaints, the average dose should be one to ½ tablet 50 mg of SITERONE once daily for 21 days, followed by a 7-day tablet-free interval.

Do not halve the 100 mg tablet. Dose equivalence when the tablet is divided has not been established.

4.3 Contraindications

- Pregnancy
- Lactation
- Liver diseases
- A history of jaundice or persistent itching during a previous pregnancy
- A history of herpes of pregnancy
- Dubin-Johnson syndrome
- Rotor syndrome

- Previous or existing liver tumours (in carcinoma of the prostate only if these are not due to metastases)
- Wasting diseases (with the exception of carcinoma of the prostate)
- Severe chronic depression
- Previous or existing thromboembolic processes
- Severe diabetes with vascular changes
- Sickle-cell anaemia
- Meningioma or a history of meningioma
- Hypersensitivity to any of the components of SITERONE

In patients with inoperable prostatic carcinoma presenting with a history of thromboembolic processes or suffering from sickle-cell anaemia or from severe diabetes with vascular changes, the risk: benefit ratio must be considered carefully in each individual case before SITERONE is prescribed.

With regard to the cyclical combination therapy of severe signs of androgenization, attention is also drawn to the data on contraindications contained in the product information for progestogen-oestrogen preparation, which is used in addition to SITERONE.

4.4 Special warnings and precautions for use

The drive-reducing effect of SITERONE can be diminished under the disinhibitory influence of alcohol.

SITERONE should not be given before the conclusion of puberty since an unfavourable influence on longitudinal growth and the still unstabilised axes of endocrine function cannot be ruled out.

During treatment, liver function, adrenocortical function and the red blood-cell count should be checked regularly.

Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, which have been fatal in some cases, has been reported in patients treated with 100 – 300 mg cyproterone acetate. Most reported cases are in men with prostatic cancer although cases involving women and patients treated with lower doses have been reported.

Toxicity is dose-related and develops, usually, several months after treatment has begun. Liver function tests should be performed pre-treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, cyproterone acetate should normally be withdrawn, unless the hepatotoxicity can be explained by another cause, e.g. metastatic disease, in which case cyproterone acetate should be continued only if the perceived benefit outweighs the risk.

As with other sex steroids, benign and malignant liver changes have been reported in isolated cases. In very rare cases, liver tumours may lead to life-threatening intra-abdominal haemorrhage. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be included in the differential-diagnostic considerations.

Strict medical supervision is necessary if the patient suffers from diabetes.

Meningiomas: The occurrence of (multiple) meningiomas has been reported in association with longer term use (years) of cyproterone acetate at doses of 25 mg/day and above. If a patient treated with SITERONE is diagnosed with meningioma treatment with SITERONE must be stopped.

A sensation of shortness of breath may occur in individual cases under high-dosed treatment with SITERONE. The differential diagnosis in such cases must include the stimulating effect on breathing known for progesterone and synthetic progestogens which is accompanied by hypocapnia and compensated respiratory alkalosis and which is not considered to require treatment.

In extremely rare cases, the occurrence of thromboembolic events has been reported in temporal association with the use of SITERONE although a causal relationship seems to be questionable. Rarely cases of osteoporosis have also been reported.

The therapy of sexual deviations with SITERONE is usually ineffective in chronic alcoholism.

Before the start of therapy, a thorough general medical and gynaecological examination (including the breasts and a cytological smear of the cervix) should be carried out in women. Pregnancy must be excluded in women of childbearing age.

If, during the combined treatment, persistent or recurrent bleeding occurs at irregular intervals, a gynaecological examination must be carried out to exclude organic disease. With regard to the necessary additional use of the progestogen-oestrogen preparation, attention is drawn to all the data contained in the product information for this preparation.

4.5 Interaction with other medicines and other forms of interaction

The requirement for oral antidiabetics or insulin can change.

4.6 Fertility, pregnancy and lactation

Pregnancy

The administration of SITERONE during pregnancy is contraindicated.

Breast feeding

The administration of SITERONE during lactation is contraindicated. About 0.2% of the dose is excreted with the breast milk.

Fertility

Not applicable.

4.7 Effects on ability to drive and use machines

It should be pointed out to patients whose occupation demands great concentration (e.g. road users, machine operators) that SITERONE can lead to tiredness and diminished vitality and can impair the ability to concentrate.

4.8 Undesirable effects

Treatment of men:

The most commonly observed side effects in male patients treated with cyproterone are decreased libido, erectile dysfunction and reversible inhibition of spermatogenesis.

The most serious side effects in patients treated with cyproterone are liver toxicity, benign and malignant liver tumors, which can lead to intra-abdominal bleeding and thromboembolic events.

The frequency of reported adverse reactions is summarized in the table below. Frequency is defined as very common (> 1/10), common (> 1/100, <1/10), less common (> 1/1000,

<1/100), rare (> 1/10,000, <1 / 1000) and very rare (<1/10 000). Adverse reactions that are only identified during post-marketing surveys and for which the frequency could not be calculated are listed under "no known frequency".

System organ class	Very common (> 1/10)	Common (> 1/100, <1/10)	Uncommon (> 1/1000, <1/100)	Rare (> 1/10,000, <1/1000)	Very rare (<1/10 000)	No known frequency
Neoplasms benign, malignant and unspecified including cysts and polyps					Benign and malignant liver tumors *)	Meningiomas. §) *)
Blood and lymphatic system disorders						Anemia*)
Immune system disorders				Hypersensitivity		
Metabolism and nutrition disorders		Weight gain Weight loss				
Psychiatric disorders	Reduced libido Erectile dysfunction	Depressive mood Restlessness (temporary) Diminished vitality				
Vascular disorders						Thromboembolic events *) **)
Respiratory, thoracic and mediastinal disorders		Dyspnea *)				
Gastrointestinal disorders						Intra-abdominal bleeding *)
Hepato-biliary disorders		Liver toxicity, incl. jaundice, hepatitis, liver failure *)				
Skin and subcutaneous tissue disorders			Rash			
Musculoskeletal system and connective tissue disorders						Osteoporosis
Reproductive system disorders	Reversible inhibition of spermatogenesis	Gynecomastia				
General disorders and administration site conditions		Fatigue Hot flushes Sweating				

§) See section 4.3.

*) For further information see section 4.4.

**) Causal relationship with cyproterone has not been established.

In male patients treated with cyproterone, sexual drive and potency are reduced and gonadotropic function is inhibited. These changes are reversible upon completion of treatment.

After several weeks of treatment, spermatogenesis is inhibited as a result of the antiandrogenic and antigonadotropic effect of cyproterone. Spermatogenesis gradually recovers within a few months after the end of treatment.

In male patients, treatment with cyproterone can cause gynecomastia (sometimes even with sensitivity to the nipple), which usually subsides after discontinuation.

As with other antiandrogen therapy, long-term treatment with cyproterone can cause osteoporosis in men due to androgen deficiency.

Prevalence of meningioma has been reported in association with prolonged use (several years) of cyproterone acetate at doses of 25 mg / day and beyond (see sections 4.3 and 4.4).

Treatment of women:

The most commonly reported side effects in female patients treated with cyproterone 50 mg are spotting, weight gain and depressed mood.

The most serious side effects in patients treated with cyproterone are liver toxicity, benign and malignant liver tumors, which can lead to intra-abdominal bleeding and thromboembolic events.

The reported side effects are shown in the table below and are based on data obtained after marketing and cumulative experience where a side effect frequency could not be calculated.

System organ class	Very common (> 1/10)	Common (> 1/100, <1/10)	Uncommon (> 1/1000, <1/100)	Rare (> 1/10,000, <1/1000)	Very rare (<1/10 000)	No known frequency
Neoplasms benign, malignant and unspecified including cysts and polyps						Benign and malignant liver tumors *), meningiomas
Immune system disorders						Hypersensitivity reaction
Metabolism and nutrition disorders						Weight gain Weight loss
Psychiatric disorders						Depressed mood. Restlessness (temporary) Increased libido Lower libido Diminished vitality
Vascular disorders						Thromboembolic events *) **)
Respiratory, thoracic and mediastinal disorders						Dyspnea *)
Gastrointestinal disorders						Intra-abdominal bleeding *)
Hepato-biliary disorders						Liver toxicity, incl. jaundice, hepatitis, liver failure *)
Skin and						Rash

System organ class	Very common (> 1/10)	Common (> 1/100, <1/10)	Uncommon (> 1/1000, <1/100)	Rare (> 1/10,000, <1/1000)	Very rare (<1/10 000)	No known frequency
subcutaneous tissue disorders						
Reproductive system disorders						Ovulation suppression, breast tenderness, spotting *)
General disorders and administration site conditions						Tiredness

§) See section 4.3.

*) For further information see section 4.4.

***) Causal relationship with cyproterone has not been established.

In women, ovulation is inhibited during combination therapy, leading to infertility.

In women who are on combination therapy with cyproterone acetate and combined oral contraceptives, the same type of side effect as with oral contraceptives can occur.

Prevalence of meningiomas has been reported in association with prolonged use (several years) of cyproterone acetate at doses of 25 mg / day and beyond (see sections 4.3 and 4.4).

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. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Acute toxicity studies following single administration showed that cyproterone acetate, the active ingredient of SITERONE, can be classified as practically non-toxic. Nor is any risk of acute intoxication to be expected after a single inadvertent intake of a multiple of the dose required for therapy.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: sex hormones and modulators of the genital system, antiandrogens, plain, ATC code: G03HA01

SITERONE is an antiandrogenic hormone preparation. It inhibits the influence of androgens, which are also produced - to a slight extent- in the female organism, and also exerts a progestational and antigonadotrophic effect.

Cyproterone acetate inhibits competitively the effect of androgens at androgen-dependent target organs, e.g. it shields the prostate from the effect of androgens originating from the gonads and/or the adrenal cortex.

In the man, under treatment with SITERONE, sexual drive and potency are reduced and gonadal function is inhibited. These changes are reversible following discontinuation of the therapy.

In the woman, hirsutism is reduced, but also androgen-dependent alopecia and elevated sebaceous gland function are reduced. During treatment, ovarian function is reduced.

5.2 Pharmacokinetic properties

Following oral administration, cyproterone acetate is completely absorbed over a wide dose range. The ingestion of 50 mg of cyproterone acetate gives maximum serum levels of about 140 ng/ml at about 3 hours. Thereafter drug serum levels decline during a time interval of typically 24 to 120 hours, with a terminal half-life of 43.9 ± 12.8 hours. The total clearance of cyproterone acetate from serum was determined to be 3.5 ± 1.5 ml/min/kg. Cyproterone acetate is metabolised by various pathways, including hydroxylation and conjugation. The main metabolite in human plasma is 15 β -hydroxy derivative.

Some dose parts are excreted unchanged with bile fluid. Most of the dose is excreted in the form of metabolites at a urinary to biliary ratio of 3:7. The renal and biliary excretion was determined to proceed with a half-life of 1.9 days. Metabolites from plasma were eliminated at a similar rate (half-life of 1.7 days).

Cyproterone acetate is almost exclusively bound to plasma albumin. About 3.5 - 4% of total drug levels are unbound. Because protein binding is non-specific, changes in SHBG (sex hormone binding globulin) levels do not affect the pharmacokinetics of cyproterone acetate.

According to the long half-life of the terminal disposition phase from plasma (serum) and the daily intake, an accumulation of cyproterone acetate by a factor of about 3 can be expected in the serum during repeated daily administration.

The absolute bioavailability of cyproterone acetate is almost complete (88% of dose).

5.3 Preclinical safety data

Investigations into the toxicity following repeated administration of cyproterone acetate gave no indication of specific risks from the use of SITERONE.

Experimental investigations produced corticoid-like effects on the adrenal glands in rats and dogs following higher dosages, which could indicate similar effects in humans at the highest given dose (300 mg/day).

Experimental investigations into possible sensitising effects of cyproterone acetate have not been carried out.

The temporary inhibition of fertility in male and female rats brought about by daily oral treatment did not in any way indicate that treatment with SITERONE leads to spermatozoa or ovocyte damage which could lead to malformations or impairment of fertility in the offspring.

Investigations into embryotoxic or teratogenic effects were not carried out with cyproterone acetate but only in combination with ethinylestradiol. Such investigations produced no effects after treatment during the foetal organogenesis before development of the external genital organs, which would indicate a general teratogenic potential in humans. Administration of high doses of cyproterone acetate during the hormone-sensitive differentiation phase of the genital organs (starting roughly on day 45 of gravidity) could cause feminisation effects in male foetuses. Observation of male newborn children who had been exposed in the uterus

to cyproterone acetate revealed no indications of feminisation. However, pregnancy is a contraindication for use of SITERONE. Women of child-bearing age should only be treated if reliable contraceptive measures are taken at the same time.

Recognised first-line tests of genotoxicity gave negative results when conducted with cyproterone acetate. However further tests showed that cyproterone acetate was capable of producing adducts with DNA (and an increase in DNA repair activity) in liver cells from rats and monkeys and also in freshly isolated human hepatocytes. This DNA-adduct formation occurred at exposures that might be expected to occur in the recommended dose regimens for cyproterone acetate. One in vivo consequence of cyproterone acetate treatment was the increased incidence of focal, possibly pre-neoplastic liver lesions in which cellular enzymes were altered in female rats. The clinical relevance of these findings is presently uncertain. Clinical experience to date would not support an increased incidence of hepatic tumours in man. Nor did investigations into the tumorigenicity of cyproterone acetate in rodents reveal any indication of a specific tumorigenic potential. However, it must be borne in mind that sexual steroids can promote the growth of certain hormone-dependent tissues and tumours.

On the whole the available toxicological findings do not raise any objection to the use of SITERONE in humans if used in accordance with the directions for the given indications and at the recommended dosages.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize starch
Povidone
Colloidal Silicon Dioxide
Magnesium stearate
Purified Water
Pregelatinised Starch (Starch 1500)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life is 36 months (3 years) from manufacture.

6.4 Special precautions for storage

Store below 25°C protected from light.

6.5 Nature and contents of container

SITERONE 50 mg and 100 mg tablets are available in blisters of 50 tablets.

6.6 Special precautions for disposal and other handling

Not applicable.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

REX Medical Ltd
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AUCKLAND.

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9 DATE OF FIRST APPROVAL

50 mg tablet: 24 May 2001
100 mg tablet 17 January 2008

10 DATE OF REVISION OF THE TEXT

30 March 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Warning on hepatotoxicity updated
4.8	Adverse event frequencies added
4.8	Diminished vitality added as psychiatric disorder