SCHEDULING STATUS:

S4

ERIOX 20 / ERIOX 80:

ERIOX 20 Diluent/ ERIOX 80 Diluent:

PROPRIETARY NAME AND DOSAGE FORM:

ERIOX 20 concentrate for infusion

ERIOX 20 Diluent

ERIOX 80 concentrate for infusion

ERIOX 80 Diluent

COMPOSITION:

ERIOX 20: Each vial contains 20 mg docetaxel anhydrous.

Excipient: polysorbate 80

ERIOX 20 Diluent: Each vial contains 1,5 ml anhydrous ethanol and water for injection

ERIOX 80: Each vial contains 80 mg docetaxel anhydrous.

Excipient: polysorbate 80

ERIOX 80 Diluent: Each vial contains 6 ml anhydrous ethanol and water for injection.

PHARMACOLOGICAL CLASSIFICATION:

ERIOX 20/ ERIOX 80 concentrate for infusion: A 26 Cytostatic Agents

ERIOX 20 Diluent/ ERIOX 80 Diluent: A 34 Others

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Docetaxel is an antineoplastic agent which acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly which leads to a marked decrease of free tubulin. The binding of docetaxel to microtubules does not alter the number of protofilaments.

Docetaxel has been shown in vitro to disrupt the microtubular network in cells, which is essential for vital mitotic and interphase cellular functions. Docetaxel achieves high intracellular concentrations with a long cell residence time. In addition, docetaxel was found to be active on some, but not all, cell lines overexpressing the para-glycoprotein which is encoded by the multidrug resistance gene, in vivo, docetaxel is schedule independent.

Pharmacokinetic properties:

The kinetic profile of docetaxel is dose independent and consistent with a three compartment pharmacokinetic model with half-lives for the alpha, beta and gamma phases of 4 minutes, 36 minutes and 11,1 hours respectively. The late phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment.

Following the administration of 100 mg/m^2 doses given as one-hour infusions, a mean peak plasma level of 3,7 µg/ml was obtained with a corresponding AUC of 4,6 h.µg/ml. Mean values for total body clearance and steady-state volume of distribution were 21 L/h/m^{2}and 113 L, respectively. Docetaxel is more than 95 % bound to plasma proteins.

Faecal excretion is the main route of elimination of docetaxel and its metabolites. The faecal and urinary excretions account for about 75 % and 6 % of the dose, respectively. Only a minor fraction of the dose is excreted as the parent drug. Based on in vitro studies, isoenzymes of the cytochrome P450-3A subfamily appear to be involved in docetaxel metabolism.

INDICATIONS:

1. Breast cancer:

ERIOX, in combination with doxorubicin, is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition.

ERIOX monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer, after failure of cytotoxic therapy.

ERIOX, in combination with capecitabine, is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline.

2. Non-small cell lung cancer:

ERIOX, in combination with cisplatin, is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer, who have not previously received chemotherapy for this condition.

ERIOX is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer, even after failure of platinum-based chemotherapy.

3. Ovarian cancer:

ERIOX is indicated, after failure of first-line or subsequent chemotherapy, for treatment of metastatic carcinoma of the ovary.

4. Prostate cancer:

ERIOX in combination with prednisone or prednisolone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.

CONTRAINDICATIONS:

ERIOX is contraindicated in patients who have a history of severe hypersensitivity reactions to the medicine or polysorbate 80.

ERIOX should not be used in patients with baseline neutrophil count of <1500 cells/mm^3.

Pregnancy and lactation as **ERIOX** is teratogenic in animals.

The safe use of **ERIOX** in children has not been established.

ERIOX should not be used in patients with severe liver impairment since there is no data available (see **WARNINGS and SPECIAL PRECAUTIONS** and **DOSAGE AND DIRECTIONS FOR USE**).

Contraindications for other medicines also apply when combined with **ERIOX**.

WARNINGS and SPECIAL PRECAUTIONS:

ERIOX should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents.

Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

The incidence of treatment-related mortality associated with **ERIOX** therapy is increased in patients with abnormal liver function and in patients receiving higher doses.

ERIOX should generally not be given to patients with serum bilirubin levels > upper limit of normal (ULN), or to patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase levels >2,5 x ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity and toxic death.

Patients with isolated elevations of transaminase >1.5 x ULN also had a higher rate of febrile neutropenia grade 4, but did not have an increased incidence of toxic death. Bilirubin, AST or ALT and alkaline phosphatase values should be obtained prior to each

cycle of **ERIOX** therapy and reviewed by the treating physician.

ERIOX therapy should not be given to patients with neutrophil counts of <1500 cells/mm^3.

In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed on all patients receiving **ERIOX**.

Severe hypersensitivity reactions characterised by hypotension and/or bronchospasm, or generalised rash/erythema occurred in 2,2 % patients who received the recommended 3-day dexamethasone premedication.

Hypersensitivity reactions requiring discontinuation of **ERIOX** were reported in 5 % of patients who did not receive premedication. These reactions resolved after discontinuation of the infusion and the administration of appropriate therapy.

ERIOX must not be given to patients who have a history of severe hypersensitivity reactions to **ERIOX** or to other drugs formulated with polysorbate 80.

Severe fluid retention occurred in 6,5 % (6/92) patients despite use of a 3-day dexamethasone premedication regimen. It was characterised by one or more of the following events: poorly tolerated peripheral oedema, generalised oedema, pleural effusion requiring urgent drainage, dyspnoea at rest, cardiac tamponade or pronounced abdominal distension (due to ascites).

The use of **ERIOX** should be confined to units specialised in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a qualified oncologist. Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available. During the infusion, it is recommended that vital functions should be closely monitored. Premedication consisting of an oral corticosteroid (see below for prostate cancer) such as dexamethasone 16 mg per day (e.g. 8 mg twice daily) for 3 days, starting one day prior to **ERIOX** administration, unless contra-indicated, may reduce the incidence and severity of fluid retention as well as the

severity of hypersensitivity reactions. The pretreatment regimen for prostate cancer is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the **ERIOX** regimen.

Haematology:

Neutropenia is the most frequent adverse reaction of **ERIOX** and occurs in almost all patients. Severe neutropenia (grade 3-4) occurred in 99 % of patients on combination therapy with doxorubicin.

Neutrophil nadirs occurred at a median of 7 days but this interval may be shorter in heavily pre-treated patients. Frequent monitoring of complete blood counts should be conducted on all patients receiving **ERIOX**. Patients should be re-treated with **ERIOX** only after neutrophils recover to a level > 1500 cells/mm^3 (see **DOSAGE AND DIRECTIONS FOR USE**).

In the case of severe neutropenia (<500 cells/mm^3 for seven days or more) during a course of **ERIOX** therapy, a reduction in dose for subsequent courses of therapy and the use of appropriate symptomatic measures are recommended.

Hypersensitivity reactions:

Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of **ERIOX**, thus facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require interruption of therapy. However, more severe reactions, such as hypotension with a reduction of more than 20 mmHg, bronchospasm or generalised rash/erythema require immediate discontinuation of the infusion and appropriate symptomatic therapy.

Patients who have developed severe hypersensitivity reactions should not be re-challenged with **ERIOX**.

Fluid retention:

A premedication consisting of a corticosteroid such as oral dexamethasone 16 mg per day (e.g. 8 mg twice daily) for 3 days, starting one day prior to **ERIOX** administration, may reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

Patients with severe fluid retention such as pleural effusion, pericardial effusion and ascites should be monitored closely.

Patients with liver impairment:

In patients treated with **ERIOX** at 100 mg/m^2 who have serum transaminase levels (ALT and/or AST) greater than 1,5 times the upper limit of the normal range (ULN) concurrent with serum alkaline phosphatase levels greater than 2,5 times the upper limit of the normal range (ULN), there is a higher risk of developing severe adverse reactions such as toxic deaths, including sepsis and gastrointestinal haemorrhage which can be fatal, febrile neutropenia, infections, thrombocytopenia, stomatitis and asthenia. Therefore, the recommended dose of **ERIOX** in patients with elevated liver function test (LFTs) is 75 mg/m^2 and LFTs should be measured at baseline and before each cycle (see **DOSAGE AND DIRECTIONS FOR USE**).

For patients with serum bilirubin levels >ULN and/or ALT and AST >3,5 times the ULN concurrent with serum alkaline phosphatase levels >6 times the ULN, no dose-reduction can be recommended and **ERIOX** should not be used unless strictly indicated.

Cutaneous reactions:

Localised skin erythema of the extremities (palms of the hands and soles of the feet) with oedema followed by desquamation has been observed. This type of toxicity can lead to the interruption or discontinuation of treatment.

Nervous system:

The development of severe peripheral neurotoxicity including paraesthesia, dysaesthesia and pain has been observed in patients and requires a reduction of dose. When

symptoms persist, treatment should be stopped.

Elderly:

An analysis of safety data in patients equal to or greater than 60 years of age treated with **ERIOX** and capecitabine combination therapy showed an increase in the incidence of treatment-related Grade 3 and 4 adverse events, treatment-related serious adverse events and early withdrawals from treatment due to adverse events compared to patients less than 60 years of age. In patients treated with **ERIOX** every three weeks the incidence of anaemia, infection, nail changes, anorexia and weight loss occurred at rates > 10 % higher in patients who were 65 years of age.

Others:

Contraceptive measures must be taken during and for at least three months after cessation of therapy.

INTERACTIONS:

There have been no formal clinical studies to evaluate the drug interactions of **ERIOX**.

In vitro studies have shown that the metabolism of **ERIOX** may be modified by the concomitant administration of compounds which induce, inhibit or are metabolised by (and thus may inhibit the enzyme competitively) cytochrome P450-3A such as cyclosporine, ketoconazole, erythromycin and troleandomycin. As a result, caution should be exercised when treating patients with these drugs as concomitant therapy, since there is a potential for a significant interaction.

ERIOX is highly protein bound (> 95 %). Although the possible in vivo interaction of **ERIOX** with concomitantly administered medication has not been investigated formally, in vitro interactions with tightly protein-bound drugs such as erythromycin, diphenhydramine, propranolol, propafenone, phenytoin, salicylate, sulfamethoxazole and sodium valproate did not affect protein binding of **ERIOX**. In addition, dexamethasone did not affect protein

binding of **ERIOX**. **ERIOX** did not influence the binding of digitoxin.

In the doxorubicin/ **ERIOX** combination, the clearance of **ERIOX** was increased. Dexamethasone did not affect protein binding of **ERIOX**. When used in combination, **ERIOX** does not influence the clearance of doxorubicin and the plasma levels of doxorubicinol (a doxorubicin metabolite). However, the clearance of **ERIOX** was increased.

Clearance of **ERIOX** in combination therapy with cisplatin was similar to that observed following monotherapy. The pharmacokinetic profile of cisplatin administered shortly after **ERIOX** infusion is similar to that observed with cisplatin alone. There is no effect by capecitabine on the pharmacokinetics of docetaxel (C_{max} and AUC) and no effect by docetaxel on the pharmacokinetics of the main capecitabine metabolite 5'-DFUR.

There is no effect of prednisone on the pharmacokinetics of **ERIOX**.

PREGNANCY AND LACTATION:

Pregnancy and lactation are contra-indicated as **ERIOX** is teratogenic in animals.

DOSAGE AND DIRECTIONS FOR USE:

ERIOX should be administered by intravenous infusion only.

Dosage:

A premedication consisting of a corticosteroid (see below for prostate cancer), such as oral dexamethasone 16 mg per day (e.g. 8 mg twice daily) for 3 days, starting one day prior to **ERIOX** administration, unless contra-indicated, can be used.

For prostate cancer, given the concurrent use of prednisone or prednisolone, the recommended premedication regimen is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the **ERIOX** infusion.

1. Breast cancer:

In first-line treatment, **ERIOX** 75 mg/m^2 is administered in combination therapy with doxorubicin (50 mg/m^2).

For the second line monotherapy for previously treated patients, the recommended dosage of **ERIOX** therapy is 100 mg/m^2 in monotherapy.

In combination with capecitabine, the recommended dose of **ERIOX** is 75 mg/m^2 every three weeks, combined with capecitabine at 1250 mg/m^2 orally twice daily (within 30 minutes after a meal) for 2 weeks followed by 1-week rest period.

For capecitabine dose calculation according to body surface area, see capecitabine manufacturers' prescribing information.

2. Non-small cell lung cancer:

In combination therapy (chemotherapy naïve patients)

The recommended dosage regimen is **ERIOX** 75 mg/m^2 immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes.

In monotherapy (for previously treated patients)

The recommended dosage of **ERIOX** therapy is 100 mg/m^2 as a single agent.

3. Ovarian cancer:

The recommended dosage of **ERIOX** therapy is 100 mg/m^2.

4. Prostate cancer:

The recommended dose of **ERIOX** is 75 mg/m^2. Prednisone or prednisolone 5 mg orally twice daily is administered continuously.

Patients should be observed closely, especially during the first and second infusion of **ERIOX**, because of the risk of hypersensitivity reactions.

<u>Dosage adjustments during treatment:</u>

General:

ONLY the physician can modify the schedule of administration.

ERIOX should be administered when the neutrophil count is >1500 cells/mm^3. Patients

who experienced either febrile neutropenia, neutrophil count <500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or severe neurosensory signs and/or symptoms, during **ERIOX** therapy, should have the dosage of **ERIOX** reduced, during the subsequent cycle, from 100 mg/m^2 to 75 mg/m^2 and/or from 75 mg/m^2 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, the treatment should be discontinued.

Combination therapy with ERIOX for non-small cell lung cancer (NSCLC):

For patients who are dosed initially at **ERIOX** 75 mg/m^2 in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy is <25000 cells/mm^3, or in patients who experience febrile neutropenia, or in patients with serious non-haematologic toxicities, the **ERIOX** dosage in subsequent cycles should be reduced to 65 mg/m^2. For cisplatin dosage adjustments, see manufacturers' prescribing information.

Combination therapy with ERIOX for breast cancer:

Patients who receive adjuvant therapy for breast cancer and who experience febrile neutropenia should receive G-CSF in all subsequent cycles. Patients who continue to experience this reaction should remain on G-CSF and have their **ERIOX** dose reduced to 60 mg/m^2. If G-CSF is not used, the **ERIOX** dose should be reduced from 75 to 60 mg/m^2.

For capecitabine dose modifications when combined with **ERIOX**, see capecitabine manufacturers' prescribing information.

For patients developing the first appearance of a Grade 2 toxicity which persists at the time of the next **ERIOX**/capecitabine treatment, delay treatment until resolved to Grade 0-1, and resume at 100 % of the original dose. For patients developing the second appearance of Grade 2 toxicity, or the first appearance of Grade 3 toxicity, at any time during the treatment cycle, delay treatment until resolved to Grade 0-1, and then resume treatment with **ERIOX** 55 mg/m^2. For any subsequent appearances of toxicities, or any Grade 4 toxicities, discontinue the **ERIOX** dose.

For **ERIOX** dose modifications due to hepatic impairment, (see **WARNINGS and SPECIAL PRECAUTIONS)** section.

Special populations:

Patients with hepatic impairment:

Patients with bilirubin >ULN should generally not receive **ERIOX**. Also patients with AST and/or ALT >1,5 x ULN concomitant with alkaline phosphatase >2,5 x ULN, should generally not receive **ERIOX**.

Children:

The safety and effectiveness of **ERIOX** in children have not been established.

Elderly:

Based on a population pharmacokinetic analysis, there are no special instructions for the use in the elderly. For capecitabine dosage reduction when combined with **ERIOX,** see capecitabine manufacturers' prescribing information.

Recommendations for safe handling:

Handling precautions for cytostatic agents should be followed:

- Only trained personnel should reconstitute the agent in a designated area.
- **ERIOX** concentrate for infusion is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing **ERIOX** infusion solutions.
- The work surface should be covered with disposable plastic-backed absorbent paper.
- Adequate protective gloves and clothing should be worn.
- If **ERIOX** concentrate for infusion, premix solution or infusion solution should come into contact with the skin, wash immediately and thoroughly with soap and water. If **ERIOX** concentrate for infusion, premix solution or infusion solution should come into contact with the eyes or mucous membranes wash immediately and thoroughly with water.

- The cytotoxic preparation must not be handled by pregnant staff.
- Adequate care and precautions should be taken in the disposal of items used to reconstitute the medicine.

Directions for use:

ERIOX 20 VIAL AND ERIOX 20 DILUENT VIAL:

Each **ERIOX 20** vial contains 20 mg of docetaxel per 0,5 ml of polysorbate 80.

Each **ERIOX 20 Diluent** vial contains 1,5 ml diluent.

ERIOX 80 VIAL AND ERIOX 80 DILUENT VIAL:

Each **ERIOX 80** vial contains 80 mg docetaxel per 2 ml of polysorbate 80.

Each **ERIOX 80 Diluent** vial contains 6 ml diluent.

Preparation for intravenous administration

a) Preparation of the ERIOX premix solution (10 mg docetaxel/ml):

The vials are stored under refrigeration. Allow the required number of **ERIOX** boxes to stand at room temperature for 5 minutes.

Using a syringe fitted with a needle, aseptically withdraw the entire contents of the **ERIOX** diluent vial by partially inverting the vial.

Inject the entire contents of the syringe into the corresponding **ERIOX** vial. Remove the syringe and needle and mix manually by repeated inversions for at least 45 seconds. Do not shake.

Allow the premix vial to stand for 5 minutes at room temperature. The solution should be homogenous and clear. There may be foaming which is normal, even after 5 minutes, due to the presence of polysorbate 80 in the formulation. The premix solution contains 10 mg/ml docetaxel and should be used immediately to prepare the infusion solution. It is however stable for a maximum of 8 hours at room temperature or in the refrigerator.

b) Preparation of the infusion solution:

More than one premix vial may be necessary to obtain the required dose for the patient. Based on the required dose for the patient expressed in mg, aseptically withdraw the required amount of premix solution from the appropriate number of premix vials using graduated syringes fitted with a needle. For example, a dose of 140 mg docetaxel would require 14 ml docetaxel premix solution.

Inject the required premix volume into a 250 ml infusion bag or bottle containing either 5 % dextrose solution or 0,9 % sodium chloride solution to provide a final concentration of 0,3 to 0,74 mg docetaxel/ml. If a dose greater than 200 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0,74 mg/ml docetaxel is not exceeded.

Mix the infusion bag or bottle manually using a rocking motion.

The **ERIOX** infusion solution should be aseptically administered intravenously as soon as possible after preparation as a one-hour infusion, under room temperature and normal lighting conditions. The total duration of manipulation from start of the preparation of the bag to the end of the infusion must not exceed 4 hours.

As with all parenteral products, **ERIOX** premix solution and infusion solution should be visually inspected prior to use. Solutions containing a precipitate should be discarded.

Do not admix with other medications.

ERIOX infusion is compatible with commonly available administration sets, including PVC sets.

SIDE-EFFECTS:

Haematology:

The most frequent adverse reaction to **ERIOX** was neutropenia which was reversible and not cumulative. The median day to nadir was 7 days and the median duration of severe neutropenia (< 500 cells/mm^3) was 7 days.

Fever in absence of infection, in patients with non-small cell lung cancer, was reported in 17,2 % (1,2 % severe) of patients treated in combination with cisplatin.

Bleeding episodes have occurred and were rarely associated with severe thrombocytopenia (<50000 cells/mm^3).

Bone marrow suppression and other haematologic adverse reactions to **ERIOX** include:

		% Patients			
		Single Agent		Combination with doxorubicin	Combination with cisplatin
Number of patients		**n = 1312**	**n = 121**	**n = 258**	**n = 406**
		100 mg/m^2	**75 mg/m^2**	**75 mg/m^2**	**75 mg/m^2**
Neutropenia:	**All**	96,	89,8	99,2	91,1
	Severe **				74,8
	Severe *	76,4	54,2	91,7	51,5
Febrile Neutropenia:	**All**	11,8	8,3	34,1	4,9
	Severe	4.6			
Thrombocytopenia:	**All**	7,8	10	28,1	14,9
	Severe **				2,7
	Severe *	0,2	1,7	0,8	0,5
Anaemia:	**All**	90,4	93,3	96,1	88,6
	Severe **	8,9	10,8	9,4	6,9
Infections:	**All**	20	10,7	35,3	14,3
	Severe **	5,7	5	7,8	5,7

*NCI grade 4

**NCI grade 3-4

Hypersensitivity reactions:

Hypersensitivity reactions may occur usually within a few minutes following the start of the infusion of **ERIOX** and are mostly mild to moderate.

The most frequently reported symptoms are flushing, rash with or without pruritus, chest tightness, back pain, dyspnoea and drug fever or chills.

Severe reactions characterised by hypotension and/or bronchospasm or generalized rash/erythema, requiring therapeutic intervention may occur. These may resolve after discontinuing the infusion and appropriate therapy.

	% Patients			
	Single Agent		Combination with doxorubicin	Combination with cisplatin
	100mg/m^2	75 mg/m^2	75 mg/m^2	75 mg/m^2
All	25.9	2.5	4.7	10.6
Severe *	5.3	0	1.2	2.5

* NCI grade 3-4

Cutaneous:

Reversible cutaneous reactions may occur and were generally considered as mild to moderate. The majority of these events were reversible within 21 days. The cutaneous reactions were characterised by a rash including localised eruptions mainly on the feet and hands, but also on the arms, face or thorax and frequently associated with pruritus. Eruptions generally occurred within one week after the **ERIOX** infusion, but many recovered before the next infusion and were not disabling.

Nail disorders may occur. These were characterised by hypo- or hyperpigmentation and sometimes pain and onycholysis.

Less frequently, severe symptoms such as eruptions followed by desquamation which may rarely lead to interruption or discontinuation of **ERIOX** treatment may occur.

Cases of bullous eruptions such as erythema multiform or Stevens-Johnson syndrome have been reported. Multiple factors such as concomitant infections, concomitant medications and underlying disease may have contributed to the development of these effects.

	% Patients

		Single Agent		Combination with doxorubicin	Combination with cisplatin
		100 mg/m^2	**75 mg/m^2**	**75 mg/m^2**	**75 mg/m^2**
Cutaneous:	**All**	56.6	15.7	13.6	11.1
	Severe *	5.9	0.8	0	0.2
Nail Changes:	**All**	27.9	9.9	20.2	13.3
	Severe	2.6	0.8	0.4	0.7

*NCI grade 3-4

Fluid accumulation:

Events such as peripheral oedema and less frequently, pleural effusion, pericardial effusion, ascites, increased capillary permeability and weight gain, have been reported. The peripheral oedema usually starts at the lower extremities and may become generalised with a weight gain of 3 kg or more after 4 cycles or a cumulative dose >400 mg/m^2.

Fluid retention is cumulative in incidence and severity. The onset of moderate and severe retention is delayed in patients with premedication compared with patients without premedication; however, it has been reported in some patients during the early courses of therapy. The median time to fluid retention reversibility was 16,4 weeks (range 0 to 42 weeks) in patients receiving the recommended premedication. Fluid retention has not been accompanied by acute episodes of oliguria or hypotension.

Fluid retention has been less frequently reported in patients receiving the recommended premedication compared with patients without premedication. Dehydration and pulmonary oedema have been reported.

	% Patients			
	Single Agent		Combination with doxorubicin	Combination with cisplatin
	100 mg/m^2	**75 mg/m^2**	**75 mg/m^2**	**75 mg/m^2**
All	64.1	24.8	35.7	25.9
Severe	6.5	0.8	1.2	0.7

Gastrointestinal:

Gastrointestinal effects such as nausea, vomiting, diarrhoea and abdominal pain were observed. Constipation has occurred.

Stomatitis, oesophagitis and taste perversion have been reported.

Gastrointestinal bleeding has been observed.

Anorexia has been reported and was infrequently severe.

Occurrences of dehydration as a consequence of gastrointestinal events, gastrointestinal perforation, ischaemic colitis, colitis and neutropenic enterocolitis have been reported.

Individual cases of ileus and intestinal obstruction have been reported.

		% Patients			
		Single Agent		**Combination with doxorubicin**	**Combination with cisplatin**
		100 mg/m^2	**75 mg/m^2**	**75 mg/m^2**	**75 mg/m^2**
Nausea:	**All**	40.5	28.9	64	69.0
	Severe *	4	3.3	5	9.6
Vomiting:	**All**	24.5	16.5	45	53.4
	Severe*	3	0.8	5	7.6
Diarrhoea:	**All**	40.6	11.6	45.7	41.1
	Severe *	4	1.7	6.2	6.4
Anorexia:		16.8	19.0	8.5	28.8
Constipation:		9.8	6.6	14.3	9.4
Stomatitis:	**All**	41.8	24.8	58.1	23.4
	Severe *	5.3	1.7	7.8	2.0

*NCI grade 3-4

Neurological:

Neurosensory signs characterised by paraesthesia, dysesthesia or pain including burning, may occur.

Neuromotor events, mainly characterised by weakness, may occur.

The events were spontaneously reversible within 3 months in 35,3 % of patients with neurotoxicity following **ERIOX** treatment at 100 mg/m^2 as a single agent. Cases of convulsion or transient loss of consciousness have been observed with **ERIOX** administration. These reactions may appear during the infusion of the drug.

		% Patients			
		Single Agent		Combination with doxorubicin	Combination with cisplatin
		100 mg/m^2	75 mg/m^2	75 mg/m^2	75 mg/m^2
Neurosensory:	**All**	50	24	30.2	40.4
	Severe *	4.1	0.8	0.4	3.7
Neuromotor:	**All**	13.8	9.9	2.3	12.8
	Severe **	4	2.5	0.4	2.0

*NCI grade 3

**NCI grade 3-4

Cardiovascular:

Venous thromboembolic events and myocardial infarction have rarely been reported.

Hypertension has been reported.

		% Patients		
		Single Agent		Combination with doxorubicin
		100 mg/m^2	75 mg/m^2	75 mg/m^2
Hypotension		3.8	1.7	0.4
Cardiac dysrhythmia:	**All**	4.1	2.5	1.2
	Severe *	0.7	0	0
Heart Failure		0.5	0	2.3

* NCI grade 3-4

Hepatic:

In patients treated at 100 mg/m^2 as a single agent, increases in serum levels of AST, ALT, bilirubin and alkaline phosphatase greater than 2,5 times the ULN were observed.

In patients treated at 75 mg/m^2 as a single agent, no NCI grade 3-4 increases in serum levels of AST, ALT and alkaline phosphatase were observed and less than 2 % of the patients experienced grade 3-4 increase in bilirubin.

In patients treated in combination with doxorubicin at 75 mg/m^2, less than 1 % of patients

experienced grade 3-4 increases in AST and ALT. Grade 3-4 increase in bilirubin and alkaline phosphatase were observed in less than 2,5 % of the patients. Rare cases of hepatitis have been reported.

		% Patients		
		Single Agent		Combination with doxorubicin
		100 mg/m^2	75 mg/m^2	75 mg/m^2
AST increase:	**Severe ***	<3.0	0	<1.0
ALT increase:	**Severe ***	<2.0	0	< 1.0
Bilirubin increase:	**Severe ***	<5.0	<2.0	<2.5
Alkaline phosphatase increase:	**Severe ***	<4.0	0	<2.5

*NCI grade 3-4

Other:

Infusion site reactions were generally mild and consisted of hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis or extravasation and swelling of the vein.

In patients treated with 100 mg/m^2 as single agent, alopecia has been observed in 79 % of patients. Alopecia was considered severe in about 0,5 % of the patients.

Asthenia has been observed in 62,6 % of patients. Asthenia was severe in 11,2 % of the patients.

Arthralgias and myalgia have been observed.

Dyspnoea may occur and is frequently associated with acute hypersensitivity reactions, respiratory infections and cancerous lung involvement.

Generalised or localised pain may occur, including chest pain without any cardiac or respiratory involvement.

Acute respiratory distress syndrome, interstitial pneumonia, pulmonary fibrosis and

radiation recall phenomena have been reported.

In clinical trials rare cases of lacrimation, with or without conjunctivitis, have been reported and individual cases of lacrimal duct obstruction resulting in excessive tearing have been reported.

Rare cases of transient visual disturbances (flashes, flashing lights, scotomata) typically occurring during drug infusion and in association with hypersensitivity reactions have been reported. These were reversible upon discontinuation of the infusion.

		% Patients			
		Single Agent		**Combination with doxorubicin**	**Combination with cisplatin**
		100	**75 mg/m^2**	**75 mg/m^2**	**75 mg/m^2**
Alopecia:	**All**	79	38	94.6	73.6
	Severe*	0.5			
Asthenia:	**All**	62.6	48.8	54.7	51.5
	Severe	11.2	12.4	8.1	9.9
Myalgia:	**All**	20	5.8	8.5	13.8
	Severe	1.4	0	0	0.5
Infusion Site Reactions		5.6	0	3.1	6.2
Pain		16.5	10.7	17.1	5.4

*****NCI grade 3-4

<u>Combination therapy with ERIOX in the adjuvant treatment of breast cancer:</u>

Clinically important treatment related adverse events in patients receiving ERIOX in combination with doxorubicin and cyclophosphamide

	ERIOX 75 mg/m^2 + Doxorubicin 50 mg/m^2 + Cyclophosphamide 500 mg/m^2 n = 744 %	
Adverse Event	**Any**	**G 3/4**
Blood disorders		
Anemia	91.5	4.3
Neutropenia	71.4	65.5

Fever in absence of infection	43.1	1.2
Thrombocytopenia	39.4	2.0
Infection	27.2	3.2
Febrile neutropenia	24.7	N/A
Neutropenic infection	12.1	N/A
Immune system		
Hypersensitivity reactions	10.5	1.1
Fluid retention		
Peripheral oedema	26.7	0.4
Lymphoedema	0.3	0.0
Neurological		
Neuropathy sensory	23.8	0.0
Neuro-cortical	2.8	0.3
Neuropathy motor	2.8	0.0
Neuro-cerebellar	1.1	0.1
Syncope	0.5	0.0
Skin and subcutaneous		
Alopecia	97.7	N/A
Skin toxicity	18.4	0.7
Nail disorders	18.4	0.4
Gastrointestinal		
Nausea	80.4	5.1
Stomatitis	69.1	7.1
Vomiting	42.6	4.3
Diarrhoea	30.9	3.2
Taste perversion	27.4	0.7
Constipation	22.6	0.4
Abdominal pain	7.3	0.5
Metabolism		
Anorexia	19.9	2.2
Weight gain or loss	15.2	0.3
Reproductive		
Amenorrhoea	57.6	N/A
Respiratory		
Cough	3.1	0.0
Cardiovascular		
Cardiac dysrhythmias	3.9	0.1
Vasodilatation	20.3	0.9
Hypotension	1.5	0.0
Vascular		
Phlebitis	0.7	0.0
General		
Asthenia	79.2	11.0
Musculoskeletal		
Myalgia	22.8	0.8
Arthralgia	15.1	0.4
Eye		
Lacrimation disorder	9.8	0.1
Conjunctivitis	4.6	0.3

Of the 744 patients treated with TAC, 33,1 % experienced severe treatment emergent adverse events. Dose reductions due to hematologic toxicity occurred in 1 % of cycles. Six percent of patients discontinued treatment due to adverse events; fever in the absence of infection and allergy being the most common reasons for withdrawal. Two patients died within 30 days of their last study treatment; 1 death was considered to be related to study drug.

Fever and infection:

Fever in the absence of infection was seen in 43,1 % (G3/4: 1,3 %) of patients and infection was seen in 27,2 % (G3/4: 3,9 %) of patients. There were no septic deaths.

Gastrointestinal events:

In addition to gastrointestinal events reflected in the above table, 4 patients were reported to have colitis/enteritis/large intestine perforation. Two of these patients required treatment discontinuation; no deaths due to these events occurred.

Cardiovascular events:

The following cardiovascular events were reported: dysrythmias, all grades (3,9 %), hypotension, all grades (1,5 %) and CHF (1, 6 %). One patient died due to heart failure.

Acute myeloid leukemia/Myelodysplastic syndrome:

At a median follow-up time of 55 months, 2 patients were diagnosed with leukemia.

An additional case of leukemia was reported in the TAC arm after the follow-up period. No cases of myelodysplastic syndrome occurred.

Other persistent reactions

Ongoing events at the median follow-up time of 55 months: alopecia (22/687), amenorrhoea (133/233), neurosensory (9/73) and peripheral oedema (18/112).

<u>Combination therapy with ERIOX and capecitabine for breast cancer</u>

Summary of at least remotely related adverse events reported in >5 % of patients treated with ERIOX and capecitabine in combination

Body system Adverse Event	**Capecitabine with ERIOX (n=251)**	
	Total (%)	**Grade ¾ %**
Gastrointestinal		
Stomatitis	67	18
Diarrhoea	64	14
Nausea	43	6
Vomiting	33	4
Constipation	14	1
Abdominal pain	14	2
Dyspepsia	12	-
Abdominal pain upper	9	-
Dry mouth	5	-
Skin and subcutaneous		
Hand-foot syndrome*	63	24
Alopecia	41	6
Nail disorder	14	2
Dermatitis	8	-
Rash erythema	8	<1
Nail discolouration	6	-
Onycholysis	5	1
General		
Asthenia	23	3
Pyrexia	21	1
Fatigue	21	4
Weakness	13	1
Pain in limb	9	<1
Lethargy	6	-
Pain	6	-
Neurological		
Taste disturbance	15	<1
Paresthesia	11	<1
Dizziness	9	-
Headache	7	<1
Peripheral neuropathy	5	-
Metabolism		
Anorexia	12	1
Appetite decreased	10	-
Dehydration	8	2
Weight decreased	6	-
Eye		
Lacrimation increased	12	-
Musculoskeletal		
Myalgia	14	2
Arthralgia	11	1

Back pain	7	1
Cardiovascular		
Lower limb oedema	14	1
Respiratory		
Sore throat	11	2
Dyspnoea	7	1
Cough	6	<1
Epistaxis	5	<1
Infection		
Oral candidiasis	6	<1

- Not observed

* Grade 3 only

Frequent grade 3 and 4 laboratory abnormalities were

Adverse event	**Capecitabine with ERIOX (n=251)**
Laboratory abnormalities (according to NCI/CTC)	**Grade 3/4 %**
Neutropenia	63
Anemia	10
Thrombocytopenia	3
Hyperbilirubinemia	9

Combination therapy with ERIOX in prostate cancer patients

The following data are based on the experience of 332 patients, who were treated with **ERIOX** 75 mg/m^2 every 3 weeks in combination with prednisone or prednisolone 5 mg orally twice daily.

Clinically important treatment related adverse events in patients with prostate cancer who received ERIOX in combination with prednisone or prednisolone

	ERIOX 75 mg/m'^{2} every three weeks + prednisone (or prednisolone) 5 mg twice daily n=33 %	
Adverse event	**Any**	**G3/4**
Blood disorders:		

Anemia	66.5	4.9
Infection	12.0	3.3
Neutropenia	40.9	32.0
Thrombocytopenia	3.4	0.6
Febrile neutropenia	2.7	-
Immune system:		
Allergic reactions	6.9	0.6
Fluid retention:		
Fluid retention	24.4	0.6
Neurological:		
Neuropathy sensory	27.4	1.2
Neuropathy motor	3.9	0.0
Skin and subcutaneous:		
Alopecia	65.1	-
Nail changes	28.3	0.0
Rash/desquamation	3.3	0.3
Gastrointestinal:		
Nausea	35.5	2.4
Diarrhoea	24.1	1.2
Stomatitis/pharyngitis	17.8	0.9
Taste disturbance	17.5	0.0
Vomiting	13.3	1.2
Anorexia	12.7	0.6
Respiratory:		
Epistaxis	3.0	0.0
Cough	1.2	0.0
Dyspnoea	4.5	0.6
Cardiovascular:		
Cardiac left ventricular function	3.9	0.3
Eye:		
Tearing	9.3	0.6
General:		
Fatigue	42.8	3.9
Musculoskeletal:		
Myalgia	6.9	0.3
Arthralgia	3.0	0.3

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

In case of overdose, the patient should be kept in a specialised unit and vital functions closely monitored. There is no known antidote for **ERIOX** overdosage. The primary anticipated complications of overdosage would consist of neutropenia, mucositis, cutaneous reactions and paraesthesia. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures

should be taken, as needed.

IDENTIFICATION:

ERIOX 20 and **ERIOX 80:** Clear, oily, yellow or brown-yellow solution essentially free from particulate matter. The diluted solution is a clear, yellow solution.

ERIOX 20 Diluent and **ERIOX 80 Diluent:** Colourless, clear solution, essentially free of particulate matter.

PRESENTATION:

ERIOX 20: Transparent glass type I vials of 6 ml with a 20 mm Teflon-bromobutyl stopper, aluminium crimp cap and aqua safety flip-off.

ERIOX 20 Diluent: Transparent glass type I vials of 6 ml with a 20 mm Teflon-bromobutyl stopper, aluminium crimp cap and blue safety flip-off.

ERIOX 80: Transparent glass type I vials of 15 ml with a 20 mm Teflon-bromobutyl stopper, aluminium crimp cap and aqua safety flip-off.

ERIOX 80 Diluent: Transparent glass type I vials of 15 ml with a 20 mm Teflon-bromobutyl stopper, aluminium crimp cap and blue safety flip-off.

STORAGE INSTRUCTIONS:

Unopened vials should be stored between 2 °C and 8 °C, protected from bright light. Freezing does not adversely affect the product.

The **ERIOX** premix solution (10 mg docetaxel/ml) is stable for 8 hours in a refrigerator or at room temperature.

The **ERIOX** infusion solution must be administered as soon as possible after preparation. Discard any unused solution.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

ERIOX 20: 42/26/0006

ERIOX 20 Diluent: 42/34/0007

ERIOX 80: 42/26/0008

ERIOX 80 Diluent: 42/34/0009

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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DATE OF PUBLICATION OF THE PACKAGE INSERT:

Original date of registration and approved package insert: 4 December 2009