laboratorios filaxis

ADENEX Docetaxel

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

Sale under recorded prescription
Manufactured in Argentina

FORMULA

Each vial of Adenex of contains:	20 mg	80 mg
Docetaxel anhydrous	20.0 mg	80.0 mg
Polysorbate 80 q.s.	0.50 ml	2.00 ml
Citric acid anhydrous e.q. to adjust pH 3.0-5.0		
Filling volume	*0.59 ml*	*2.36 ml*
Solvent vial contains:		
Ethanol	13% (w/v)	13% (w/v)
Water for injection q.s.	1.50 ml	6.00 ml
Filling volume	*1.77 ml*	*7.08 ml*

THERAPEUTIC ACTION
Antineoplastic drug

INDICATIONS
- Breast cancer:
Adenex in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with breast cancer with operable positive axilla node.
Adenex 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.
Adenex 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.
Adenex 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.
Adenex 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:
Adenex is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.
Adenex 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:
Adenex in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer.
- Gastric adenocarcinoma:
Adenex 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:
Adenex 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 *in vitro* that docetaxel disrupts the tubular network of the cells that is essential for mitotic and cellular interphase functions.

-Pharmacokinetics: At doses of 20-115 mg/m^2, 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^2 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 *clearance* and distribution volumes in steady state conditions were 21 L/hr/m^2 and 113 L, respectively. The inter-individual variation for total body *clearance* 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 hepatic impairment (SGOT and SGPT ≥ 1.5 times the upper limit of normal joint with alkaline phosphatase ≥ 2.5 times the upper limit of normal), the total *clearance* was lowered by an average 27%. *Clearance* 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.

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

Dosage:

• **Breast Cancer**

The recommended dose of Adenex 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/m² for the treatment of patients with metastatic or locally advanced breast cancer. In first line treatments, 75 mg/m² of docetaxel are administered in a combined therapy with 50 mg/m² of doxorubicin.

In combination with trastuzumab, the recommended dose of docetaxel is 100 mg/m² 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 posology and administration.

In combination with capecitabine, the recommended dose of docetaxel is 75 mg/m² every 3 weeks, combined with capecitabine with dose of 1250 mg/m² 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/m², followed immediately by cisplatin 75 mg/m², for 30-60 minutes. In the case of failure of prior platinum-based chemotherapy, the recommended dose of docetaxel is 75 mg/m², as single agent.

• **Prostate Cancer**

The recommended dose of docetaxel is 75 mg/m². Oral prednisone or prednisolone 5 mg shall be administered orally twice a day.

• **Gastric Adenocarcinoma**

The 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/m² 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/m² 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 preserving 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/m² 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

Adenex shall be administered when the neutrophil count is ≥ 1500 cels/mm³.

In patients who have developed febrile neutropenial, neutrophils < 500 cels/mm³ 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/m², 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/m².

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/m².

- **In combination with cisplatin**

In patients who are initially dosed at docetaxel 75 mg/m² in combination with cisplatin and whose nadir of platelet count during the previous course of therapy was < 25,000 cells/mm³, 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/m². 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/m² 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-fluorouracil**

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/m². If subsequent episodes of severe neutropenia with infectious complications occur, docetaxel dose should be reduced from 60 to 45 mg/m². In case of Grade 4 thrombocytopenia, docetaxel dose should be reduced from 75 to 60 mg/m². Patients should not be retreated with subsequent cycles of docetaxel until neutrophils recover to a level > 1,500 cells/mm³ and platelets recover to a level > 100,000 cells/mm³. Discontinue the treatment if these toxicities persist.

Recommended 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%.

For the adjustments of cisplatin and 5-fluorouracil dose, see their leaflets.

Special population

-Patients with liver dysfunction

Based on pharmacokinetics data with docetaxel dosed 100 mg/m² in monotherapy, in patients with increased transaminases values (GOT and/or GPT) higher than 1.5 times ULN as well as the alkaline phosphatase higher than 2.5 times the ULN, the recommended dose of docetaxel is 75 mg/m². Patients with serum bilirrubin higher than ULN and/or GOT and GPT values higher than 3.5 times ULN associated with values of alkaline phosphatase higher than 6 times the ULN, docetaxel should not be used unless strictly indicated and dose reduction can not be recommended.

In a pivotal clinical assay of cisplatin and 5-fluououracil combination for the treatment of gastric adenocarcinoma, patients with values GOT and/or GPT higher than 1.5 times ULN associated with values of alkaline phosphatase higher than 2.5 times the ULN and bilirrubin higher than once ULN were excluded; dose reduction can not be recommended and docetaxel should not be used unless strictly indicated.

There are no data of patients with liver impairment treated with docetaxel in combined therapy for other indications.

-Children and adolescents

Experience with children is limited.

-Elderly

Based on pharmacokinetics data in this population, there are no special instructions for the use in elderly.

When it is administered combined with capecitabine, in patients older than 60 years old, an initial dose reduction of capecitabine 75% is recommended (see capecitabine leaflet).

Preparation and handling

I- Recommendations about security for the handling of this drug

Adenex is a cytotoxic antineoplastic drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Adenex solutions. The use of gloves is recommended.

If the Concentrate for infusion, the "Pre-mixture solution" or the "Solution for infusion" comes in contact with the skin or mucus, immediately and thoroughly wash with abundant soap and water.

II- Preparation for the intravenous administration

Adenex concentrate for injection requires two dilutions prior to administration. Please follow the preparation instructions provided below.

As with all parenteral products, the solutions of Adenex "Pre-mixture solution" or "Concentrate for infusion" should be inspected visually prior to administration. If they appear to have precipitation, these should be discarded.

Each vial of concentrate for infusion and diluent contains an over-fill to compensate for liquid loss during preparation of pre-mixture due to foam, adhesion to the sides of the vial and the unused volumes. This overfill ensures that after dilution with the entire contents of the accompanying diluent, there is a concentration containing 10 mg/ml docetaxel in the "Pre-mixture solution".

A- Preparation of the Pre-mixture solution:

1- Separate the necessary quantity of vials of Adenex concentrate for injection vials and diluent. If the vials are stored under refrigeration, allow them at room temperature for approximately 5 minutes.

2- Aseptically withdraw the entire contents with a syringe with needle by partially inverting the vial and transfer it to the appropriate vial of Adenex Concentrate for injection vial. If the procedure is followed as described, the Pre-mixture solution of 10 mg docetaxel/ml will result.

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.

4- Stand the vial with the Pre-mixture solution for 5 minutes at room temperature and then check the solution is homogeneous and clear (any foam is normal, also after 5 minutes due to the polysorbate 80 in the formula).

5- The Pre-mixture solution (10 mg of docetaxel/ml) should be used immediately after to prepared the Solution for infusion; however the chemical and physical stability of the Pre-mixture solution for a period of 8 hours was demonstrated when it is stored at room temperature (under 25°C) or refrigerated (2-8°C).

B- Preparation of the Solution for infusion:

1- More than one vial of the Pre-mixture may be needed in order to obtain the required dose for the patient.

2- Based on the dose required for the patient expressed in mg, withdraw the necessary corresponding volume of Pre-mixture solution (10 mg/ml de docetaxel) aseptically using gauged syringes (with needle). For example, 140 mg docetaxel dose would require 14 ml Pre-mixture solution.

3- Inject the necessary volume of the Pre-mixture solution in a bag or vial of 250 ml containing glucose solution 5% or sodium chloride 0.9%.

4- If a dose higher than 200 mg of docetaxel is required, use a higher volume of injection fluid so that a concentration no higher than 0.74 mg/ml is obtained.

5- Manually, mix the bag or the infusion vial with a rotary movement.

6- Aseptically, administrate Adenex concentrate for injection intravenously within 4 hours after the preparation (including the injection time) at room temperature (less than 25°C) and in normal lighting conditions.

C- Discard

All the materials used for the dilutions and the administration should be discarded in accordance with the standard procedures for these cases.

CONTRAINDICATIONS

Hypersensitivity to docetaxel or any of the excipients.

Adenex must not be used in patients with basal neutrophil count under 1500 cel/mm³.

Adenex must not be used in pregnant women or during lactation.

Adenex must not be used in patients with severe liver insufficiency since there are no data about it.

The contraindications of other drugs are applied when they are combined with docetaxel.

WARNINGS

Adenex should be administered under the supervision of a qualified physician experienced in the use of anti-neoplastics. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities and equipment are readily available.

Premedication:

For breast cancer and non-small cell lung cancer, the premedication consisting of oral corticoesteroids, such as dexamethasone 16 mg daily (ex. 8 mg BID) for three days starting 1 day prior to docetaxel administration, unless contraindicated, can reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

For prostate cancer, the recommended premedication regimen is oral dexamethasone 8 mg, at 12 hours, 3 hours and 1 hour before infusion of docetaxel.

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 administered docetaxel until neutrophils are lower than 1500 cel/mm³.
In case of severe neutropenia (lower than 500 cel/mm³ for 7 days or more) during a course of docetaxel therapy, dose reduction for later courses or the use of 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 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.

Hypersensitivity reactions:
Patients given docetaxel should be observed closely 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 events such as flushing or localized cutaneous reactions do not require discontinuing the therapy.
Severe hypersensitivity reactions, characterized by severe hypotension, bronchospasm, generalized rash/erythema, require the immediate discontinuation of docetaxel therapy and an appropriate therapy. Patients developing severe hypersensitivity reactions must not be administered docetaxel again.

Cutaneous reactions:
Cutaneous erythema localized in the extremities (hand palms and planta pedis) with edema followed by desquamation was observed. Severe symptoms such as eruptions followed by desquamation which have led to interruption or discontinuation of docetaxel therapy were reported.

Fluid retention:
Patients with severe fluid retention such as pleural effusion, pericardial effusion and ascitis should be strictly monitored.

Neurologic:
The development of severe peripheral neurotoxicity requires dose reduction.

Heart failure:
Heart insufficiency has occurred in patients who received docetaxel in combination with trastuzumab, particularly after anthracydine chemotherapy (doxorubicin or epirubicin). It may be mild to severe and it has been associated to death.
When patients have to be administered docetaxel in combination with tratuzumab, they should have a heart evaluation performed. The heart function should be monitored during therapy (for example, every 3 months) in order to facilitate the identification of the patients who may develop a heart failure.

PRECAUTIONS

Drug interactions:
In vitro 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 drugs when treating patients receiving Adenex as there is a potential risk for a significant interaction.
Docetaxel binding to proteins is high (>95%). Even though the possible interactions *in vivo* of docetaxel with drugs administered concomitantly have not been studied formally, *in vitro* interactions with strong-binding drugs to proteins such as erythromycin, diphenhydramine, propanolol, propafenone, phenytoin, salicylcates, 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 digoxin binding to proteins.
Docetaxel, doxorubicin and cyclophosphamide pharmacokinetics is not affected by their co-administration. There exists limited data from a no-controlled study that suggest an interaction between docetaxel and carboplatin. When carboplatin-docetaxel is co-administered, carboplatin *clearance* will be 50% higher than the value obtained with carboplatin in monotherapy.
Docetaxel pharmacokinetics in presence of prednisone was studied in patients with metastatic prostate cancer. Docetaxel is metabolized through CYP3A4 and it is 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 antifungal such as ketoconazole or itraconazole). An interaction drug test performed to patients who received ketoconazole and docetaxel showed that docetaxel *clearance* 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.

Carcinogenesis, mutagenesis and fertility:
Carcinogenic potential of docetaxel has not been studied yet.
Docetaxel has shown to be mutagenic *in vitro* in the micronudeous test and in the chromosome aberration test on CHO-K1 cells and *in vivo* in the micronudeus test in mice. However, docetaxel did not induce mutagenicity in the Ames test or in the CHO/HGPRT gene mutation assay.
These results are coherent with the pharmacological activity of docetaxel.
The adverse effects of testis observed in toxicity studies in rodents suggest that docetaxel may produce impairment male fertility.

Pregnancy:
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 therapy with docetaxel, if this happened, the treating physician should be told immediately.
Contraceptive measures should be taken during treatment, and also at least three months after finishing it.

Nursing mothers:
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.

Pediatric use:
The safety and effectiveness of docetaxel in pediatric patients have not been established.

Geriatric use:
Based on pharmacokinetic data in this population, there are no special instructions about its use in elderly patients.
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).

Hepatic impairment use:
Patients administered 100 mg/m² docetaxel in monotherapy with serum transaminase (GOT and/or GPT) higher than 1.5 times ULN 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, infections, thrombocytopenia, stomatitis and asthenia. Therefore, the recommended dose in those patients with high marker levels of the hepatic 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.
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

patients docetaxel should not be used unless strictly prescribed and no dosage reduction can be recommended.
There is no data in patients with hepatic insufficiency receiving docetaxel in therapy combined for the rest of the indications.

Renal impairment use:
There is no data in patients with renal insufficiency administered docetaxel and with renal impairment severely altered.

Additional precautions in the adjuvant treatment of breast cancer
- Severe neutropenia
The use of G-CSF and a dose reduction should be considered in patients who experience severe neutropenia (prolonged neutropenia, febrile neutropenia or infection).

- Gastrointestinal reactions
Early symptoms such as pain and abdominal sensitivity, fever, diarrhea with or without neutropenia may be early symptoms of severe gastrointestinal toxicity and they should be considered and treated immediately.

- Congestive heart failure
Patients should be monitored to find symptoms of congestive heart failure during therapy and during the follow-up period.

- Leukemia
In patients treated with docetaxel, doxorubicin and cyclophosphamide, a hematological follow-up is required, since myelodysplasia or secondary myeloid leukemia can occur.

- Patients with 4 or more nodules
The relation risk/benefit for docetaxel, doxorubicin and cyclophosphamide in patients with 4 or more nodules is not completely defined.

ADVERSE REACTIONS

The adverse reactions considered as possibly or probably related with the administration of docetaxel were obtained from:
- 1312 and 121 patients who received 100 mg/m^2 and 75 mg/m^2 of docetaxel in monotherapy, respectively.
- 258 patients who received docetaxel in combination with doxorubicin.
- 406 patients who received docetaxel in combination with cisplatin.
- 92 patients treated with docetaxel in combination with trastuzumab.
- 255 patients who received docetaxel in combination with capecitabine
- 332 patients who received docetaxel in combination with prednisone or prednisolone (there are clinically important adverse reactions related to the therapy).
- 744 patients who received docetaxel in combination with doxorubicin and cyclophosphamide (the clinically important adverse reactions related with the therapy are described).
- 300 patients with gastric adenocarcinoma (221 patients included in a phase III study and 79 patients included in a phase II study) who received docetaxel in combination with cisplatin and 5-fluorouracil (the clinically important adverse reactions related to the therapy are described).
- 174 and 251 patients with head and neck cancer who received docetaxel in combination with cisplatin and 5-fluorouracil (the clinically important adverse reactions related with the therapy are described).

These reactions were described using the NCI (Common Toxicity Criteria); grade 3=G3; grade 3-4=G3/4; grade 4=G4) and COSTART term. The frequency are defined as: frequent ($\geq$1/10), occasionally ($\geq$1/100, <1/10) and rare (<1/100).
The adverse reactions are listed in a decreasing order in accordance with the seriousness in each frequency interval.
The adverse reactions described more frequently for docetaxel alone were: neutropenia (reversible and non-cumulative; the median time to nadir was 7 days and the median duration of severe neutropenia < 500 cells/mm^3 was 7 days), anemia, alopecia, nausea, vomiting, stomatitis, diarrhea and asthenia. The seriousness of docetaxel adverse reactions may increase when administered in combination with other chemotherapeutic agents.
For the combination with trastuzumab, there are adverse reactions (all grades) observed in $\geq$10%. There was a higher incidence of serious adverse reactions (40% as against 31%) and grade 4 adverse reactions (34% as against 23%) in the group treated in association with trastuzumab, compared to the monotherapy of docetaxel.
For the combination with capecitabine, there are more frequent adverse reactions related to the therapy ($\geq$ 5%) observed in a phase III assay in patients with breast cancer who do not respond to anthracycline therapy.

The following adverse reactions were observed frequently with docetaxel:
Neurologic Alterations
The development of peripheral neurotoxicity requires dose reduction. Mild to moderate neurosensory signs are characterized by paresthesias, dysesthesia or pain with burning sensation. Neuromotor signs are mainly characterized by weakness.

Skin and cutaneous alterations
Reversible mild to moderate cutaneous reactions were observed. The reactions were characterized by rash, which included localized eruptions, mainly on the hands and/or feet (included severe hand-foot syndrome), but also in arms, face or thorax and frequently associated to pruritus have been observed. Eruptions generally occurred within one week after docetaxel infusion. Less frequently, serious symptoms were observed as eruptions followed by desquamation that rarely caused interruption or discontinuation of docetaxel therapy. Serious alterations in the nails are characterized by hypo- or hyperpigmentation and sometimes, pain and onycholysis.

General alterations and infusion site alterations
Infusion site reactions were generally mild and consisted of hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis, extravasation, or swelling of the vein.
Fluid retention has been reported, including peripheral edema; and less frequently, pleural effusion, pericardial effusion, ascites and weight gaining. Peripheral edema usually starts in the lower extremities and may become generalized with a weight gain of 3 kg or more. Fluid retention is cumulative in incidence and seriousness.

Immunologic system alterations
Hypersensitivity reactions occur generally a few minutes after initiating docetaxel infusion, and generally they were mild to moderate. The symptoms reported more frequently were: redness, rash with or without pruritus, tightness, backache, dyspnea and fever or shivering. Severe reactions were characterized by hypotension and / or bronchospasm or generalized rash / erythema.

Adenex 100 mg/m^2 in monotherapy

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 (<5%) ↑ Blood alkaline phosphatase G3/4 (<4%) ↑ GOT G3/4 (<3%) ↑ GPT G3/4 (<2%)	
Heart disorders		Arrhythmia (G3/4: 0.7%)	Heart failure

Adenex 75 mg/m² in combination with doxorubicin

System of organ classification MedDRA	Frequent adverse reactions ≥ 10% of the patients	Occasional adverse reactions 1% - 10% of the patients	Rare adverse reactions ≤ 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%)	

Adenex 75 mg/m² in combination with cisplatin

System of organ classification MedDRA	Frequent adverse reactions ≥ 10% of the patients	Occasional adverse reactions 1% - 10% of the patients	Rare adverse reactions ≤ 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	Asthenia (serious: 9.9%) Fluid retention (serious: 0.7%) Fever (G3/4: 1.2%)	Reaction in the infusion site Pain	
Immunologic system disorders	Hypersensitivity		

Blood disorders and lymphatic system	Neutropenia (G4: 76.4%) Anemia (G3/4: 8.9%) Febrile neutropenia	Thrombocytopenia (G4: 0.2%)	
Nervous system disorders	Peripheral sensory neuropathy (G3: 4.1%) Peripheral motor neuropathy (G3/4: 4%) Dysgeusia (serious: 0.07%)		
Respiratory, thorax and mediastinum disorders	Dyspnea (serious: 2.7%)		
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: 1%) Gastrointestinal hemorrhage (serious: 0.3%)	Esophagitis (serious: 0.4%)
Skin and subcutaneous tissue disorders	Alopecia Cutaneous reactions (G3/4: 5.9%) Nail alterations (serious: 2.6%)		
Musculoskeletal and connective tissue disorders	Myalgia (serious: 1.4%)	Arthralgia	
Metabolism and nutrition disorders	Anorexia		
Infections and infestations	Infections (G3/4: 5.7%; including sepsis and fatal pneumonia in 1.7%)	Infection associated to neutropenia G4 (G3/4: 4.6%)	
General disorders and alterations in the infusion site	Fluid retention (serious: 6.5%) Asthenia (serious: 11.2%) Pain	Infusion site reaction Non-cardiac thorax pain (serious: 0.4%)	
Immunologic system disorders	Hypersensitivity (G3/4: 5.3%)		

Blood and lymphatic system disorders
Rare: hemorrhagic events associated with thrombocytopenia G3/4.

Nervous system disorders
There are reversibility data in 35.3% of the patients who developed neurotoxicity after the therapy with 100 mg/m² docetaxel in monotherapy. These reactions were reversible spontaneously within 3 months.

Skin and subcutaneous tissue disorders
Rare: a case of non-reversible alopecia at the end of the study. The 73% of the cutaneous reactions were reversible within 21 days.

General disorders and alterations in the administration site
The median of the dose accumulated for interrupting the therapy was more than 1000 mg/m² and the median time for the reversibility of the fluid retention was 16.4 weeks (rate of 0 to 42 weeks). The baseline of the moderate to severe retention is delayed (median of the dose accumulated: 818.9 mg/m²) in patients with pre-medication, compared with patients without pre-medication (median of the dose accumulated: 489.7 mg/m²); nevertheless, it was observed in some patients in the baseline courses of the therapy.

Adenex 75 mg/m² in monotherapy

System of organ classification MedDRA	Frequent adverse reactions ≥ 10% of the patients	Occasional adverse reactions 1% - 10% of the patients
Complementary exploration		↑ Blood bilirrubin G3/4 (<2%)
Heart disorders		Arrhythmia (non serious)
Blood and lymphatic system disorders	Neutropenia (G4: 54.2%) Anemia (G3/4: 10.8%) Thrombocytopenia (G4: 1.7%)	Febrile neutropenia
Nervous system disorders	Peripheral sensory neuropathy (G3/4: 0.8%)	Peripheral motor neuropathy (G3/4: 2.5%)
Gastrointestinal disorders	Nauseas (G3/4: 3.3%) Stomatitis (G3/4: 1.7%) Vomiting (G3/4: 0.8%) Diarrhea (G3/4: 1.7%)	Constipation
Skin and subcutaneous tissue disorders	Alopecia Cutaneous reactions (G3/4: 0.8%)	Nails alterations (serious 0.8%)
Musculoskeletal and connective tissue disorders		Myalgia
Metabolism and the nutrition disorders	Anorexia	
Infections and infestations	Infections (G3/4: 5%)	
Vascular disorders		Hypotension
General disorders and alterations in the administration site	Asthenia (serious: 12.4%) Fluid retention (serious: 0.8%) Pain	
Immunologic system disorders		Hypersensitivity (non-serious)

(G3/4:2.5%)			

Adenex 100 mg/m² in combination with trastuzumab

System of organ classification MedDRA	Frequent adverse reactions ≥ 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 anthracydine 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/m² 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).

Adenex 75 mg/m² in combination with capecitabine

System of organ classification MedDRA	Frequent adverse reactions ≥ 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%) Nausea (G3/4: 6%) 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%)

Musculoskeletal and connective tissue disorders	Myalgia (G3/4: 2%) Arthralgia (G3/4: 1%)	Extremities pain (G3/4: <1%) Backache (G3/4: 1%)
Metabolism and nutrition disorders	Anorexia (G3/4: 1%) Appetite lost	Dehydration (G3/4: 2%)
Infections and infestations		Oral candidiasis (G3/4: < 1%)
General disorders and alterations in the administration site	Asthenia (G3/4: 3%) Pyrexia (G3/4: 1%) Fatigue/weakness (G3/4: 5%) Peripheral edema (G3/4: 1%)	Lethargy. Pain.

Adenex 75 mg/m² in combination with prednisone or prednisolone

System of organ classification MedDRA	Frequent adverse reactions ≥ 10% of the patients	Occasional adverse reactions 1% - 10% of the patients
Heart disorders		Reduction of the cardiac function of the left ventricle (G3/4: 0.3%)
Blood and lymphatic system disorders	Neutropenia (G3/4: 32%) Anemia (G3/4:4.9%)	Thrombocytopenia (G3/4: 0.6%) Febrile neutropenia
Nervous system disorders	Neuropathy sensory peripheral (G3/4: 1.2%) Dysgeusia (G3/4: 0%)	Peripheral motor neuropathy (G3/4: 0%)
Ocular disorders		Lacrimation increase (G3/4: 0.6%)
Respiratory, thorax and mediastinal disorders		Epistaxis (G3/4: 0%) Dyspnea (G3/4: 0.6%) Cough (G3/4: 0%)
Gastrointestinal disorders	Nausea (G3/4: 2.4%) Diarrhea (G3/4: 1.2%) Stomatitis/ Pharyngitis 0.9%) Vomiting (G3/4: 1.2%)	
Skin and subcutaneous tissue disorders	Alopecia Nail alteration (non-serious)	Exfoliative rash (G3/4: 0.3%)
Musculoskeletal and connective tissue disorders		Arthralgia (G3/4: 0.3%) Myalgia (G3/4: 0.3%)
Metabolism and nutrition disorders	Anorexia (G3/4: 0.6%)	
Infections and infestations	Infection (G3/4: 3.3%)	
General disorders and alterations in the administration site	Fatigue (G3/4: 3.9%) Fluid retention (serious 0.6%)	
Immunologic system disorders		Hypersensitivity (G3/4: 0.6%)

Adenex 75 mg/m² in combination with doxorubicin and cyclophosphamide

System of organ classification MedDRA	Frequent adverse reactions ≥ 10% of the patients	Occasional adverse reactions 1% - 10% of the patients	Rare adverse reactions ≤ 1% of the patients
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/ Large intestine perforation
Skin and subcutaneous tissue disorders	Alopecia Skin toxicity (G3/4: 0.7%) Nail alterations (G3/4: 0.4%)		

Musculoskeletal and connective tissue alterations	Myalgia (G3/4: 0.8%) Arthralgia (G3/4: 0.4%)		
Metabolism and nutrition disorders	Anorexia (G3/4: 2.2%)		
Infections and infestations	Infection (G3/4: 3.2%) Neutropenic infection There were no deaths due to sepsis		
Vascular disorders	Vasodilatation (G3/4: 0.9%)	Hypotension (G3/4: 0%)	Phlebitis (G3/4: 0%) Lymphoedema (G3/4: 0%)
General disorders and alterations in the administration site	Asthenia (G3/4: 11%) Fever (G3/4: 1.2%) Peripheral edema (G3/4: 0.4%)		
Immunologic system disorders	Hypersensitivity (G3/4: 1.1%)		
Breast and reproduction system disorders	Amenorrhea		

Heart disorders
Congestive heart failure was reported, too (2.3% with a follow-up median time of 70 months). In each therapy group, a patient died due to heart failure.
Nervous system disorders
It was observed that peripheral sensory neuropathy continued in the follow-up median time of 55 months in 9 of the patients out of 73 patients with peripheral sensory neuropathy at the end of chemotherapy.
Skin and subcutaneous disorders
It was observed that alopecia continued in the follow-up median time of 55 months in 22 patients out of 687 patients with alopecia at the end of chemotherapy.
General disorders and alterations in the administration site
It was observed that peripheral edema continued in the follow-up median time of 55 months in 18 patients out of 112 patients who had peripheral edema at the end of the chemotherapy.
Breast and reproduction system disorders
It was observed that amenorrhea continued in the follow-up median time of 55 months in 133 patients out of 233 patients with amenorrhea at the end of the chemotherapy.

Adenex 75 mg/m² in combination with cisplatin and 5-fluorouracil (for gastric adenocarcinoma)

System of organ classification MedDRA	Frequent adverse reactions ≥ 10% of the patients	Occasional adverse reactions 1% - 10% of the patients
Heart disorders		Arrhythmia (G3/4: 1.0%)
Blood and lymphatic system disorders	Anemia (G3/4: 20.9%) Neutropenia (G3/4: 83.2%) Thrombocytopenia (G3/4: 8.8%) Febrile neutropenia	
Nervous system disorders	Peripheral sensory neuropathy (G3/4: 8.7%)	Sickness (G3/4: 2.3%) Peripheral motor neuropathy (G3/4: 1.3%)
Ocular disorders		Lacrimation increase (G3/4: 0%)
Ear and labyrinth disorders		Altered hearing (G3/4: 0%)
Gastrointestinal disorders	Diarrhea (G3/4: 19.7%) Nausea (G3/4: 16%) Stomatitis (G3/4: 23.7%) Vomiting (G3/4: 14.3%)	Constipation (G3/4: 1.0%) Gastrointestinal pain (G3/4: 1.0%) Esophagitis/dysphagia/odynophagia (G3/4: 0.7%)
Skin and subcutaneous tissue disorders	Alopecia (G3/4: 4.0%)	Rash/pruritus (G3/4: 0.7%) Nail alterations (G3/4: 0.7%) Cutaneous desquamation (G3/4: 0%)
Metabolism and nutrition disorders	Anorexia (G3/4: 11.7%)	
Infections and infestations	Neutropenic infection Infection (G3/4: 11.7%)	
General disorders and alterations in the administration site	Lethargy (G3/4: 19%) Fever (G3/4: 2.3%) Fluid retention (serious/death threat: 1%)	
Immunologic system disorders	Hypersensitivity (G3/4: 1.7%)	

Blood and lymphatic system disorders
Febrile neutropenia and neutropenic infection appeared, respectively, in 17.2% and the 13.5% of the patients, regardless of using G-CSF. G-CSF was used as secondary prophylaxis in 19.3% of the patients (10.7% of the courses). Febrile neutropenia and the infection associated with neutropenia appeared, respectively, in 12.1% and 3.4% of the patients when they were administered G-CSF in prophylaxis and in 15.6% and 12.9% of the patients without G-CSF in prophylaxis.

Adenex 75 mg/m² in combination with cisplatin and 5-fluorouracil (for head and neck cancer)
- Induction therapy followed by radiotherapy (TAX 323)

System of organ classification MedDRA	Frequent adverse reactions ≥ 10% of the patients	Occasional adverse reactions 1% - 10% of the patients	Rare adverse reactions ≤ 1% of the patients
Complementary explorations		Weight gaining	
Heart disorders		Myocardial ischemia (G3/4: 1.7%)	Arrhythmia (G3/4: 0.6%)

Blood and lymphatic system disorders	Neutropenia (G3/4: 76.3%) Anemia (G3/4: 9.2%) Thrombocytopenia (G3/4: 5.2%)	Febrile neutropenia	
Nervous system disorders	Dysgeusia/Parosmia Peripheral sensory neuropathy (G3/4: 0.6%)	Sickness	
Ocular disorders		Lacrimation increase Conjunctivitis	
Ear and labyrinth disorders		Hearing failure	
Gastrointestinal disorders	Nausea (G3/4: 0.6%) Stomatitis (G3/4: 4.0%) Diarrhea (G3/4: 2.9%) Vomiting (G3/4: 0.6%)	Constipation Esophagitis/dysphagia/odynophagia (G3/4: 0.6%) Abdominal pain Dyspepsia Gastrointestinal hemorrhage (G3/4: 0.6%)	
Skin and subcutaneous tissue disorders	Alopecia (G3/4: 10.9%)	Rash/pruritus Skin dryness Cutaneous desquamation (G3/4: 0.6%)	
Musculoskeletal and connective tissue alterations		Myalgia (G3/4: 0.6 %)	
Metabolism and nutrition disorders	Anorexia (G3/4: 0.6%)		
Infections and infestations	Infection (G3/4: 6.3%) Neutropenic infection		
Benign, malignant and no specified neoplasias (including cysts and polyps)		Neoplastic pain (G3/4: 0.6%)	
Vascular disorders		Venous disorders (G3/4: 0.6%)	
General disorders and alterations in the administration site	Lethargy (G3/4: 3.4%) Pyrexia (G3/4: 0.6%) Fluid retention Edema		
Immunologic system disorders		Hypersensitivity (non serious)	

- **Induction therapy followed by chemoradiotherapy (TAX 324)**

System of organ classification MedDRA	Frequent adverse reactions ≥ 10% of the patients	Occasional adverse reactions 1% - 10% of the patients	Rare adverse reactions ≤ 1% of the patients
Complementary explorations	Weight loss		Weight gaining
Heart disorders		Arrhythmia (G3/4: 2.0%)	Myocardial ischemia
Blood and lymphatic system disorders	Neutropenia (G3/4: 83.5%) Anemia (G3/4: 12.4%) Thrombocytopenia (G3/4: 4.0% Febrile neutropenia		
Nervous system disorders	Dysgeusia/parosmia (G3/4: 0.4%) Peripheral sensory neuropathy (G3/4: 1.2%)	Sickness (G3/4: 2.0%) Peripheral motor neuropathy (G3/4: 0.4%)	
Ocular disorders		Lacrimation increase	Conjunctivitis
Ear and labyrinth disorders	Hearing failure (G3/4: 1.2%)		
Gastrointestinal disorders	Nausea (G3/4: 13.9%) Stomatitis (G3/4: 20.7%) Vomiting (G3/4: 8.4%) Diarrhea (G3/4: 6.8%) Esophagitis/dysphagia/odynophagia (G3/4: 12.0%) Constipation (G3/4: 0.4%)	Dyspepsia G3/4: 0.8%) Gastrointestinal pain G3/4: 1.2%) Gastrointestinal hemorrhagia (G3/4: 0.4%)	
Skin and subcutaneous tissue disorders	Alopecia (G3/4: 4%) Rash/pruritus	Skin dryness Cutaneous desquamation	
Musculoskeletal and connective tissue alterations		Myalgia (G3/4: 0.4 %)	
Metabolism and nutrition disorders	Anorexia (G3/4: 12.0%)		
Infections and infestations	Infection (G3/4: 3.6%)	Neutropenic infection	
Benign, malignant and non specified neoplasia (including cysts and polyps)		Neoplastic pain (G3/4: 1.2%)	
Vascular disorders			Venous disorders

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 were reported.

Blood and lymphatic system disorders

Bone marrow suppression and other hematological adverse reactions were informed. Disseminated intravascular coagulation, frequently associated to sepsis or multiorgan failure, was reported.

Nervous system disorders

Rare episodes of seizures or temporary consciousness loss were observed. These reactions sometimes occur while administering the drug.

Ocular disorders

Rare episodes of temporary visual disorders were informed (sparkles, blinding lights, scotoma) which appear during the drug administration and associated with 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 lacrimation were reported.

Ear and labyrinth disorders

Rare episodes of ototoxicity, disorders and/or hearing loss were informed.

Respiratory, thorax and mediastinal disorders

Acute respiratory distress syndrome, interstitial pneumonia and fibrosis of the lungs were rarely reported. Rare cases of neumonitis due to radiation in patients who had already received radiotherapy concomitantly were informed.

Gastrointestinal disorders

Rare episodes of dehydration as a consequence of gastrointestinal episodes, gastrointestinal perforation, ischemic colitis and neutropenic enterocolitis were reported. There were rare cases of paralytic ileus and intestinal obstruction.

Skin and subcutaneous tissue disorders

Very rare cases of cutaneous erythematosus lupus and bullous eruptions, like multiform erythema, Stevens-Johnson syndrome, toxic epidermal necrolysis were informed with docetaxel. In some episodes, other concomitant factors may have contributed in the development of these effects. Scleroderma-kind modifications generally preceded by peripheral lymphoedema were informed.

Benign and malignant and non specified neoplasia (including cysts and polyps)

Very rare cases of acute myeloid leukemia and mielodisplastic syndrome related to docetaxel when it was used in combination with other chemotherapeutic agents and/or radiotherapy were reported.

Vascular disorders

Rarely venous thromboembolic events were reported.

General disorders and alterations in the administration site

Rarely radiation recollection events were informed.

Fluid retention was not accompanied by acute episodes of oliguria or hypotension.

Rarely dehydration or pulmonary edema was reported.

Immunologic system disorders

Some anaphilactic shock events, sometimes fatal, were informed.

Hepatobiliary disorders

Very rare cases of hepatitis, sometime fatal, mainly in patients with prior hepatic alterations were reported.

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 below 25°C and protected from light.

HOW SUPPLIED

Adenex 20 mg/0.5 ml x 1 concentrate vial and 1 solvent vial.
Adenex 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 N° 47.910.

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