# GP Pharm

# Concentrate for injection 20 mg/0.5 ml and 80 mg/2 ml

# ale under recorded prescriptio Manufactured in Argentina

### Each vial of Docetaxel GP Pharm of 20 mg 80 mg contains: 20.0 mg Docetaxel anhydrous 80 0 ma 0.50 mľ Polysorbate 80 a.s. 2.00 ml Citric acid anhydrous e.q. to adjust pH 3.0-5.0 olvent vial contains: 13% (w/v) 13% (w/v)

### 1.50 ml 6.00 ml Water for injection q.s

# THERAPEUTIC ACTION

Antineoplastic drug

### INDICATIONS Breast cancer:

Docetaxel GP Pharm in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with breast cancer with operable positive axilla node.

Docetaxel GP Pharm in combination with doxorubicin is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have not received prior cytotoxic treatment for this condition.

Docetaxel GP Pharm as monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior cytotoxic treatment. Previous administered chemotherapy should have included anthracycline or an alkylating agent.

Docetaxel GP Pharm in combination with trastuzumab is indicated for the treatment of patients with metastatic breast cancer which tumors over-expressed HER2 and that have not been treated with chemotherapy for the metastatic disease.

Docetaxel GP Pharm in combination with capecitabine is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior cytotoxic chemotherapy. Previous administered chemotherapy should have included anthracycline

# - Non-small cell lung cancer:

Docetaxel GP Pharm is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy. Docetaxel GP Pharm 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.

# - Prostate cancer:

Docetaxel GP Pharm in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer. - Gastric adenocarcinoma:

Docetaxel GP Pharm in combination with cisplatin and 5-fluorouracil is indicated for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophage junction, who have not received prior chemotherapy for the metastatic disease.

### - Head and neck cancer:

Docetaxel GP Pharm in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of head and neck.

### PHARMACOLOGICAL CHARACTERISTICS

-Pharmacological action: Docetaxel is an antineoplastic agent which acts stimulating the assembly of tubulin into stable microtubules while inhibiting their depolarization. This leads to a marked decrease of free tubuline. It was proved that docetaxel disrupts the tubular network of the cells that is essential for mitotic and cellular interphase functions.

-Pharmacokinetics: At doses of 20-115 ma/m<sup>2</sup>, kinetic profile of docetaxel is dose-independent and it follows a three-compartment pharmacokinetic model, with a half-life for phase alpha, beta and gamma of 4 minutes, 36 minutes and 11.1 hours, respectively. Following the administration with a dose at 100 mg/m<sup>2</sup> as one hour infusion, the mean value for the plasma level was 3.7 µg/ml with ABC of 4.6 µg,h/ml. Mean values for total body and distribution volumes in steady state conditions were 21 L/hr/m² and 113 L, respectively. The inter-individual variation for total body was approximately 50%. Docetaxel is bound to proteins in more than 95%. Docetaxel is eliminated in both the urine and feces following oxidative metabolism by the cytochrome 450. Fecal excretion is the most important representing

approximately 75% of the total excretion.

In a pharmacokinetic test with 577 patients, docetaxel pharmacokinetics was not altered by age or genre of the patient. In a small number of patients (n=23) with laboratory data showed mild to moderate heaatic impairment (SGOT and SGPT  $\geq$  1.5 times the upper limit of normal joint with alkaline phosphatase  $\geq$  2.5 times the upper limit of normal), the total was lowered by an average 27%. of docetaxel was not modified in patients with fluid retention mild to moderate, and there are no data on patients with severe fluid retention.

## POSOLOGY / DOSAGE - ADMINISTRATION

The use of docetaxel should be restricted to units specialized in the administration of cytotoxic chemotherapy, and should be administered only under the supervision of a qualified physician experienced in the use of anti-cancerous chemotherapy.

### Premedication:

The premedication consisting of oral corticosteroids, such as dexamethasone 16 mg daily (e.g. 8 mg b.i.d.) for 3 days starting one day prior to docetaxel administration can be used for breast cancer, non-small cell lung cancer, gastric cancer and head and neck cancer, unless it is contraindicated. For hormone-refractory metastatic prostate cancer, which includes the concomitant use of prednisone or prednisolone, the recommended premedication regimen is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the docetaxel infusion

G-CSF can be used as prophylaxis in order to reduce the risk of hematologic toxicity.

Docetaxel is administered as infusion for 1 hour every three weeks.

# Docetaxel Breast Cancer

**GP** Pharm

he recommended dose of Docetaxel GP Pharm is 75 mg/m², administered 1 hour following 50 mg/m² of doxorubicin y 500 mg/m² of cyclophosphamide, every 3 weeks for 6 courses for the adjuvant therapy of breast cancer with operable positive axilla node.

The recommended dosage of docetaxel in monotherapy is 100 mg/m<sup>2</sup> for the treatment of patients with metastatic or locally advanced breast cancer. In first line treatments. 75 ma/m<sup>2</sup> of docetaxel are administered in a combined therapy with 50 ma/m<sup>2</sup> of doxorubicin.

In combination with trastuzumab, the recommended dose of docetaxel is 100 mg/m<sup>2</sup> every 3 weeks with weekly administration of trastuzumab. In an assay, the initial infusion of docetaxel started the day following the first dose of trastuzumab. Later doses of docetaxel were administered immediately after finishing the infusion of trastuzumab if the prior dose of trastuzumab was well tolerated. Consult the leaflet of trastuzumab for posoloay and administration.

In combination with capecitabine, the recommended dose of docetaxel is 75 mg/m<sup>2</sup> every 3 weeks, combined with capecitabine with dose of 1250 mg/m<sup>2</sup> b.i.d. (within 30 minutes following the meal) for 2 weeks followed by 1 week without its administration. Consult the leaflet of capecitabine to calculate the dose of capecitabine in accordance with the body weight.

### Non-small Lung Cancer

Patients with non-small cell lung cancer who have not received chemotherapy previously, the recommended dose is docetaxel 75 mg/m<sup>2</sup>, followed immediately by cisplatin 75 ma/m<sup>2</sup>, for 30-60 minutes. In the case of failure of prior platinum-based chemotherapy, the recommended dose of docetaxel is 75 ma/m<sup>2</sup>, as single gaent.

### Prostate Cancer

The recommended dose of docetaxel is 75 mg/m<sup>2</sup>. Oral prednisone or prednisolone 5 mg shall be administered orally twice a day.

### Gastric Adenocarcinoma

he recommended dose of docetaxel is 75 mg/m² for one hour infusion, followed by 75 mg/m² of cisplatin in 1 to 3 hours infusion (both just on the 1st day), followed by 750 mg/m<sup>2</sup> of 5-fluorouracil to the administered day with continuous infusion of 24 hours for 5 days and starting the end of the infusion with cisplatin. The treatment shall be repeated every 3 weeks. Patients shall receive the medicine with antiemetics and adequate hydration due to cisplatin administration. G-CSF is administered as prophylaxis in order to reduce the hematologic toxicity risk.

### Head and Neck Cancer

Patients should receive premedicine with antiemetics and adequate hydration (prior and after cisplatin administration). G-CSF can be used as prophylaxis in order to reduce the hematologic toxicity risk.

In TAX 323 and TAX 324 studies, all patients who were receiving docetaxel were administered antibiotics as prophylaxis.

- Induction chemotherapy followed by radiotherapy (TAX 323).

For the induction treatment of patients with inoperable and locally advanced head and neck squamous carcinoma, the recommended dose of docetaxel is 75 mg/m<sup>2</sup> for one-hour infusion, followed by 75 mg/m² of cisplatin, in one-hour infusion (both just on the 1st day), followed by 750 mg/m² of 5-fluorouracil daily administered in a continuous infusion for 5 days. The therapy shall be administered every 3 weeks in 4 courses. Followed the chemotherapy, patients shall receive radiotherapy. - Induction chemotherapy followed by chemo-radiotherapy (TAX 324).

For the induction treatment of patients with locally advanced head and neck squamous carcinoma (unresectable, with low possibility of surgical cure or with the aim of eserving the organs), the recommended dose of docetaxel is 75 mg/m² for one-hour infusion, followed by 100 mg/m² of cisplatin in infusion between 30 minutes and 3 hours, on the 1st day, followed by 1000 mg/m<sup>2</sup> of 5-fluorouracil daily, administered in a continuous infusion from the 1st day to the 4th day. The treatment shall be administered every 3 weeks in 3 courses. Following chemotherapy, patients must receive chemo-radiotherapy.

# Dosage adjustments during treatment

- General

Docetaxel GP Pharm shall be administered when the neutrophil count is  $\geq$  1500 cels/mm<sup>3</sup>.

In patients who have developed febrile neutropenial, neutrophils < 500 cels/mm<sup>3</sup> for more than one week, severe or accumulative skin reactions or severe peripheral neuropathy during the therapy with docetaxel, the dose with docetaxel 100 mg/m² to 75 mg/m² and/or 75 mg/m² at 60 mg/m² should be reduced. If the patient continues developing these reactions with 60 mg/m<sup>2</sup>, the treatment should be interrupted.

### - Adjuvant therapy for breast cancer

In the pivotal assay, the patients who received adjuvant therapy for breast cancer and that developed severe neutropenia (including prolonged neutropenia, febrile neutropenia or infection), the use of G-CSF was recommended in order to provide a prophylactic measure (for e.g., from the 4th day to the 11th day) in all the following courses. Patients who continue to experience this reaction should remain on G-CSF and have docetaxel dose reduced to 60 mg/m<sup>2</sup>. Nevertheless, in the clinical practice neutropenia may appear before. Thus, the use of G-CSF should be considered according to the patient's neutropenia risk and the recommendations at the moment. Patients who experience Grade 3 or 4 stomatitis should have their docetaxel dose reduced to 60 mg/m<sup>2</sup>.

### In combination with cisplatin

In patients who are initially dosed at docetaxel 75 mg/m<sup>2</sup> in combination with cisplatin and whose nadir of platelet count during the previous course of therapy was < 25,000 cells/mm<sup>1</sup>, or in patients who have experienced febrile neutropenia, or in patients with serious non-hematologic toxicities, docetaxel dosage in subsequent courses should be reduced to 65 mg/m<sup>2</sup>. For cisplatin dosage adjustments, see cisplatin leaflet.

### - In combination with capecitabine

Patients who develop Grade 2 toxicity for the first time that continues at the time of the following treatment with docetaxel/capecitabine, the administration should be delayed until it has resolved at Grade 0-1, going back to 100% of the original dose.

Patients who develop Grade 2 toxicity for the second time or Grade 3 toxicity for the first time, at any time of the treatment course, should have the administration withheld until resolution at Grade 0-1, and resuming the treatment at 55 mg/m<sup>2</sup> of docetaxel.

In case of appearance of the following toxicities or toxicity Grade 4, discontinue docetaxel therapy.

### See capecitabine leaflet to adjust capecitabine dose.

### See trastuzumab leaflet to adjust trastuzumab dose

### In combination with cisplatin and 5-fluorouraci

In case of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs despite G-CSF use, the docetaxel dose should be reduced from 75 to 60 mg/m<sup>2</sup>. If subsequent episodes of severe neutropenia with infectious complications occur, docetaxel dose should be reduced from 60 to 45 ma/m<sup>2</sup>. In case of Grade 4 thrombocytopenia, docetaxel dose should be reduced from 75 to 60 ma/m<sup>2</sup>. Patients should not be retreated with subsequent cycles of docetaxel until neutrophils recover to a level > 1,500 cells/mm<sup>3</sup> and platelets recover to a level > 100,000 cells/mm<sup>3</sup>. Discontinue the treatment if these toxicities persist.

## tecommended dose adjustments for toxicities in patients treated with docetaxel in combination with cisplatin and 5-fluorouracil (5-FU) are:

Toxicity	Dosage adjustment
Diarrhea Grade 3	First episode: reduce 5-FU dose by 20%. Second episode: reduce docetaxel dose by 20%.
Diarrhea Grade 4	First episode: reduce docetaxel and 5-FU dose by 20%. Second episode: discontinue the treatment.
Stomatitis/mucositis Grade 3	First episode: reduce 5-FU dose by 20%. Second episode: stop 5-FU only at all subsequent cycles Third episode: reduce docetaxel dose by 20%.

Stomatitis/mucositis Grade 4	First episode: stop 5-FU only at all subsequent cycles Second episode: reduce docetaxel dose by 20%.	Hematologic: The adverse effect frequently reported of docetaxel is neutropenia. The lowest level of neutrophils happen in 7 days, though this interval may be shorter in patients strongly pre-treated. During the therapy with docetaxel, frequent monitoring of plasma count should be performed to all patients. Patients should not be		nless strictly prescribed and no dosage red c insufficiency receiving docetaxel in therag			Blood disorders and lymphatic system	Neutropenia (G4: 76.4%) Anemia (G3/4: 8.9%) Febrile neutropenia	Thrombocytopenia (G4: 0	J.2%)
For the adjustments of cisplatin and 5-fluorou	acil dose, see their leaflets.	storing pre-neural. Doring the interpy with operators, requent monitoring or pushe could should be performed to an panelis. Foreins should not be administered docetaxel until neutrophils are lower than 1500 cel/mm <sup>3</sup> . In case of severe neutropenia (lower than 500 cel/mm <sup>3</sup> for 7 days or more) during a course of docetaxel therapy, dose reduction for later courses or the use of	<b>Renal impairment use:</b> There is no data in patients with renal in	nsufficiency administered docetaxel and w	ith renal impairment severely altered.		Nervous system disorders	Peripheral sensory neuropathy		
Special population -Patients with liver dysfunction		appropriate symptomatic measures is recommended. In patients administered docetaxel in combination with cisplatin and 5-fluorouracil, there was a lower incidence of febrile neutropenia and neutropenic infection when	Additional precautions in the adju	vant treatment of breast cancer				(G3: 4.1%) Peripheral motor neuropathy		
times ULN as well as the alkaline phosphatase	el dosed 100 mg/m² in monotherapy, in patients with increased transaminases values (GOT and/or GPT) higher than 1.5 higher than 2.5 times the ULN, the recommended dose of docetaxel is 75 mg/m². Patients with serum bilirrubin higher	they received G-CSF in prophylaxis. Patients administered 5-fluorouracil should be given G-CSF in prophylaxis to decrease the risk of neutropenia with complications (febrile neutropenia, prolonged neutropenia or neutropenic infection). Patients administered 5-fluorouracil should be monitored strictly.	- <u>Severe neutropenia</u> The use of G-CSF and a dose reduction s	hould be considered in patients who expe	rience severe neutropenia (prolonged neut	tropenia, febrile neutropenia or infection).		(G3/4: 4%) Dysgeusia (serious: 0.07%)		
used unless strictly indicated and dose reduction In a pivotal clinical assay of cisplatin and 5-flu	than 3.5 times ULN associated with values of alkaline phosphatase higher than 6 times the ULN, docetaxel should not be n can not be recommended. iououracil combination for the treatment of gastric adenocarcinoma, patients with values GOT and/or GPT higher than ne phosphatase higher than 2.5 times the ULN and bilirrubin higher than once ULN were excluded; dose reduction can	Hypersensitivity reactions: Patients given docetaxel should be observed dosely due to hypersensitivity reactions risk, especially during the first and second infusions. Hypersensitivity reactions may appear soon after initiating docetaxel infusion therefore means for the treatment of hypotension and bronchospasm should be available. Minor hypersensitivity	- <u>Gastrointestinal reactions</u> Early symptoms such as pain and abdor should be considered and treated imme		thout neutropenia may be early symptoms	of severe gastrointestinal toxicity and they	Respiratory, thorax and mediastinum disorders	Dyspnea (serious: 2.7%)		
not be recommended and docetaxel should not		ner papera son the mining declarate mattern mattern means on the real of the provision and the provision mattern theory and the provision of t	- Congestive heart failure	mptoms of congestive heart failure during	therapy and during the follow-up period.		Gastrointestinal disorders	Stomatitis (G3/4: 5.3%) Diarrhea (G3/4: 4%) Nauseas (G3/4: 4%) Vomiting (G3/4: 3%)	Constipation (serious: 0.2 Abdominal pain (serious: Gastrointestinal hemorrh (serious: 0.3%)	s: 1%)
- <u>Elderly</u>	tion, there are no special instructions for the use in elderly.	Cutaneous reactions: Cutaneous erythema localized in the extremities (hand palms and planta pedis) with edema followed by desquamation was observed. Severe symptoms such as	- <u>Leukemia</u> In patients treated with decetavel, dex	orubicia and curlonbocabamido, a bomat	alonical follow up is required, since much	odysplasia or secondary myeloid leukemia	Skin and subcutaneous	Alopecia		
	non, mere d'en special instructions for me use in allery. citabine, in patients older than 60 years old, an initial dose reduction of capecitabine 75% is recommended (see	control of a system to concern the extremines from a participation of docetaxel therapy were reported. Fluid retention:	can occur. - Patients with 4 or more nodules	orobicin una cyclophosphannae, a nemai	סוטקונטו וטווטש-טף וז ופקטוופט, אוונפ ווואפונ	aryspinsin of secondary inversion reovening	tissue disorders	Cutaneous reactions (G3/4: 5.9%) Nail alterations (serious: 2.6%)	1	
Preparation and handling I- <u>Recommendations about security for the har</u>	udling of this drug	Patients with severe fluid retention such as pleural effusion, pericardial effusion and ascitis should be strictly monitored.		doxorubicin and cyclophosphamide in pat	ients with 4 or more nodules is not complete	ely defined.	Musculoskeletal and connective tissue disorders	Myalgia (serious: 1.4%)	Arthralgia	
Docetaxel GP Pharm is a cytotoxic antineople Docetaxel GP Pharm solutions. The use of glov	sstic drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing es is recommended.	Neurologic: The development of severe peripheral neurotoxicity requires dose reduction.	ADVERSE REACTIONS				Metabolism and nutrition disorders	Anorexia		
If the Concentrate for infusion, the "Pre-mixte with abundant soap and water.	rre solution" or the "Solution for infusion" comes in contact with the skin or mucus, immediately and thoroughly wash	Heart failure: Heart insufficiency has occurred in patients who received docetaxel in combination with trastuzumab, particularly after anthracycline chemotherapy (doxorubicin or		ssibly or probably related with the adminis 00 mg/m² and 75 mg/m² of docetaxel in ma a combination with docerybicin			Infections and infestations	Infections (G3/4: 5.7%; including sepsis and fatal pneumonia in 1.7		utrope
II- <u>Preparation for the intravenous administra</u>	tion	rear instances in the second of a parents who receive a occase in communities in instazional, particularly are annayoune demonerapy (associated to reprivate a particularly are annayoune demonerapy (associated to reprivate a community and the second s	<ul> <li>406 patients who received docetaxel in - 406 patients who received docetaxel in - 92 patients treated with docetaxel in or</li> </ul>	a combination with cisplatin.			General disorders and alterations	Fluid retention (serious: 6.5%)	Infusion site reaction	
Docetaxel GP Pharm concentrate for injection As with all parenteral products, the solution	requires two dilutions prior to administration. Please follow the preparation instructions provided below. s of Docetaxel GP Pharm "Pre-mixture solution" or "Concentrate for infusion" should be inspected visually prior to	monitored during therapy (for example, every 3 months) in order to facilitate the identification of the patients who may develop a heart failure.	<ul> <li>- 255 patients who received docetaxel in</li> <li>- 332 patients who received docetaxel in</li> </ul>	n combination with capecitabine n combination with prednisone or prednisc	olone (there are clinically important advers	e reactions related to the therapy).	in the infusion site	Asthenia (serious: 11.2%) Pain	Non-cardiac thorax pain (serious: 0.4%)	
administration. If they appear to have precipit		PRECAUTIONS	described).			erse reactions related with the therapy are	Immunologic system disorders	Hypersensitivity (G3/4: 5.3%)		
of the vial and the unused volumes. This over 10 mg/ml docetaxel in the "Pre-mixture solution	it contains an over-fill to compensate for liquid loss during preparation of pre-mixture due to foam, adhesion to the sides fill ensures that after dilution with the entire contents of the accompanying diluent, there is a concentration containing on".	Drug interactions: studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450-3A4, such as cyclosporine, terfenadine, ketoconazole, erythromycin, and troleandomycin. Caution should be exercised with these	combination with cisplatin and 5-fluore - 174 and 251 patients with head and r	ouracil (the clinically important adverse re neck cancer who received docetaxel in com	actions related to the therapy are described	phase II study) who received docetaxel in I). (the clinically important adverse reactions	Blood and lymphatic system disorders Rare: hemorrhagic events associated v	ith thrombocytopenia G3/4.		
A- <u>Preparation of the Pre-mixture solution</u> : 1- Separate the necessary quantity of vials of I room temperature for approximately 5 minute	Docetaxel GP Pharm concentrate for injection vials and diluent. If the vials are stored under refrigeration, allow them at 55.	drugs when treating patients receiving Docetaxel GP Pharm as there is a potential risk for a significant interaction. Docetaxel binding to proteins is high (>95%). Even though the possible interactions of docetaxel with drugs administered concomitantly have not been studied formally, interactions with strong-binding drugs to proteins such as erythromycin, diphenhydramine, propanolol, propetence, phenytoin,				4) and COSTART terrm. The frequency are	<u>Nervous system disorders</u> There are reversibility data in 35.3% reversible spontaneously within 3 mon		xicity after the therapy with 100 .	mg/m²
	ith a syringe with needle by partially inverting the vial and transfer it to the appropriate vial of Docetaxel GP Pharm is followed as described, the Pre-mixture solution of 10 mg docetaxel/ml will result.	salicyicates, sulfametoxazole and sodium valproic acid do not affect docetaxel binding to proteins. Besides, dexamethasone does not affect docetaxel binding to proteins. Docetaxel does not affect digaxin binding to proteins. Docetaxel, doxarubicin and cyclophosphamide pharmacokinetics is not affected by their co-administration. There exists limited data from a no-controlled study that	The adverse reactions are listed in a dea The adverse reactions described more f	reasing order in accordance with the serio requently for docetaxel alone were: neutr	usness in each frequency interval. openia (reversible and non-cumulative; th	ne median time to nadir was 7 days and the diarrhea and asthenia. The seriousness of	Skin and subcutaneous tissue disorder Rare: a case of non-reversible alopecic			ihle wit
3-Withdraw the syringe and needle, manually	and gently by repeated inversions of each vial containing Pre-mixture solution for at least 45 seconds, do not shake.	suggest an interaction between docetaxel and carboplatin. When carboplatin-docetaxel is co-administered, carboplatin will be 50% higher than the value obtained with carboplatin monotherapy. Docetaxel pharmacokinetics in presence of prednisone was studied in patients with metastatic prostate cancer. Docetaxel is metabolized through CYP3A4 and it is	docetaxel adverse reactions may increa	se when administered in combination with	other chemotherapeutic agents.	cidence of serious adverse reactions (40%	General disorders and alterations in th	· · · · · ·	TOTATIGOOS LEACTIONS MELE LEVELSIC	Die will
4- Stand the vial with the Pre-mixture solutio after 5 minutes due to the polysorbate 80 in the	n for 5 minutes at room temperature and then check the solution is homogeneous and clear (any foam is normal, also formula).	known that prednisone induces CYP3A4. Stadistically significant effects of prednisone on docetaxel pharmacokinetics have not been observed. Docetaxel should be administered with caution in patients receiving potent inhibitors CYP3A4 concomitantly (e.g. protease inhibitors such as ritonavir, azolic	as against 31%) and grade 4 adverse docetaxel.	e reactions (34% as against 23%) in the	e group treated in association with trastu	zumab, compared to the monotherapy of	The median of the dose accumulated f weeks (rate of 0 to 42 weeks). The bo medication, compared with patients w	or interrupting the therapy was more the seline of the moderate to severe reter	ntion is delayed (median of the d	dose a
	xxel/ml) should be used immediately after to prepared the Solution for infusion; however the chemical and physical d of 8 hours was demonstrated when it is stored at room temperature (under 25°C) or refrigerated (2-8°C).	antifungal such as ketoconazole or itraconazole). An interaction drug test performed to patients who received ketoconazole and docetaxel showed that docetaxel came down to the half on account of ketoconazole, probably because CYP3A4 takes part in docetaxel metabolism as main (unique) metabolic pathway. A reduction of docetaxel tolerance may happen, also with low dosage.	cancer who do not respond to anthracyc	line therapy.		nn a buase nu assay ni baneius wini preasi	baseline courses of the therapy.		Jose accontotatea: 407.7 mg/m )	); nev
B - <u>Preparation of the Solution for infusion</u> : 1 - More than one vial of the Pre-mixture may b	e needed in order to obtain the required dose for the patient.	Carcinogenesis, mutagenesis and fertility: Carcinogenic potential of docetaxel has not been studied vet.	Neurologic Alterations	ere observed frequently with docetas		ed by paresthesias, dysesthesia or pain with	Docetaxel GP Pharm 75 mg/m² in System of organ classification Me		reactions > 10%	00
2- Based on the dose required for the patier	t expressed in mg, withdraw the necessary corresponding volume of Pre-mixture solution (10 mg/ml de docetaxel)	Docetures I have shown to be mutagenic in the micronucleous test and in the chromosome aberration test on CHO-KT cells and <b>in-the</b> micronucleus test in mice. However, docetaxel did not induce mutagenicity in the Ames test or in the CHO/HGPRT gene mutation assay.	burning sensation. Neuromotor signs a		, ,		, , , , , , , , , , , , , , , , , , ,	of the patients		Oct of
	). For example, 140 mg docetaxel dose would require 14 ml Pre-mixture solution.	These results are coherent with the pharmacological activity of docetaxel. The adverse effects of testis observed in taxicity studies in rodents suggest that docetaxel may produce impairment male fertility.				l localized eruptions, mainly on the hands	Complementary exploration			1
	re solution in a bag or vial of 250 ml containing glucose solution 5% or sodium chloride 0.9%. required, use a higher volume of injection fluid so that a concentration no higher than 0.74 mg/ml is obtained.	Pregnancy:	occurred within one week after doceto	axel infusion. Less frequently, serious sy	mptoms were observed as eruptions follo	have been observed. Eruptions generally wed by desquamation that rarely caused erpigmentation and sometimes, pain and	Heart disorders	N	(4.00/1)	Ari
5- Manually, mix the bag or the infusion vial wi		There is no data about the use of docetaxel in pregnant women. Embryotoxic and fetotoxic effects were observed in rabbits and rats and it produced impairment of fertility in rats. As other cytotoxic drugs, docetaxel may cause fetal harm when administered to pregnant women. Therefore, docetaxel must not be administered during pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant during thetaxet with this happened. The treating	onycholysis.	enater merupy. Jerrous uneranons in me	, hans are characterized by hype- of hype	apignenianon ana somennes, pan ana	Blood and lymphatic system disorders	Neutropenia (G4: 54 Anemia (G3/4: 10.8 Thrombocytopenia (	3%)	ret
6- Aseptically, administrate Docetaxel GP Pho	rm concentrate for injection intravenously within 4 hours after the preparation (including the injection time) at room	physician should be told immediately. Contraceptive messures should be taken during treatment, and also at least three months after finishing it.	• •		inflammation, redness or dryness of the sl	kin, phlebitis, extravasation, or swelling of	Nervous system disorders		neuropathy (G3/4: 0.8%)	Per
temperature (less than 25°C) and in normal lig	hting conditions.	Nursing mothers:				on, ascites and weight gaining. Peripheral	Gastrointestinal disorders	Nauseas (G3/4: 3.3		Cor
	administration should be discarded in accordance with the standard procedures for these cases.	Docetaxel is a lipophilic substance but it is not known whether it is excreted in human milk. Therefore, because of the risk for potential adverse reactions in nursing infants, lactation should be discontinued during docetaxel treatment.	seriousness.	remities and may become generalized w	ith a weight gain of 3 kg or more. Fluid	retention is cumulative in incidence and		Stomatitis (G3/4: 1. Vomiting (G3/4: 0.8 Diarrhea (G3/4: 1.7	3%)	
	nts with basal neutrophil count under 1500 cel/mm³.	Pediatric use: The safety and effectiveness of docetaxel in pediatric patients have not been established.	frequently were: redness, rash with or v	vithout pruritus, tightness, backache, dysp		o moderate. The symptoms reported more ns were characterized by hypotension and /	Skin and subcutaneous tissue disorde	s Alopecia Cutaneous reactions	; (G3/4: 0.8%)	Na
	nts with severe liver insufficiency since there are no data about it.	Geriatric use: Based on pharmacokinetic data in this population, there are no special instructions about its use in elderly patients.	or bronchospasm or generalized rash /				Musculoskeletal and connective tissue	disorders		My
The contraindications of other drugs are applie WARNINGS	d when they are combined with docetaxel.	Patients administered docetaxel in combination with capecitabine who are over 60 years old, a baseline dose reduction of capecitabine 75% is recommended (see capecitabine leaflet).	Docetaxel GP Pharm 100 mg/m <sup>2</sup> in System of organ classification		Occasional adverse reactions	Rare adverse reactions	Metabolism and the nutrition disorde	s Anorexia		┢
Docetaxel GP Pharm should be administered	under the supervision of a qualified physician experienced in the use of anti-neoplastics. Appropriate management of fiagnostic and treatment facilities and equipment are readily available.	Hepatic impairment use:	MedDRA	Frequent adverse reactions $\geq$ 10% of the patients	1% - 10% of the patients	<pre>&lt; 1% of the patients</pre>	Infections and infestations	Infections (G3/4: 5%	(o)	$\square$
Premedication:		Patients administered 100 mg/m <sup>2</sup> docetaxel in monotherapy with serum transaminase (GOT and/or GPT) higher than 1.5 times ULV concomitant with serum alkaline phosphatase > 2.5 x ULN are at risk of developing severe adverse reactions such as toxic deaths including sepsis, gastrointestinal hemorrhage that may result fatal, febrile neutropenia, interioris, thrombocytopenia, stomatifis and asthenia. Therefore, the recommended dose in those pointers with high marker levels of the hepatic	Complementary exploration		<ul> <li>↑ Blood bilirrubin G3/4 (&lt;5%)</li> <li>↑ Blood alkaline phosphatase G3/4</li> </ul>		Vascular disorders			Ну
days starting 1 day prior to docetaxel admir hypersensitivity reactions.	cer, the premedication consisting of oral corticoesteroids, such as dexamethasone 16 mg daily (ex. 8 mg BID) for three histration, unless contraindicated, can reduce the incidence and severity of fluid retention as well as the severity of	function is 75 mg/m², and such markers' levels shall be controlled at the beginning of the treatment and before each course. In patients with serum bilirrubin greater than the ULN and/or GOT and GPT higher than 3.5 times the ULN concurrent with serum levels of alkaline phosphatase higher than 6 times the ULN, a dose reduction can not be recommended and docetaxel should not be used unless strictly prescribed.			(<4%) ↑ GOT G3/4 (<3%) ↑ GPT G3/4 (<2%)		General disorders and alterations in t administration site	he Asthenia (serious: 1: Fluid retention (seri Pain		
rot prostate cancer, the recommended premed	ication regimen is oral dexamethasone 8 mg, at 12 hours, 3 hours and 1 hour before infusion of docetaxel.	In the clinic pivotal assay with cisplatin and 5-fluorouracil for the treatment of gastric adenocarcinoma, patients with levels of GOT and/or GPT higher than 1.5 times the ULN were excluded, they were associated with levels of alkaline phosphatase higher than 2.5 times the ULN and bilirrubin higher than once the ULN; in these	Heart disorders		Arrhythmia (G3/4: 0.7%)	Heart failure	Immunologic system disorders			Ну

0.2%)	
.2%) s: 1%) hage	Esophagitis (serious: 0.4%)
ieutropenia	
1	

therapy with 100 mg/m<sup>2</sup> docetaxel in monotherapy. These reactions were

ctions were reversible within 21 days.

<sup>2</sup> and the median time for the reversibility of the fluid retention was 16.4 l (median of the dose accumulated: 818.9 mg/m²) in patients with preted: 489.7 mg/m<sup>2</sup>); nevertheless, it was observed in some patients in the

10%	Occasional adverse reactions 1% - 10% of the patients
	↑ Blood bilirrubin G3/4 (<2%)
	Arrhythmia (non serious)
	Febrile neutropenia
4: 0.8%)	Peripheral motor neuropathy (G3/4: 2.5%)
	Constipution
	Nails alterations (serious 0.8%)
	Myalgia
	Hypotension
	Hypersensitivity (non-serious)

# Docetaxel GP Pharm 75 mg/m<sup>2</sup> in combination with doxorubicin

5			
System of organ classification MedDRA	Frequent adverse reactions $\geq$ 10% of the patients	Occasional adverse reactions 1% - 10% of the patients	Rare adverse reactions $\leq 1\%$ of the patients
Complementary exploration		↑ Blood bilirrubin G3/4 (<2.5%) ↑ Blood alkaline phosphatase G3/4 (< 2.5%)	↑ GOT G3/4 (<1%) ↑ GPT G3/4 (<1%)
Cardiac disorders		Cardiac failure Arrhythmia (non-serious)	
Blood and lymphatic system disorders	Neutropenia (G4: 91.7%) Anemia (G3/4: 9.4%) Febrile neutropenia Thrombocytopenia (G4: 0.8%)		
Nervous system disorders	Peripheral sensory neuropathy (G3: 0.4%)	Peripheral motor neuropathy (G3/4: 0.4%)	
Gastrointestinal disorders	Nausea (G3/4: 5%) Stomatitis (G3/4: 7.8%) Diarrhea (G3/4: 6.2%) Vomiting (G3/4: 5%) Constipation		
Skin and subcutaneous tissue disorders	Alopecia Nails alterations (serious: 0.4%) Cutaneous reactions (non-serious)		
Musculoskeletal and connective tissue alterations		Myalgia	
Metabolism and nutrition disorders		Anorexia	
Infections and infestations	Infection (G3/4: 7.8%)		
Vascular disorders			Hypotension
General disorders and alterations in the administration site	Asthenia (serious: 8.1%) Fluid retention (serious: 1.2%) Pain		
Immunologic system disorders		Hypersensitivity (G3/4: 1.2%)	

# Docetaxel GP Pharm 75 mg/m² in combination with cisplatin

System of organ classification MedDRA	Frequent adverse reactions $\geq$ 10% of the patients	Occasional adverse reactions 1% - 10% of the patients	Rare adverse reactions $\leq 1\%$ of the patients
Complementary exploration		↑ Blood bilirrubin G3/4 (2.1%) ↑ GPT G3/4 (1.3%)	↑ GOT G3/4 (0.5%) ↑ Blood alkaline phosphatase G3/4 (0.3%)
Cardiac disorders		Arrythmia (G3/4: 0.7%)	Cardiac failure
Blood and lymphatic system disorders	Neutropenia (G4: 51.5%) Anemia (G3/4: 6.9%) Thrombocytopenia (G4: 0.5%)	Febrile neutropenia	
Nervous system disorders	Peripheral sensory neuropathy (G3: 3.7%) Peripheral motor neuropathy (G3/4: 2%)		
Gastrointestinal disorders	Nausea (G3/4: 9.6%) Vomiting (G3/4: 7.6%) Diarrhea (G3/4: 6.4%) Stomatitis (G3/4: 2%)		
Skin and subcutaneous tissue disorders	Alopecia Nails alteration (serious: 0.7%) Cutaneous reactions (G3/4: 0.2%)		
Musculoskeletal and connective tissue alterations	Myalgia (serious: 0.5%)		
Metabolism and the nutrition disorders	Anorexia		
Infections and infestations	Infection (G3/4: 5.7%)		
Vascular disorders		Hypotension (G3/4: 0.7%)	
General disorders and alterations in the administration site Immunologic system disorders	Asthenia (serious: 9.9%) Fluid retention (serious: 0.7%) Fever (G3/4:1.2%) Hypersensitivity	Reaction in the infusion site Pain	

(G3/4:2.5%)		

# Docetaxel GP Pharm 100 mg/m<sup>2</sup> in combination with trastuzumab

System of organ classification MedDRA	Frequent adverse reactions $\geq$ 10% of the patients	Occasional adverse reactions 1% - 10% of the patients
Complementary exploration	Weight gaining	
Cardiac disorders		Cardiac failure
Blood and lymphatic system disorders	Neutropenia (G4: 32%) Febrile neutropenia (including neutropenia associated to fever and antibiotic administration) or neutropenic sepsis	
Nervous system disorders	Paresthesias. Headache. Dysgeusia. Hypoesthesia	
Ocular disorders	Lacrimation increase. Conjunctivitis	
Respiratory, thorax and mediastinal disorders	Epistaxis. Dolor pharyngolaringeo. Nasopharyngitis. Dyspnea. Cough. Rhinorrhea.	
Gastrointestinal disorders	Nausea. Diarrhea. Vomiting. Constipation. Stomatitis. Dyspepsia. Abdominal pain	
Skin and subcutaneous tissue disorders	Alopecia. Erythema. Rash. Nails alterations.	
Musculoskeletal and connective tissue alterations	Myalgia. Arthralgia. Extremities pain. Bone pain. Back pain.	
Metabolism and nutrition disorders	Anorexia	
Vascular disorders	Limphoedema	
General disorders and alterations in the administration site	Asthenia. Peripheral edema. Pyrexia. Fatigue. Mucous inflammation. Pain. Similar disease to influenza. Thorax pain. Shivering.	Lethargy
Psychiatric disorders	Insomnia	

# Heart disorders

Symptomatic heart failure was observed in 2.2% of the patients receiving docetaxel with trastuzumab, compared to 0% of the patients administered docetaxel in monotherapy. In the group treated with docetaxel in association with trastuzumab, the 64% had received anthracycline as adjuvant therapy, compared to 55% in the group treated with docetaxel in monotherapy.

# Blood and lymphatic system disorders

Frequent: the hematologic toxicity increased in patients who received trastuzumab and docetaxel, compared with docetaxel in monotherapy (neutropenia grade 3/4, 32% as against 22%, according to the criterion NCI-CTC). It should be taken into account that this is probably subestimated, since it is known that 100 mg/m<sup>2</sup> docetaxel dose in monotherapy produces neutropenia in 97% of the patients, 76% grade 4, according to blood count in the lowest point. The incidence of febrile neutropenia/sepsis associated to neutropenia increased in patients administered trastuzumab and docetaxel (23% as against 17% in patients treated only with docetaxel).

# Docetaxel GP Pharm 75 $\mathrm{mg}/\mathrm{m}^2$ in combination with capecitabine

System of organ classification MedDRA	Frequent adverse reactions $\geq$ 10% of the patients	Occasional adverse reactions 1% - 10% of the patients
Complementary exploration		Weight lost ↑ Blood bilirrubin G3/4 (9%)
Blood and lymphatic system disorders	Neutropenia (G3/4: 63%); Anemia (G3/4: 10%)	Thrombocytopenia (G3/4: 3%)
Nervous system disorders	Dysgeusia (G3/4: < 1%) Paresthesias (G3/4: < 1%)	Sickness Headache (G3/4: < 1%) Neuropathy peripheral
Ocular disorders	Lacrimation increase	
Respiratory, thorax and mediastinal disorders	Pharyngolaringeo pain (G3/4: 2%)	Dispnea (G3/4: 1%) Cough (G3/4: < 1%) Epistaxis (G3/4: < 1%)
Gastrointestinal disorders	Stomatitis (G3/4: 18%) Diarrhea (G3/4: 14%) Nousea (G3/4: 4%) Vomiting (G3/4: 4%) Constipation (G3/4: 1%) Abdominal pain (G3/4: 2%) Dyspepsia	Upper abdominal pain. Mouth dryness.
Skin and subcutaneous tissue disorders	Hand=foot syndrome (G3/4: 24%) Alopecia (G3/4: 6%) Nails alterations (G3/4: 2%)	Dermatitis Erythematous rash (G3/4: <1%) Nail bleach Onycholysis (G3/4: 1%)

									1		
Musculoskeletal and connective tissue di	orders Myalgia (G3/4: 2%) Arthralgia (G3/4: 1%)		Extremities pain (G3/4: <1%) Backache (G3/4: 1%)	Musculoskeletal and connective tissue alterations	Myalgia (G3/4: 0.8%) Arthralgia (G3/4: 0.4%)			Blood and lymphatic system disorders	Neutropenia (G3/4: 76.3%) Anemia (G3/4: 9.2%) Thrombocytopenia (G3/4: 5.2%)	Febrile neutropenia	
Metabolism and nutrition disorders	Anorexia (G3/4: 1%) Appetite lost		Dehydration (G3/4: 2%)	Metabolism and nutrition disorders	Anorexia (G3/4: 2.2%)			Nervous system disorders	Dysgeusia/Parosmia Peripheral	Sickness	
Infections and infestations			Oral candidiasis (G3/4: < 1%)	Infections and infestations	Infection (G3/4: 3.2%) Neutropenic infection				sensory neuropathy (G3/4: 0.6%)		
General disorders and alterations in the	Asthenia (G3/4: 3%)		Lethargy. Pain.		There were no deaths due to sepsis			Ocular disorders		Lacrimation increase Conjunctivitis	
administration site	Pyrexia (G3/4: 1%) Fatigue/weakness (G3/4 Peripheral edema (G3/4			Vascular disorders	Vasodilatation (G3/4: 0.9%)	Hypotension (G3/4: 0%)	Phlebitis (G3/4: 0%) Lymphoedema (G3/4: 0%)	Ear and labyrinth disorders		Hearing failure	
Docetaxel GP Pharm 75 mg/m² in co	nbination with prednisone or predr	isolone		General disorders and alterations in the administration site	Asthenia (G3/4: 11%) Fever (G3/4: 1.2%)			Gastrointestinal disorders	Nausea (G3/4: 0.6%) Stomatitis (G3/4: 4.0%)	Constipation Esophagitis/dysphagia/odynophagia	
System of organ classification Med	DRA Frequent adverse rea of the patients	ctions <u>≥</u> 10%	Occasional adverse reactions 1% - 10% of the patients	Immunologic system disorders	Peripheral edema (G3/4: 0.4%) Hypersensitivity (G3/4: 1.1%)				Diarrhea (G3/4: 2.9%) Vomiting (G3/4: 0.6%)	(G3/4: 0.6%) Abdominal pain Dyspepsia - Gastrointestinal	
Heart disorders			Reduction of the cardiac function of the left ventricle (G3/4: 0.3%)	Breast and reproduction system disorders	Amenorrhea			Skin and subcutaneous tissue disorders	Alopecia (G3/4: 10.9%)	hemorrhage (G3/4: 0.6%) Rash/pruritus Skin dryness	
Blood and lymphatic system disorders	Neutropenia (G3/4: 329 Anemia (G3/4:4.9%)	6)	Thrombocytopenia (G3/4: 0.6%) Febrile neutropenia		too (2.3% with a follow-up median time of	70 months). In each therapy gro	up, a patient died due to heart failure.	W 11111 1 2		Cutaneous desquamation (G3/4: 0.6%)	
Nervous system disorders	Neuropathy sensory peri Dysgeusia (G3/4: 0%)	pheral (G3/4: 1.2%)	Peripheral motor neuropathy (G3/4: 0%)	neuropathy at the end of chemotherap		edian time of 55 months in 9 of th	e patients out of 73 patients with peripheral sensory	Musculoskeletal and connective tissue alterations	A	Myalgia (G3/4: 0.6 %)	
Ocular disorders			Lacrimation increase (G3/4: 0.6%)			s in 22 patients out of 687 patient	s with alopecia at the end of chemotherapy.	Metabolism and nutrition disorders	Anorexia (G3/4: 0.6%)		
Respiratory, thorax and mediastinal disc	rders		Epistaxis (G3/4: 0%) Dyspnea (G3/4: 0.6%)	the chemotherapy.	continued in the follow-up median time of	55 months in 18 patients out of 1	12 patients who had peripheral edema at the end of	Infections and infestations	Infection (G3/4: 6.3%) Neutropenic infection		
Gastrointestinal disorders	Nausea (G3/4: 2.4%)		Cough (G3/4: 0%)	Breast and reproduction system disord It was observed that amenorrhea con chemotherapy.		55 months in 133 patients out a	f 233 patients with amenorrhea at the end of the	Benign, malignant and no specified neoplasias (including cysts and polyps)		Neoplastic pain (G3/4: 0.6%)	
	Diarrhea (G3/4: 1.2%) Stomatitis/ Pharyngitis				ombination with cisplatin and 5-fluo	rouracil (for gastric adenoca	rcinoma)	Vascular disorders		Venous disorders (G3/4: 0.6%)	
Skin and subcutaneous tissue disorders	Vomiting (G3/4: 1.2%) Alopecia Nail alteration (non-ser		Exfoliative rash (G3/4: 0.3%)	System of organ classification Me	dDRA Frequent adverse rea of the patients		ccasional adverse reactions 1% - 10% the patients	General disorders and alterations in the administration site	Lethargy (G3/4: 3.4%) Pyrexia (G3/4: 0.6%) Fluid retention Edema		
Musculoskeletal and connective tissue di		,	Arthralgia (G3/4: 0.3%)	Heart disorders		A	rrhythmia (G3/4: 1.0%)	Immunologic system disorders		Hypersensitivity (non serious)	
			Myalgia (G3/4: 0.3%)	Blood and lymphatic system disorders	Neutropenia (G3/4: 83.	2%)		Induction therapy followed by a	ı hemoradiotherapy (TAX 324)		
Metabolism and nutrition disorders	Anorexia (G3/4: 0.6%)				Thrombocytopenia (G3/ Febrile neutropenia	(4: 8.8%)		System of organ classification	Frequent adverse reactions	Occasional adverse reactions	Rare adverse reactions
Infections and infestations General disorders and alterations in the	Infection (G3/4: 3.3%)			Nervous system disorders	Peripheral sensory neur		ickness (G3/4: 2.3%) eripheral motor neuropathy (G3/4: 1.3%)	MedDRA Complementary explorations	≥ 10% of the patients Weight loss	1% - 10% of the patients	<u>&lt; 1% of the patients</u> Weight gaining
administration site	Fatigue (G3/4: 3.9%) Fluid retention (serious	0.6%)		Ocular disorders			acrimation increase (G3/4: 0%)	Heart disorders	weight loss	Arrhythmia (G3/4: 2.0%)	Weight gaining Myocardial ischemia
Immunologic system disorders			Hypersensitivity (G3/4: 0.6%)	Ear and labyrinth disorders			Itered hearing (G3/4: 0%)	Blood and lymphatic system disorders	Neutropenia (G3/4: 83.5%)	Annymine (00/1.2.070)	
Docetaxel GP Pharm 75 mg/m <sup>2</sup> in co	nbination with doxorubicin and cyc	ophosphamide		Gastrointestinal disorders	Diarrhea (G3/4: 19.7%		onstipation (G3/4: 1.0%)		Anemia (G3/4: 12.4%) Thrombocytopenia (G3/4: 4.0%		
System of organ classification MedDRA	Frequent adverse reactions $\geq$ 10% of the patients	Occasional adverse rea 1% - 10% of the patie			Nausea (G3/4: 16%) Stomatitis (G3/4: 23.7% Vomitina (G3/4: 14.3%	%) E	sastrointestinal pain (G3/4: 1.0%) sophagitis/dysphagia/odynophagia (G3/4: 0.7%)	Nervous system disorders	Febrile neutropenia Dysgeusia/parosmia (G3/4: 0.4%)	Sickness (G3/4: 2.0%)	
Complementary exploration	Weight gaining or loss (G3/4: 0.3 %)			Skin and subcutaneous tissue disorder	s Alopecia (G3/4: 4.0%)	, F	ash/pruritus (G3/4: 0.7%)		Peripheral sensory neuropathy (G3/4: 1.2%)	Peripheral motor neuropathy (G3/4: 0.4%)	
Heart disorders		Arrhythmia (G3/4: 0.1%) Congestive heart failure					lail alterations (G3/4: 0.7%) utaneous desquamation (G3/4: 0%)	Ocular disorders		Lacrimation increase	Conjunctivitis
Blood and lymphatic system disorders	Anemia (G3/4: 4.3%)			Metabolism and nutrition disorders	Anorexia (G3/4: 11.7%	)		Ear and labyrinth disorders	Hearing failure (G3/4: 1.2%)		
	Neutropenia (G3/4: 65.5%) Thrombocytopenia (G3/4: 2.0%) Febrille neutropenia			Infections and infestations	Neutropenic infection Infection (G3/4: 11.7%)	)		Gastrointestinal disorders	Nausea (G3/4: 13.9%) Stomatitis (G3/4: 20.7%)	Dyspepsia G3/4: 0.8%) Gastrointestinal pain G3/4: 1.2%)	
Nervous system disorders	Dysgeusia (G3/4: 0.7%) Peripheral sensory neutropenia (G3/4: 0%)	Peripheral motor neuropa (G3/4: 0%) Neurocortical (G3/4: 0.3% Neurocerebellar (G3/4: 0.	6)	General disorders and alterations in the administration site	Lethargy (G3/4: 19%) Fever (G3/4: 2.3%) Fluid retention (serious,				Vomiting (G3/4: 8.4%) Diarrhea (G3/4: 6.8%) Esophagitis/dysphagia/odynophagia (G3/4: 12.0%) Constipation (G3/4: 0.4%)	Gastrointestinal hemorrhagia (G3/4: 0.4%)	
Ocular disorders		Lacrimation alteration G3 Conjunctivitis (G3/4: 0.3%		Immunologic system disorders Blood and lymphatic system disorders	Hypersensitivity (G3/4:			Skin and subcutaneous tissue disorders	Alopecia (G3/4: 4%) Rash/pruritus	Skin dryness Cutaneous desquamation	
		Cough (G3/4: 0%)		secondary prophylaxis in 19.3% of the		neutropenia and the infection ass	its, regardless of using G-CSF. G-CSF was used as ociated with neutropenia appeared, respectively, in te patients without G-CSF in prophylaxis.	Musculoskeletal and connective tissue alterations		Myalgia (G3/4: 0.4 %)	
			5%) Colitis/enteritis/ Large intestine	Docetaxel GP Pharm 75 mg/m² in a • Induction therapy followed by	combination with cisplatin and 5-fluo	rouracil (for head and neck c	ancer)	Metabolism and nutrition disorders	Anorexia (G3/4: 12.0%)		
disorders "	Nausea (G3/4: 5.1%) Stomatitis (G3/4: 7.1%)	Abdominal pain (G3/4: 0.	nerforation	- muuchon merapy tonowed by	radiomerupy (TAX 323)			Infections and infestations	Infection (G3/4: 3.6%)	Neutropenic infection	
lisorders	Stomatitis (G3/4: 7.1%) Vomiting (G3/4: 4.3%)	Abdominal pain (63/4: 0.	perforation	System of organ elassification	Frequent adverse reactions	Occasional adverse react	ions Rare adverse reactions		1		
disorders " Gastrointestinal disorders	Stomatitis (G3/4: 7.1%) Vomiting (G3/4: 4.3%) Diarrhea (G3/4: 3.2%) Constipation (G3/4: 0.4%)	Abdominal pain (63/4: 0.	perforation	System of organ classification MedDRA	Frequent adverse reactions $\geq 10\%$ of the patients	Occasional adverse react 1% - 10% of the patient		Benign, malignant and non specified neoplasia (including cysts and polyps)		Neoplastic pain (G3/4: 1.2%)	
Respiratory, thorax and mediastinal disorders Gastrointestinal disorders Skin and subcutaneous tissue disorders	Stomatitis (G3/4: 7.1%) Vomiting (G3/4: 4.3%) Diarrhea (G3/4: 3.2%) Constipation (G3/4: 0.4%)	Abdominal pain (G3/4: 0.	perforation				is ≤ 1% of the patients				Venous disorders

System of organ classification MedDRA	Frequent adverse reactions $\geq 10\%$ of the patients	Occasional adverse reactions 1% - 10% of the patients	Rare adverse respectively $\leq 1\%$ of the p
Complementary exploration	Weight gaining or loss (G3/4: 0.3 %)		
Heart disorders		Arrhythmia (G3/4: 0.1%) Congestive heart failure	
Blood and lymphatic system disorders	Anemia (G3/4: 4.3%) Neutropenia (G3/4: 65.5%) Thrombocytopenia (G3/4: 2.0%) Febrille neutropenia		
Nervous system disorders	Dysgeusia (G3/4: 0.7%) Peripheral sensory neutropenia (G3/4: 0%)	Peripheral motor neuropathy (G3/4: 0%) Neurocortical (G3/4: 0.3%) Neurocerebellar (G3/4: 0.1%)	Syncope (G3/4: 0
Ocular disorders		Lacrimation alteration G3/4: 0.1%) Conjunctivitis (G3/4: 0.3%)	
Respiratory, thorax and mediastinal disorders		Cough (G3/4: 0%)	
Gastrointestinal disorders	Nausea (G3/4: 5.1%) Stomatitis (G3/4: 7.1%) Vomiting (G3/4: 4.3%) Diarrhea (G3/4: 3.2%) Constipation (G3/4: 0.4%)	Abdominal pain (G3/4: 0.5%)	Colitis/enteritis/ I perforation
Skin and subcutaneous tissue disorders	Alopecia Skin toxicity (G3/4: 0.7%) Nail alterations (G3/4: 0.4%)		

General disorders and alterations in the administration site	Lethargy (G3/4: 4.0%) Pyrexia (G3/4: 3.6%) Fluid retention (G3/4: 1.2%) Edema (G3/4: 1.2%)						
Immunologic system disorders			Hypersensitivity				
Post-marketing experience	•						
Heart disorders							
Rare cases of myocardial infarction we	re reported.						
Blood and lymphatic system disorders							
	hematological adverse reactions were info	ormed. Disseminated intravascular coagul	ation, frequently associated to sepsis a				
multiorgan failure, was reported.							
Nervous system disorders							
	consciousness loss were observed. These re	actions sometimes occur while administerin	ig the drug.				
Ocular disorders							
	orders were informed (sparkles, blinding l						
hypersensitivity reactions. They were reversible when interrupting the infusion. Rare episodes of lacrimation with or without conjunctivitis, as the lacrimal canal							
occlusion which causes excessive lacrim	ation were reported.						
Ear and labyrinth disorders							
Rare episodes of ototoxicity, disorders o							
Respiratory, thorax and mediastinal di							
	nterstitial pneumonia and fibrosis of the lu	ngs were rarely reported. Rare cases of neu	umonitis due to radiation in patients wh				
had already received radiotherapy con	comitantly were informed.						
Gastrointestinal disorders							
	sequence of gastrointestinal episodes, gastr	ointestinal perforation, ischemic colitis and	neutropenic enterocolitis were reported				
There were rare cases of paralytic ileus							
Skin and subcutaneous tissue disorders							
	atosus lupus and bullous eruptions, like i						
	sodes, other concomitant factors may have	e contributed in the development of these	effects. Scleroderma-kind modification				
generally preceded by peripheral lymp							
	ed neoplasia (including cysts and polyps)						
	emia and mielodisplastic syndrome related	to docetaxel when it was used in combinat	tion with other chemotherapeutic agen				
and/or radiotherapy were reported. Vascular disorders							
<u>vascular alsoraers</u> Rarely venous thromboembolic events	ware reported						
General disorders and alterations in th							
Rarely radiation recollection events we							
	y acute episodes of oliguria or hypotension.						
Rarely dehydration or pulmonary eder							
Immunologic system disorders	nu wustopolicu.						
Some anaphilartic shock events, somet	times fatal were informed						
Some anaphilactic shock events, somet Hepatobiliary disorders	times fatal, were informed.						

# OVERDOSE

Few cases of overdose have been reported. It is not known whether there exist antidotes for docetaxel overdose. In this case, the patient must be admitted to a specialized unit where vital signs can be monitored and support therapy can be administered as needed. In case of overdose, adverse reactions are expected to worsen. The earliest and the most important complications of overdose may include bone marrow suppression, peripheral neurotoxicity and mucositis. The patient should receive therapy with G-CSF as soon as possible when the overdose is known. When necessary, appropriate symptomatic measures shall be adopted.

# STORING CONDITIONS

Store at temperature at 2 to 8°C and protected from light.

# HOW SUPPLIED

Docetaxel GP Pharm 20 mg/0.5 ml x 1 concentrate vial and 1 solvent vial. Docetaxel GP Pharm 80 mg/2 ml x 1 concentrate vial and 1 solvent vial.

# **KEEP AWAY FROM CHILDREN**

Medicine Authorized by the Ministry of Health of Argentina. Certificate Nº 47.910.

# Manufacturer: GP Pharm S.A. Panamá 2121, (B1640DKC) Martínez, Pcia. de Buenos Aires, Argentina.

Technical Director: Carlos Donolo, Pharmacist.

