PRODUCT MONOGRAPH

PrEMCYT*

(estramustine sodium phosphate capsules B.P.)

140 mg/capsule

Antineoplastic

Pfizer Canada Inc
17,300 Trans-Canada Highway
Kirkland, Quebec H9J 2M5

Date of Revision:
10 December 2015

Control No. 186447

* TM Pharmacia AB
Pfizer Canada Inc, Licensee

PRODUCT MONOGRAPH

NAME OF DRUG

PrEMCYT

Estramustine sodium phosphate capsules B.P.

THERAPEUTIC CLASSIFICATION

Antineoplastic

CAUTION: EMCYT (ESTRAMUSTINE SODIUM PHOSPHATE) IS A POTENT DRUG AND SHOULD BE PRESCRIBED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE WARNINGS & PRECAUTIONS). BLOOD COUNTS, AS WELL AS RENAL AND HEPATIC FUNCTION TESTS, SHOULD BE PERFORMED REGULARLY. DISCONTINUE THE DRUG IF ABNORMAL RENAL OR HEPATIC FUNCTION IS SEEN. CAPSULES SHOULD NOT BE OPENED.

ACTION

Emcyt (estramustine sodium phosphate) has a dual mode of action. The intact molecule acts as an anti-mitotic agent and after hydrolysis of the carbamate ester bridge the released estrogens exert an anti-gonadotrophic effect.

The low level of clinically manifested side effects may be due to the fact that estramustine binds to a protein present in the tumor tissue, which results in an accumulation of the drug at the target site.

INDICATIONS

The treatment of metastatic prostatic carcinoma (stage D) in patients whose disease is refractory to hormonal therapy. Emcyt (estramustine sodium phosphate) may produce either a stabilization or regression of the disease process and improvement in ability to function.

CONTRAINDICATIONS

Emcyt should not be used in patients with any of the following conditions:

* known hypersensitivity to either estradiol or to nitrogen mustard
* severe hepatic or cardiac disease
* active thrombophlebitis or thromboembolic disorders

WARNINGS

Emcyt (estramustine sodium phosphate) should be used with caution in patients with a history of thrombophlebitis, thrombosis or thromboembolic disorders, especially if associated with estrogen therapy. Caution should also be used in patients with cerebral vascular or coronary artery disease.

Angioneurotic oedema has been reported in few cases during Emcyt therapy, with or without concomitant medication. Discontinue therapy with estramustine immediately should angioedema occur.

Glucose Tolerance- Because glucose tolerance may be decreased, diabetic patients should be carefully observed while receiving Emcyt.

Elevated Blood Pressure - Because hypertension may occur, blood pressure should be monitored periodically.

PRECAUTIONS

Emcyt (estramustine sodium phosphate) should be administered by individuals experienced in the use of antineoplastic therapy. Professional staff administering Emcyt should exercise particular care to prevent spillage and contact with the drug. Should skin contact occur, the area should be vigorously washed with soap and cold water and material used for cleansing disposed by incineration.

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

Calcium/Phosphorus Metabolism - Because Emcyt may influence the metabolism of calcium and phosphorus, it should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency. Patients with prostate cancer and osteoblastic metastases are at risk for hypocalcemia and should have calcium levels closely monitored.

Mutagenesis, Carcinogenesis - Although testing by the Ames method failed to demonstrate mutagenicity for estramustine sodium phosphate, it is known that both estradiol and nitrogen mustard are mutagenic. Patients should therefore be advised to use contraceptive measures during therapy with Emcyt.

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

Laboratory Tests: Certain endocrine and liver function tests may be affected by estrogen-containing drugs. Abnormalities of hepatic enzymes and of bilirubin have occurred in patients receiving Emcyt, but have seldom been severe enough to require cessation of therapy. Such tests should be done at appropriate intervals during therapy and repeated 2 months after the drug has been withdrawn.

Sexual Function and Reproduction: It is known that both estradiol and nitrogen mustard are mutagenic, and therefore males undergoing treatment with estramustine should employ contraceptive measures.

Food / Drug Interaction: Estrogens have been reported to increase both therapeutic activity and toxicity of tricyclic antidepressants, probably via inhibition of their metabolism.

Food like milk, milk products or drugs, which contain calcium or other polyvalent ions, may impair the absorption of Emcyt and must not be taken simultaneously with Emcyt.

Angioedema has been reported in a few cases, when Emcyt was administered concomitantly with ACE-inhibitors.

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.

ADVERSE REACTIONS

The most common adverse reactions include gynaecomastia, nausea/vomiting and fluid retention/edema.

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

Gastro-intestinal disturbances (most commonly transient nausea, but occasionally vomiting, and rarely diarrhoea) sometimes occur during the first two weeks of therapy. In a few cases thrombocytopenia, leukopenia and elevated transaminases / bilirubin have been noted but were completely reversible on reduction of dosage or temporary (1-2 weeks) withdrawal of the drug. Other cases of anemia, muscular weakness, depression, headache, confusion and lethargy may rarely occur.

A few cases of allergic skin rashes, oedema and anginal complaints have been reported.

Cardiovascular adverse reactions such as fluid retention/edema, thromboembolism, ischemic heart disease, congestive heart failure, myocardial infarction and hypertension may occur during treatment. A few cases of angioneurotic oedema have been reported during Emcyt therapy, with or without concomitant medication. As with conventional estradiol therapy, thromboembolic disorders, gynaecomastia, reduced libido and potency may occur.

Post-Market Adverse Drug Reactions

Additional adverse events which have been reported in temporal association with Emcyt (estramustine sodium phosphate) since market introduction are listed below. Because spontaneous reports are reported voluntarily from a population of unknown size, estimates of frequency cannot be established.

Immune system disorders: Hypersensitivity

Other Post-Market Information

The following information on adverse drug reaction frequencies is from selected published papers of clinical trials. *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Table 1 Adverse Drug Reactions Occurring in ≥ 1% of patients treated with estramustine

System Organ Class	**Very Common ≥ 1/10 (≥10%)**	**Common ≥ 1/100 to < 1/10 (≥ 1% to < 10%)**
Blood and lymphatic system disorders	Anaemia, Leukopenia	Thrombocytopenia
Metabolism and nutrition disorders	Fluid retention	
Nervous system disorders		Lethargy, Headache
Cardiac disorders	Cardiac failure congestive	Myocardial infarction
Vascular disorders		Embolism
Gastrointestinal disorders	Nausea and Vomiting, Diarrhoea	
Hepatobiliary disorders	Hepatic function abnormal	
Reproductive system and breast disorders	Gynaecomastia	

TREATMENT OF OVERDOSAGE

Although, there has been no experience with overdoses of Emcyt (estramustine sodium phosphate) to date, it is reasonable to expect that such episodes may produce pronounced manifestations of the known adverse reactions associated with estramustine, particularly gastrointestinal symptoms. In the event of overdosage, treatment should be symptomatic and supportive. Gastric lavage should be performed and measures taken to encourage diuresis. Hematologic and hepatic parameters should be monitored for at least six weeks after overdosage of Emcyt.

DOSAGE AND ADMINISTRATION

The recommended dose of estramustine sodium phosphate is 14 mg per kg of body weight per day (i.e., one 140 mg Emcyt capsule for each 10 kg), given in 3 or 4 divided doses. Most patients have been treated at a dose range of 10 to 16 mg per kg per day.

Treatment for at least 30 days is recommended before assessing the benefits of therapy and may be continued as long as a favorable response lasts. If no response is observed after 4-6 weeks, treatment should be discontinued. Some patients have been maintained on therapy for more than two years at doses ranging from 10 to 1 6 mg per kg of body weight per day.

The capsules should be taken at not less than 1 hour before or 2 hours after meals.

The capsules should be swallowed with a glass of water. Milk, milk products or calcium containing drugs (such as Ca-containing antacids) must not be used simultaneously with Emcyt capsules.

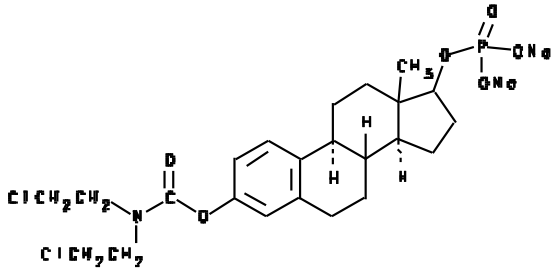
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Estramustine sodium phosphate

Chemical Name: Estradiol, 3-[N-bis(2-chloroethyl) carbamate] 17-disodium phosphate.

Structural Formula



Molecular Formula: $C_{23}H_{30}NCl_2Na_2O_6P$

Molecular Weight: 564.4

Physical form: Estramustine sodium phosphate is a white or almost white powder.

Solubility: Soluble in water.

Stability and Storage

Store between 2°- 25°C.

AVAILABILITY

Each white opaque, hard gelatin capsule contains 140 mg of estramustine sodium phosphate, as estramustine phosphate disodium - bottles of 100.

PHARMACOLOGY

Animal Pharmacology

Estramustine phosphate has been studied in a number of pharmacologic tests in animals. The compound had no effect on blood pressure, carotid sinus occlusion reflex or the blood pressure response to norepinephrine and tyramine in the anesthetized cat at a dose of 68 mg/kg i.v. In rats, this same dose caused a slight transient increase in respiratory amplitude with no effect on respiratory rate and also significantly inhibited carrageenin-induced pedal edema. No effect was seen in the carrageenin test when the drug was administered orally at 200 mg/kg.

An inhibitory effect on the development of granulomatous tissue, induced by an injection of Mycobacterium butyricum into a subcutaneous air pouch in the backs of rats, was observed at 200 mg/kg administered orally for 4 days. Significant antipyretic and diuretic effects were noted in rats receiving 27 and 68 mg/kg i.v. The diuretic action, however, was not observed in rats which had been adrenalectomized. In mice, estramustine phosphate given at a dose of 68 mg/kg i.v. showed no analgesic activity in the writhing test and had no effect on intestinal motility or hexobarbital sleeping time. This dose did, however, significantly impair the ability of mice to climb a vertical wire-mesh wall. No antagonism of reserpine-induced hypothermia in mice was observed at a dose of 200 mg/kg orally.

Antitumor Activity

In-vivo

The antitumor activity of estramustine and estramustine phosphate has been evaluated in a number of transplantable tumors of mice and rats.

The most significant effect of estramustine is seen against the spontaneous derived rat Dunning prostatic tumor models.

1) Estramustine demonstrated significant tumor inhibition when given interperitoneally to the Dunning H tumor which is sensitive to hormonal manipulation. This effect is probably mainly due to the release of the estrogen moiety as testosterone levels drop rapidly to castration level. However, estramustine is also effective in this model when the rats are castrated and substituted with high dose testosterone, indicating a cytotoxic effect over and above that of an estrogen.
2) This cytotoxic effect was confirmed in experiments against the Dunninq AT prostatic rat tumor which is unresponsive to hormone manipulation. Estramustine 20, 40, 60 mg/kg given i.p. on 5 consecutive days produced tumor inhibition respectively, 4 weeks after initiation of therapy. This clearly demonstrates the cytotoxic effect of estramustine in a hormone insensitive rat prostate tumor.
3) Estramustine phosphate was also found to be active against 7,12-dimethylbenz(α)anthracene (DMBA)-induced mammary tumor made resistant to estrogens by repeated exposure. Estramustine phosphate 20 mg/kg given every day i.p. over a four-week period resulted in 70% inhibition of tumor growth at 8 weeks, thus substantiating the cytotoxic effect of this substance.

Estramustine phosphate was also active in the following rat tumor models;

4) 3-methyl-cholanthrene induce prostate carcinoma (11095): When given orally at 20 mg/kg/day for 12 days a slight effect (21% tumour inhibition) was observed, but was inactive when given subcutaneously (10 mg/kg).
5) Also effective against a transplantable prostatic adenocarcinoma of spontaneous origin in rats (3-100 mg/kg/day for 5 days).
6) AH 130 hepatoma system: The therapeutic index was 3.5 after one treatment.
7) Walker 256 carcinosarcoma model: Subcutaneous administration at doses of 25 – 200 mg/kg/day resulted in inhibition of tumour growth ranging from 36 - 59% over the four doses utilized. In this model the substance was inactive when administered intraperitoneally (63 mg/kg/day for 5 days).

8) R35 mammary adenocarcinoma: Active when administered orally once daily for ten days at 20 mg/kg (47% tumor inhibition), but inactive when administered subcutaneously at 10 mg/kg.
9) Acute monocytic leukemia model: An inhibitory tumor effect (30%) was noted when the substance was administered orally once daily for 12 days at 20 mg/day. The substance was inactive at 10 mg/kg when given subcutaneously.

The substance was inactive in the following rat tumor models:

1) WR-6 lymphocytic leukemia and
2) LW-12 chloroleukemia when administered at doses of 10 and 20 mg/kg by either the subcutaneous or oral routes. When tested in the Ehrlich solid tumor model in mice, the therapeutic index (LD_{50}/ED_{50}) of estramustine phosphate administered intraperitoneally either as a single treatment, or for seven consecutive days, ranged from 3.8 to 3.9 and from 1.3 to 5.0 respectively.

Estramustine phosphate was inactive in the following mouse tumor models:

1) Crocker Sarcoma 180 following seven consecutive daily intraperitoneal injections.
2) Harding-Passey melanoma following 11 consecutive daily (63 mg/kg) intraperitoneal treatments.
3) L1210 ascites when given daily intraperitoneally over a dose range from 63 - 250 mg/kg.

In-vitro

The mode of action of estramustine has been studied in detail in human prostatic tumor cell lines. Estramustine exhibits dose dependent cell kill from 1 - 30 μg/mL against hormone resistant human prostatic tumor cells. This has been found to be due primarily to the anti-mitotic effect of the intact molecules. Estramustine arrests cells in metaphase and also induces abnormal cytoplasmic microtubules whilst neither nitrogen mustard nor estradiol exhibit any such effect. This inhibition by estramustine has been found to be due to the fact that the drug binds to microtubule associated proteins (MAP's) which are essential for microtubule functions. Binding to MAP's is a unique function of estramustine and is not found for other anti-mitotic drugs.

Human Pharmacology

Various analytical techniques have been employed to study the clinical pharmacokinetics of estramustine phosphate. A radioimmunoassay has been used for analyses of the parent drug and gas chromatography or liquid chromatography for its metabolites.

In a cross-over study estramustine phosphate was given intravenously (300 mg) and orally (420 mg) to five patients. Following intravenous administration the total plasma clearance was 64 ± 5 mL/kg/h (Mean + SEM). The half-life of the terminal elimination phase in plasma was 1.25 ± 0.05 h. The volume of distribution was about 110 mL/kg. The elimination occurs via metabolism and several metabolites appear in plasma during the elimination phase.

After oral administration the parent drug could not be detected in plasma which is due to dephosphorylation of estramustine phosphate already in the gastrointestinal tract. Several metabolites such as estramustine, estromustine, estradiol and estrone were found in plasma after oral as well as after intravenous administration of estramustine phosphate. Estromustine was the main metabolite. The terminal half-life of estramustine and estromustine is 15 to 20 hours.

The absorption of estramustine phosphate was markedly reduced when the drug was given together with milk. This is probably due to the formation of a poorly soluble calcium complex of estramustine phosphate when the drug is taken together with milk. In order to avoid this interaction milk and other calcium rich foods and drugs must not be used simultaneously with oral Emcyt.

As mentioned above estramustine phosphate is a subject of extensive first-pass metabolism after oral administration and thus estramustine phosphate can be regarded as a pro-drug. The anti-tumor active components, estromustine, estramustine, estrone and estradiol, are formed. These metabolites have also been detected in the human prostatic tumor. Interestingly, the estramustine levels were 5-10 times higher in tumor tissue than in plasma from the same patients. This might indicate selective uptake and accumulation of cytotoxic metabolites in the human tumor tissue. Studies with radiolabelled estramustine phosphate have revealed that its metabolites are excreted both in faeces and in urine. However, it appears that neither EMP nor estramustine or estromustine are excreted via the urine. In the faeces, however, estramustine or other metabolites with an intact carbamic ester linkage are excreted.

Hormonal Effects of Estramustine sodium phosphate in Humans

Estramustine phosphate, administered orally at 900 mg daily for 14 days, depressed plasma testosterone levels in 10 consecutive patients who had previously been treated with estrogen hormones and/or orchiectomy and who were all in relapse from carcinoma of the prostate. Approximately one half of the patients responded to the treatment clinically. The decrease in plasma testosterone did not correlate with the clinical response. The clinical effect of estramustine sodium phosphate may be due to decreased plasma testosterone levels, inhibition of 5-alpha reductase activity, and a local cytotoxic effect.

In a series of 44 male patients transcortin and cortisol levels became significantly elevated above normal. The levels observed in this study may serve as reliable indices for monitoring patients who are on this drug.

TOXICOLOGY

Acute

Species	*Route*	*LD_{50} mg/kg*
mice	p.o.	> 2,000
mice (m)	i.p.	383
mice (f)	i.p.	420
rat	p.o.	> 2,000
rat (m)	i.p.	337
rat (f)	i.p.	550

Male rats receiving 750 and 2,000 mg/kg orally or 264 mg/kg and higher intraperitoneally all showed atrophy of the reproductive organs 14 days after dosing. A dose-related depression of weight gain occurred in male and female rats after oral and intraperitoneal administration.

Chronic

One Month Oral Toxicity Study in Rats

Estramustine phosphate (disodium salt) was administered to rats by oral intubation at dosages of 0, 100, 200, or 400 mg/kg/day for 1 month.

Daily observations, body weight, food consumption, hematology and blood chemistry measurements were recorded. Rats were autopsied and a histopathological examination was performed on the control and high dose (400 mg/kg/day) group.

Marked weight reductions and anemia were observed in all treated groups. Treated males exhibited lymphopenia and females exhibited granulocytosis. Increased serum alkaline phosphatase and glutamic pyruvic transaminase, decreased cholesterol, and increased serum proteins were noted in some groups. Macroscopically, all treated groups showed atrophy of the prostate, testes, seminal vesicles, thymus, and in addition, a dilated uterus and enlarged pituitary gland. The histopathological examination at the high dose showed dilated sinusoids with vacuolated hepatocytes in the liver and hyperplasia of the basophil cells of the pituitary gland. No histopathological examination of reproductive organs was performed.

Six Month Oral Toxicity Study in Rats

Estramustine phosphate (disodium salt) was administered by oral intubation to rats daily for 26 weeks at dosages of 0, 30, 100, or 300 mg/kg/day. Ophthalmoscopic observations, appearance, growth, and food and water consumption were recorded. Hematologic and clinical chemistry evaluations and urinalyses were performed after 1, 2, 3, and 6 months. The animals were autopsied and examined macro- and microscopically.

The mortality during the study was 24, 37, and 47% in males and 33, 58, and 67% in females at doses of 30, 100, and 300 mg/kg/day, respectively. Pneumonia was considered to be the principal cause of death in males, whereas female deaths were primarily due to pyometra. Body weights

and food consumption were decreased in all treated groups and all treated groups exhibited alopecia. A slight anemia and a decrease in leukocytes were observed. Decreased cholesterol levels and an increase in levels of triglycerides and serum proteins occurred at all dose levels. Blood urea nitrogen levels were slightly increased at 100 and 300 mg/kg/day.

Increases in serum alkaline phosphatases occurred in females receiving 300 mg/kg/day.

At autopsy there were marked reduction in the weights of the gonads, prostate and seminal vesicles, and increases in uterine and pituitary weights in all treated groups. Gynecomastia in males treated at 100 and 300 mg/kg/day and proliferation of the mammary glands in females at all dosages were observed.

Increased pigmentation of the epithelium of the kidney, adrenals, liver, and lymph nodes was observed. Increased hemosiderin and erythropoiesis was seen in the spleen.

Female mortality with pyometra, decreased growth and food consumption, decreased cholesterol and increased triglycerides, increased uterine and pituitary weights, pigmentation and spleen changes were attributed to the estrogenic activity.

Male mortality with pneumonia, alopecia, lymphopenia and lymph node atrophy was attributed to the estrogenic activity.

Mutagenicity and Carcinogenicity

It is known that nitrogen mustard is mutagenic. However, no evidence of mutagenicity was reported for estramustine phosphate disodium in Ames' Test with and without a liver homogenate supernatant fluid.
Long-term administration of estrogens in certain animal species increases the frequency of the breast, pituitary gland and liver tumors. No carcinogenicity studies have been conducted with estramustine phosphate disodium.

REPRODUCTION STUDIES

Range Finding Study for Fetal Toxic Effects of Estramustine Phosphate in the Rat and Rabbit

Estramustine phosphate (disodium salt) was administered by oral intubation to rats and rabbits as a solution in distilled water. Rats were dosed with 0.01, 0.04, 0.2, 1.0, 5.0, 15, 30, 100, or 300 mg/kg from days 7-15 of gestation. Rabbits received daily doses of 5.0, 30, 100, or 300 mg/kg from days 7-18 of gestation.

In the rat, the administration of estramustine phosphate (disodium salt) resulted in total resorption at dosages of 5 mg/kg/day or more. At 1 mg/kg/day, one of three rats exhibited total absorption; the other two litters appeared normal. At dosages of 0.2 mg/kg/day or less, the resorption rates appeared to be normal. No external abnormalities were observed in surviving fetuses nor were adverse effects noted except for weight loss in the dams.

In the rabbit, dosages of 5 mg/kg/day or more of estramustine phosphate (disodium salt) resulted in weight loss and total resorption.

The results show that fetal toxic effects of estramustine sodium phosphate appear between 0.2 and 1 mg/kg/day in the rat and at dosages of less than 5 mg/kg/day in the rabbit.

Teratological Study in Rats

Estramustine phosphatase (disodium salt) in solution was administered by oral intubation to rats at doses of 0, 0.1, 0.5, 1, and 2 mg/kg/day from days 7-15 of gestation, caesarean sections were performed on 20 rats per group and 10 rats per group were allowed to deliver for post-natal evaluation of the pups.

In the groups subjected to caesarean section a markedly increased resorption rate and a decreased litter size were observed at the 2 mg/kg/day dose. A statistically non-significant increase in resorptions was observed at 0.5 and 1 mg/kg/day.

The resorption rate at 0.1 mg/kg/day was comparable to controls. No significant differences were observed in the incidence of dead fetuses or the average fetal body weights between control and treated groups. No increase in external, soft tissue or skeletal abnormalities was observed.

In the natural delivery group a decreased litter size was observed at 2 mg/kg/day. Lower dosages appeared normal. No visceral abnormalities were noted in pups at necropsy nor were skeletal abnormalities noted in dead pups.

Thus, it is concluded that estramustine phosphate is fetotoxic in the rat at dosage of 2 mg/kg/day or more. Slight fetotoxic effects were noted at dosages of 0.5 and 1 mg/kg/day; however, no abnormalities were noted at dosages of 0.1 mg/kg/day.

IRRITATION

Effects of Oral Estramustine phosphate on the G.l. Tract of the Dog

Estramustine phosphate (disodium salt) was administered to dogs at a dose of 400 mg/kg/day (31-37 mg/kg) for 5 to 14 days primarily in order to assess gastrointestinal irritation. Hematology and clinical chemistries were performed initially and 4 times during the study. All animals survived until the end of the study, when they were sacrificed and examined macroscopically, with selected tissues being examined microscopically.

Agranulocytosis was observed during the first week and thrombocytopenia was observed terminally. At autopsy hyperemia of the intestine was observed and one dog showed small sub-mucosal hemorrhages. The macroscopic changes were attributed to the hematological changes.

SELECTED BIBLIOGRAPHY

1. Burleson, GR and Pollard, M. Chemotherapy of spontaneous transplantable prostatic adenocarcinomas in lobund wistar rats. Fed Proc (1976) 35: 624.
2. Catane, R et al. Oral estramustine phosphate: prolonged therapy for advanced carcinoma of prostate. NY State J Med (1976) 76: 1978-1981.
3. Forshell, GP et al. The absorption metabolism, and excretion of estracyt (NSC 09199) in patients with prostatic cancer. Invest Urology (1976) 14(2):128-131.
4. Fredholm, B et al. Effects of estramustine phosphate (Estracyt®) on growth DMBA-induced mammary tumors in rats. Acta Pharmacol Toxicol (1974) 35 (suppl) :I.
5. Franchimont, P et al. Radioimmunoassay of prostatic acid phosphatase: validation and clinical application. Int J Cancer (1983) 31: 149-155.
6. Gunnarsson PO and Forshell GP. Clinical pharmacokinetics of estramustine phosphate. Urology (1984) 23:22-27.
7. Hartley-Asp B. Estramustine-induced mitotic arrest in two human prostatic carcinoma cell lines DU145 and PC-3. Prostate (1984) 5:93-110.
8. Hoisaeter, PA. Studies on hormone-cytostatic complexes in the cytoplasm of rat prostatic gland. Invest Urol (1974) 12: 33-37.
9. Kanje M, Deinum J, Wallin M, Ekström P, Edström A and Hartley-Asp B. Effect of estramustine phosphate on the assembly of isolated bovine brain microtubules and fast axonal transport in the frog sciatic nerve. Cancer Res (1985) 45:2234-2239.
10. Kjaer, TB et al. Effect of estramustine phosphate on plasma testosterone during treatment of carcinoma of prostat. Urol (1975) 5(6):802-804.
11. Leistenschneider, W. Control of response to estramustine phosphate therapy through cytology and DNA analysis of cell nuclei in a prospective study. Urology (1984) 23(suppl):81-88.
12. Loening, SA et al. Comparison of estramustine phosphate, methotrexate, and cis-platinum in patients with advanced, hormone refractory prostate cancer. J Urol (1983) 129: 1001-1006.
13. Mittelman, A et al. Extended therapy of stage D carcinoma of the prostate with oral estramustine phosphate. J Urol (1976) 115:409-412.
14. Mittelman, A. Effect of previous treatment on Estracyt response in advanced stage D prostatic carcinoma. Urology (1984) 23 (suppl):78-80.
15. Nilsson, I et al. Inhibition by estramustine phosphate on estradiol and androgen binding in benign and malignant prostate in humans. Urol (1976) 8(2): 118-121.
16. Sandberg, AA et al. Prostatic cancer - transcortin levels during treatment with estramustine phosphate. Urol (1975) 6(1):17-21.

17. Slack, NH et al. Clinical toxicity and long-term results of Emcyt® therapy for prostate cancer. Urology (1984) 23 (suppl):73-77.

18. Tew KD and Stearns ME. Hormone-independent, non-alkylating mechanism of cytotoxicity for estramustine. Urol Res (1987) 15:155-160.

19. Toulouse, J et al. Interet de l'estramustine phosphate dans le traitement des adénocarcinomes prostatiques oestrogéno-résistants. J Urol (Paris) (1984) 90:27-33.

20. Welvaart, K. Palliative treatment with oral estracyt in disseminated prostatic carcinoma. Arch Chirag Neerlan (1975) 27: 193.

21. Welvaart, K et al. Stage D prostatic carcinoma: survival rate in relapsed patients following new forms of palliation. Urol (1974) 4:283.

PART III: CONSUMER INFORMATION

PrEMCYT
Estramustine Sodium Phosphate

This leaflet is part III of a three-part "Product Monograph" published when EMCYT was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about EMCYT. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
EMCYT is used for the treatment of metastatic cancer of the prostate in patients whose disease is not responding to hormone therapy.

What it does:
EMCYT interferes with the growth of tumour cells and may also help to slow down the growth of prostate cancer cells.

When it should not be used:
Do not take EMCYT if you have any of the following conditions:
- allergic reactions to estramustine sodium phosphate, or estradiol, or nitrogen mustard, or any of the other ingredients in EMCYT
- severe liver disease
- severe heart disease
- active inflammation of veins (thrombophlebitis) or blood clot disorders.

What the medicinal ingredient is:
The medicinal ingredient is estramustine sodium phosphate.

What the important nonmedicinal ingredients are:
Nonmedicinal ingredients include magnesium stearate, silica (colloidal anhydrous), sodium lauryl sulphate, and talc.

What dosage forms it comes in:
EMCYT is available as 140 mg capsules.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

$ EMCYT should be prescribed and used under the supervision of a doctor experienced in the use of cancer drugs.

BEFORE you use EMCYT talk to your doctor or pharmacist if you:
- **$ Have or had severe liver disease**
- **$ Have or had blood clot disorders.**
- **Have a history of stroke or heart disease**
- **Have swelling of the legs or heart failure**
- **Have high blood pressure**
- **Have bone disease associated with high calcium levels**
- **$ Have kidney problems**
- **$ Have diabetes**

Patients receiving chemotherapy agents, including EMCYT, should not be given live vaccines, or be in contact with any person who has received live vaccines, as this may result in serious infections and death.

A male patient and his female partner must use effective contraceptive methods as EMCYT can cause harm to an unborn child.

INTERACTIONS WITH THIS MEDICATION

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Drugs that may interact with EMCYT include:
- tricyclic antidepressants.
- supplements or antacids that contain calcium or milk products.
- ACE-Inhibitors (drugs to treat high blood pressure).

PROPER USE OF THIS MEDICATION

Usual dose:
The recommended dose of EMCYT is 14 mg for every kg of body weight each day. The total dose is given in 3 or 4 divided doses during the day.

The capsules should be taken on an empty stomach, at least 1 hour before or 2 hours after meals.

The capsules should be swallowed with a glass of water. Do not take with milk, milk products or calcium containing drugs (for example, antacids).

Overdose:

If you think you have taken too much EMCYT, contact a health care professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose of this medicine, skip the missed dose and go back to your regular dosing schedule. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Nausea, vomiting, diarrhea, stomach upset
- Sleepiness, fatigue
- Headache
- Confusion
- Muscle weakness
- Erectile dysfunction
- Decreased interest in having sex (low libido)
- Breast enlargement, tenderness or pain

If any of these affects you severely, tell your doctor or pharmacist.

EMCYT can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Common	**Nausea, vomiting, diarrhea, stomach upset**	√		
	Heart failure (symptoms include trouble breathing)			√
	Anemia (fatigue, loss of energy, weakness, shortness of breath)		√	
	Decreased White Blood Cells (infections, fatigue, fever, aches, pains, and flu-like symptoms)		√	
	Edema (fluid retention, swelling)		√	
	Liver Disorder (yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite)		√	
Common	**Heart attack (sudden or sever chest pain)**			√
	Blood clot (pain, redness, warmth, swelling in the leg)			√
	Decreased Platelets (bruising, bleeding, fatigue and weakness)		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	**Stroke (sudden or sever headache, confusion, weakness or numbness in arm and leg, and vision problems)**			√
Unknown	**Allergic reaction / anaphylaxis / angioedema (itching, rash, hives, swelling, tightness in chest, trouble breathing)**			√
	Cardiac ischemia (decreased oxygen in the heart with symptoms such as chest pressure or pain, shortness of breath)			√
	Depression (sad mood)		√	
	High Blood Pressure (symptoms can include headache, dizziness, blurred vision, nausea, vomiting, chest pain, shortness of breath)		√	

This is not a complete list of side effects. For any unexpected effects while taking EMCYT, contact your doctor or pharmacist.

HOW TO STORE IT

Store between 2°- 25°C.
Keep out of reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

$ Online at MedEffect (www.healthcanada.gc.ca/medeffect);
$ By calling 1-866-234-2345 (toll-free);
$ By completing a Consumer Side Effect Reporting Form and sending it by:
- Fax to 1-866-678-6789 (toll-free), or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels and the Consumer Side Effects Reporting Form are available at MedEffect.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
www.pfizer.ca
or by contacting the sponsor, Pfizer Canada Inc., Medical Information at 1-800-463-6001

This leaflet was prepared by Pfizer Canada Inc.

Last revised: 10 December 2015