"פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר"

1. NAME OF THE MEDICINAL PRODUCT

Estracyt Capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Estramustine phosphate 140 mg as estramustine sodium phosphate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsule
White, hard, gelatin capsules with “ESTRACYT” and “K Ph 750” printed in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Second line therapy in prostatic carcinoma in advanced stages.

4.2 Posology and method of administration

Estracyt should be administered by individuals experienced in the use of antineoplastic therapy.
The dose range is 7-14 mg/kg (4 - 8 capsules) daily in 3 or 4 divided doses.
Recommended starting dose is 4-6 capsules to achieve a dose of at least 10 mg/kg. The capsules should be taken *not* ***less than 1 hour before or 2 hours after meals***. They should be swallowed with a glass of water. ***Milk, milk products or drugs containing calcium, magnesium or aluminium (e.g. antacids) must not be taken simultaneously with Estracyt capsules.***
If no effect is observed after 4 - 6 weeks the treatment should be discontinued.

Paediatric population
Estracyt should not be administered to children

4.3 Contraindications

Hypersensitivity to estramustine sodium phosphate, oestradiol or nitrogen mustard or to any of the excipients listed in section 6.1.

Use in patients with peptic ulceration, or those with severe liver dysfunction or myocardial insufficiency.

Use in patients with active thrombosis or thromboembolic disorders or complications related to fluid retention.

Use in children.

4.4 Special warnings and precautions for use

Estracyt should be used with caution in patients with a history of thrombophelebitis, thrombosis or thromboembolic disorders, especially if associated with estrogen therapy. Caution should also be used in patients with cardiovascular disease, cerebral vascular disease and coronary artery disease.

Glucose Tolerance – Because glucose tolerance may be decreased, diabetic patients should be carefully followed while receiving Estracyt.

Elevated blood pressure – Because hypertension may occur, blood pressure should be monitored periodically.

Fluid retention – Exacerbation of pre-existing or incipient peripheral oedema or congestive heart disease has been seen in some patients receiving Estracyt therapy. Other conditions which might be influenced by fluid retention, such as epilepsy, migraine, or renal dysfunction, require careful observation.

Calcium/phosphorous metabolism – Estracyt may influence the metabolism of calcium and phosphorous and should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency. Serum calcium should be performed at regular intervals. Patients with prostate cancer and osteoblastic metastases are at risk for hypocalcaemia and should have calcium levels closely monitored.

Estracyt may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients. Liver function tests should be performed at regular intervals.

Note: since certain endocrine and hepatic functions are influenced by estrogen-containing drugs the corresponding laboratory test values will be affected.

Use with caution in patients with moderate to severe bone marrow depression. Blood count should be performed at regular intervals.

Immunosuppressant Effects/Increased Susceptibility to Infections - Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including Estracyt, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving Estracyt. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

4.5 Interaction with other medicinal products and other forms of Interaction

Oestrogens have been reported to increase both therapeutic activity and toxicity of tricyclic antidepressants, probably via inhibition of their metabolism.

Milk, milk products or drugs containing calcium, magnesium or aluminium may impair the absorption of Estracyt and simultaneous intake must therefore be avoided. The mechanism behind this interaction is that estramustine forms insoluble salts with polyvalent metal ions.

An interaction between Estracyt and ACE-inhibitors, possibly leading to an increased risk of angioedema (See section **4.8**) cannot be excluded.

4.6 Fertility pregnancy and lactation

Estradiol and nitrogen mustard are potentially mutagenic, and therefore males undergoing treatment with estramustine should employ contraceptive measures (See section 5.3).

Since Estracyt is indicated for carcinoma of the prostate in males, it is not indicated for women.

4.7 Effects on ability to drive and use machines

The effect of estramustine on the ability to drive or use machinery has not been systematically evaluated.

4.8 Undesirable effects

The most common adverse reactions include gynecomastia, nausea/vomiting and fluid retention/oedema.

The most serious reactions are embolism, myocardial ischaemia , cardiac failure congestive and, angioedema.

Reported reactions arranged according to MedDRA System Organ System are the following:

System Organ Class	**Very Common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Frequency not known (cannot be estimated from available data)**
Blood and lymphatic system disorders	Anaemia, Leukopenia	Thrombocytopenia	
Immune system disorders			Hypersensitivity
Metabolism and nutrition disorders	Fluid retention		
Psychiatric disorders			Confusional state, Depression
Nervous system disorders		Lethargy, Headache	
Cardiac disorders	Cardiac failure congestive	Myocardial infarction	Myocardial ischaemia
Vascular disorders		Embolism	Hypertension
Gastrointestinal disorders	Nausea and Vomiting*, Diarrhoea*		
Hepatobiliary disorders	Hepatic function abnormal		
Skin and subcutaneous tissue disorders			Angioedema**, Dermatitis allergic
Musculoskeletal and connective tissue disorders			Muscular weakness
Reproductive system and breast disorders	Gynaecomastia		Erectile dysfunction
General disorders and administration site conditions			Injection site thrombosis (IV solution)

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Frequency not known (cannot be estimated from available data)

*Particularly during the first two weeks of treatment.
**Angioedema (Quincke oedema, larynx oedema) can occur. In many reported cases, including a fatal one, patients were concomitantly receiving ACE-inhibitors. Therapy with estramustine is to be immediately discontinued should angioedema occur.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic @moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

4.9 Overdose

There is no specific antidote. Treatment is symptomatic and supportive (as necessary the gastric contents should be evacuated by gastric lavage) and in the event of dangerously low red cell, white cell or platelet count, whole blood should be given as necessary. Liver function should be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC Code: L01XX11

Estracyt is a chemical compound of oestradiol and nitrogen mustard. It is effective in the treatment of advanced prostatic carcinoma.

Estramustine phosphate (EMP) is a unique antitumor drug with a dual mode of action. Estrone and estradiol, products of the metabolism of estramustine phosphate, have shown antigonadotrophic activity resulting in reduced testosterone levels similar to those achieved after surgical castration. Estramustine, the cytotoxic metabolite produced by dephosphorylation of the parent compound, undergoes further metabolism to estromustine; both these metabolites have antimitotic effects in tumor cells. These effects depend on an inhibition of the formation of microtubuli in metaphase and a breakdown of microtubuli in interphase. The microtubule effects have also been demonstrated in human prostate tumor xenografts in vivo. Inhibition of microtubule polymerization by estramustine has been demonstrated to be due

to a direct interaction with tubulin. In addition, an interaction between estramustine and the microtubule associated proteins has been demonstrated. Estramustine has been shown to modulate the function of the P-glycoprotein in resistant cell lines thereby increasing intracellular drug accumulation and enhancing cytotoxicity of simultaneously administered cytotoxic drugs. This modulatory ability could be the basis for the synergy found in human prostate tumor cells in vitro between estramustine and other agents such as paclitaxel, vinblastine, etoposide and doxorubicin.
Data demonstrating a synergistic effect of estramustine and etoposide in vivo against rat prostatic tumors also support this hypothesis.
Estramustine in combination with either vinblastine, etoposide or taxol has been shown to produce a better response than either drug alone without increased toxicity.

5.2 Pharmacokinetic properties

The absorption of radiolabelled EMP has been studied in a patient after oral administration of a capsule formulation. The oral absorption was found to be approximately 75% in comparison with intravenous administration.
EMP is a pro-drug. It is rapidly dephosphorylated in the gastrointestinal tract to estramustine, and intact EMP is not found in plasma after oral administration. The level of protein binding of EMP is 99%. Estramustine is metabolized to estromustine, which is the major compound in plasma. The relative oral bioavailability (AUCpo / AUCiv) of estromustine is high; about 90% in fasting patients. Both estramustine and estromustine are cytotoxic and have a high level of protein binding. The elimination half-life of estromustine is about 80 hours. Estramustine and estromustine are further metabolized into the corresponding estrogens: estradiol and estrone.
After intravenous administration, intact EMP is found in plasma but is rapidly metabolized (elimination half-life: 1.2 hours) and the same metabolites are formed as after oral administration. Estromustine is the major metabolite also after intravenous administration.
The plasma levels of EMP and its metabolites are almost linearly correlated to the given dose after oral or intravenous administration. The steady state level of the metabolites does not change during long term oral treatment.
Estramustine and estromustine are excreted via the bile and feces and do not appear in the urine. Estradiol and estrone are further metabolized and partly excreted in the urine.
Estramustine and estromustine have been detected in human prostate tumor tissue after treatment with EMP. In patients, higher levels of estramustine and estromustine in tumor tissue than in plasma have been found. The reason for this may be that estramustine and estromustine are taken up in prostate tissue via binding to a protein which has been shown to exist in prostate tumor tissue.

5.3 Preclinical safety data

In repeat dose toxicity studies in rats, dogs and monkeys the main target organs are the hemolymphopoietic and endocrine systems and male and female reproductive organs, with changes related to both oestrogenic and cytotoxic effects of estramustine phosphate.

No reproduction or oncogenicity studies have been undertaken and the mutagenicity of the compound has not fully been investigated. Nevertheless estramustine phosphate, like other oestrogenic and antimitotic agents, must be considered toxic to the reproductive organs and potentially mutagenic and carcinogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Talc,
Sodium lauryl sulfate,
Silica colloidal anhydrous
Magnesium stearate,
Titanium dioxide (E171) ,
Gelatin capsule,
Black ink (containing black iron oxide (E172), ammonium hydroxide (E527), propylene glycol (E1520) and shellac).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

5 years.
After opening, the shelf life is 25 days.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Brown (amber) glass bottle containing 40 or 100 capsules.

6.6 Special precautions for disposal and other handling

No special requirements.

Manufacturer
PFIZER ITALIA S.R.L, Italy

License holder:
PFIZER PFE PHARMACEUTICALS ISRAEL LTD, 9 Shenkar St., Herzliya Pituach 46725.