INDICATIONS AND IMPORTANT SAFETY INFORMATION, INCLUDING BLACK BOX WARNING

WARNING: TOXIC DEATHS, HEPATOTOXICITY, NEUTROPENIA, HYPERSENSITIVITY REACTIONS, and FLUID RETENTION

Treatment-related mortality associated with DOCIVYX is increased in patients with abnormal liver function, in patients receiving higher doses, and in patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who receive DOCIVYX as a single agent at a dose of 100 mg/m^2.

Avoid the use of DOCIVYX in patients with bilirubin > upper limit of normal (ULN), or to patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of severe neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with isolated elevations of transaminase >1.5 x ULN also had a higher rate of febrile neutropenia. Measure bilirubin, AST or ALT, and alkaline phosphatase prior to each cycle of DOCIVYX.

Do not administer DOCIVYX to patients with neutrophil counts of <1500 cells/mm^3. Monitor blood counts frequently as neutropenia may be severe and result in infection.

Do not administer DOCIVYX to patients who have a history of severe hypersensitivity reactions to DOCIVYX. Severe hypersensitivity reactions have been reported in patients despite dexamethasone premedication. Hypersensitivity reactions require immediate discontinuation of the DOCIVYX infusion and administration of appropriate therapy.

Severe fluid retention occurred in 6.5% (6/92) of patients despite use of dexamethasone premedication. It was characterized by one or more of the following events: poorly tolerated peripheral edema, generalized edema, pleural effusion requiring urgent drainage, dyspnea at rest, cardiac tamponade, or pronounced abdominal distention (due to ascites).

INDICATIONS

Breast Cancer

- DOCIVYX is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.
- DOCIVYX in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.

Non-small Cell Lung Cancer

- DOCIVYX as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.
- DOCIVYX 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

- DOCIVYX in combination with prednisone is indicated for the treatment of patients with metastatic CRPC.

Gastric Adenocarcinoma

DOCIVYX in combination with cisplatin and fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.

Head and Neck Cancer

- DOCIVYX in combination with cisplatin and fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATION

DOCIVYX is contraindicated in patients with:

- neutrophil counts of <1500 cells/mm^3
- a history of severe hypersensitivity reactions to docetaxel. Severe reactions, including anaphylaxis, have occurred.

WARNINGS AND PRECAUTIONS

Toxic Deaths

<u>Breast Cancer</u>

DOCIVYX administered at 100 mg/m^2 was associated with deaths considered possibly or probably related to treatment in 2.0% (19/965) of metastatic breast cancer patients, both previously treated and untreated, with normal baseline liver function and in 11.5% (7/61) of patients with various tumor types who had abnormal baseline liver function

(AST and/or ALT >1.5 times ULN together with AP >2.5 times ULN). Among patients dosed at 60 mg/m^2, mortality related to treatment occurred in 0.6% (3/481) of patients with normal liver function, and in 3 of 7 patients with abnormal liver function. Approximately half of these deaths occurred during the first cycle. Sepsis accounted for the majority of the deaths.

Non-small Cell Lung Cancer
DOCIVYX administered at a dose of 100 mg/m^2 in patients with locally advanced or metastatic non- small cell lung cancer who had a history of prior platinum-based chemotherapy was associated with increased treatment-related mortality (14% and 5% in two randomized, controlled studies). There were 2.8% treatment-related deaths among the 176 patients treated at the 75 mg/m^2 dose in the randomized trials. Among patients who experienced treatment-related mortality at the 75 mg/m^2 dose level, 3 of 5 patients had an ECOG PS of 2 at study entry.

Hepatic Impairment
Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of severe neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death.

Avoid DOCIVYX in patients with bilirubin > upper limit of normal (ULN), or to patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN.

For patients with isolated elevations of transaminase >1.5 x ULN, consider DOCIVYX dose modifications. Measure bilirubin, AST or ALT, and alkaline phosphatase prior to each cycle of DOCIVYX therapy.

Hematologic Effects
Perform frequent peripheral blood cell counts on all patients receiving DOCIVYX. Do not retreat patients with subsequent cycles of DOCIVYX until neutrophils recover to a level >1500 cells/mm^3. Avoid retreating patients until platelets recover to a level >100,000 cells/mm^3.

A 25% reduction in the dose of DOCIVYX is recommended during subsequent cycles following severe neutropenia (<500 cells/mm^3) lasting 7 days or more, febrile neutropenia, or a grade 4 infection in a DOCIVYX cycle.

Neutropenia (<2000 neutrophils/mm^3) occurs in virtually all patients given 60 mg/m^2 to 100 mg/m^2 of DOCIVYX and grade 4 neutropenia (<500 cells/mm^3) occurs in 85% of patients given 100 mg/m^2 and 75% of patients given 60 mg/m^2. Frequent monitoring of blood counts is, therefore, essential so that dose can be adjusted. DOCIVYX should not be administered to patients with neutrophils <1500 cells/mm^3.

Febrile neutropenia occurred in about 12% of patients given 100 mg/m^2 but was very uncommon in patients given 60 mg/m^2. Hematologic responses, febrile reactions and infections, and rates of septic death for different regimens are dose related.

Three breast cancer patients with severe liver impairment (bilirubin >1.7 times ULN) developed fatal gastrointestinal bleeding associated with severe drug-induced thrombocytopenia. In gastric cancer patients treated with docetaxel in combination with cisplatin and fluorouracil (TCF), febrile neutropenia and/or neutropenic infection occurred in 12% of patients receiving G-CSF compared to 28% who did not. Patients receiving TCF should be closely monitored during the first and subsequent cycles for febrile neutropenia and neutropenic infection.

Enterocolitis and Neutropenic Colitis
Enterocolitis and neutropenic colitis (typhlitis) have occurred in patients treated with DOCIVYX alone and in combination with other chemotherapeutic agents, despite the coadministration of G-CSF. Caution is recommended for patients with neutropenia, particularly at risk for developing gastrointestinal complications. Enterocolitis and neutropenic enterocolitis may develop at any time, and could lead to death as early as the first day of symptom onset. Monitor patients closely from onset of any symptoms of gastrointestinal toxicity. Inform patients to contact their healthcare provider with new, or worsening symptoms of gastrointestinal toxicity.

Hypersensitivity Reactions
Monitor patients closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or fatal anaphylaxis, have been reported in patients premedicated with 3 days of corticosteroids.

Severe hypersensitivity reactions require immediate discontinuation of the DOCIVYX infusion and aggressive therapy. Do not rechallenge patients with a history of severe hypersensitivity reactions with DOCIVYX.

Patients who have previously experienced a hypersensitivity reaction to paclitaxel may develop a hypersensitivity reaction to docetaxel that may include severe or fatal reactions such as anaphylaxis. Monitor patients with a previous history of hypersensitivity to paclitaxel closely during initiation of DOCIVYX therapy.

Hypersensitivity reactions may occur within a few minutes following initiation of a DOCIVYX infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required. All patients should be premedicated with an oral corticosteroid prior to the initiation of the infusion of DOCIVYX.

Fluid Retention
Severe fluid retention has been reported following DOCIVYX therapy. Patients should be premedicated with oral corticosteroids prior to each DOCIVYX administration to reduce the incidence and severity of fluid retention. Patients with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions.

When fluid retention occurs, peripheral edema usually starts in the lower extremities and may become generalized with a median weight gain of 2 kg.

Among 92 breast cancer patients premedicated with 3-day corticosteroids, moderate fluid retention occurred in 27.2% and severe fluid retention in 6.5%. The median cumulative dose to onset of moderate or severe fluid retention was 819 mg/m^2. Nine of 92 patients (9.8%) of patients discontinued treatment due to fluid retention: 4 patients discontinued with severe fluid retention; the remaining 5 had mild or moderate fluid retention. The median cumulative dose to treatment discontinuation due to fluid retention was 1021 mg/m^2. Fluid retention was completely, but sometimes slowly, reversible with a median of 16 weeks from the last infusion of DOCIVYX to resolution (range: 0 to 42+ weeks). Patients developing peripheral edema may be treated with standard measures, e.g., salt restriction, oral diuretic(s).

Second Primary Malignancies
Second primary malignancies, notably acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), non-Hodgkin's lymphoma (NHL), and renal cancer, have been reported in patients treated with docetaxel-containing regimens. These adverse reactions may occur several months or years after docetaxel-containing therapy.

Treatment-related AML or MDS has occurred in patients given anthracyclines and/or cyclophosphamide, including use in adjuvant therapy for breast cancer. In the adjuvant breast cancer trial (TAX316) AML occurred in 3 of 744 patients who received DOCIVYX, doxorubicin and cyclophosphamide (TAC) and in 1 of 736 patients who received fluorouracil, doxorubicin, and cyclophosphamide. In TAC-treated patients, the risk of delayed myelodysplasia or myeloid leukemia requires hematological follow-up. Monitor patients for second primary malignancies.

Cutaneous Reactions
Localized erythema of the extremities with edema followed by desquamation has been observed. In case of severe skin toxicity, an adjustment in dosage is recommended. The discontinuation rate due to skin toxicity was 1.6% (15/965) for metastatic breast cancer patients. Among 92 breast cancer patients premedicated with 3-day corticosteroids, there were no cases of severe skin toxicity reported and no patient discontinued DOCIVYX due to skin toxicity.

Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous

pustulosis (AGEP) have been reported in association with docetaxel treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. Permanent treatment discontinuation should be considered in patients who experience SCARs.

Neurologic Reactions
Severe neurosensory symptoms (e.g., paresthesia, dysesthesia, pain) were observed in 5.5% (53/965) of metastatic breast cancer patients and resulted in treatment discontinuation in 6.1%. When these symptoms occur, dosage must be adjusted. If symptoms persist, treatment should be discontinued. Patients who experienced neurotoxicity in clinical trials and for whom follow-up information on the complete resolution of the event was available had spontaneous reversal of symptoms with a median of 9 weeks from onset (range: 0 to 106 weeks). Severe peripheral motor neuropathy mainly manifested as distal extremity weakness occurred in 4.4% (42/965).

Eye Disorders
Cystoid macular edema (CME) has been reported in patients treated with DOCIVYX. Patients with impaired vision should undergo a prompt and comprehensive ophthalmologic examination. If CME is diagnosed, DOCIVYX treatment should be discontinued and appropriate treatment initiated. Alternative non-taxane cancer treatment should be considered.

Asthenia
Severe asthenia has been reported in 14.9% (144/965) of metastatic breast cancer patients but has led to treatment discontinuation in only 1.8%. Symptoms of fatigue and weakness may last a few days up to several weeks and may be associated with deterioration of performance status in patients with progressive disease.

Embryo-Fetal Toxicity
Available data from case reports in the literature and pharmacovigilance with docetaxel use in pregnant women are not sufficient to inform the drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Based on findings in animal studies and its mechanism of action, DOCIVYX can cause fetal harm when administered to a pregnant woman. DOCIVYX contains alcohol which is associated with fetal harm including central nervous system abnormalities, behavioral disorders, and impaired intellectual development.

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify pregnancy status in females of reproductive potential prior to initiating DOCIVYX. Advise females of reproductive potential to use effective contraception during treatment and for 2 months after the last dose of DOCIVYX.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the last dose of DOCIVYX.

Alcohol Content
Cases of intoxication have been reported with some formulations of docetaxel due to the alcohol content. The alcohol content in a dose of DOCIVYX may affect the central nervous system and should be taken into account for patients in whom alcohol intake should be avoided or minimized. Consideration should be given to the alcohol content in DOCIVYX on the ability to drive or use machines immediately after the infusion. Each administration of DOCIVYX at 100 mg/m^2 delivers 2.0 g/m^2 of ethanol. For a patient with a BSA of 2.0 m^2, this would deliver 4.0 grams of ethanol. Other docetaxel products may have a different amount of alcohol.

Tumor Lysis Syndrome
Tumor lysis syndrome has been reported with docetaxel. Patients at risk of tumor lysis syndrome (e.g., with renal impairment, hyperuricemia, bulky tumor) should be closely monitored prior to initiating DOCIVYX and periodically during treatment. Correction of dehydration and treatment of high uric acid levels are recommended prior to initiation of treatment.

ADVERSE REACTIONS
The most serious adverse reactions from DOCIVYX are Toxic Deaths, Hepatic Impairment, Hematologic Effects, Enterocolitis and Neutropenic Colitis, Hypersensitivity Reactions, Fluid Retention, Second Primary Malignancies, Cutaneous Reactions, Neurologic Reactions, Eye Disorders, Asthenia, Alcohol Content.

The most common adverse reactions across all DOCIVYX indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia. Incidence varies depending on the indication.

Clinical Trials Experience
Adverse events occurring in at least 5% of patients with various tumor types

Adverse reactions occurring in breast cancer patients, both treated and untreated with chemotherapy, with normal liver function tests at baseline who were treated with DOCIVYX 100 mg/m^2 and those occurring in patients with various tumor types who had normal or elevated liver function tests at baseline who were treated with DOCIVYX 100 mg/m^2 were neutropenia <2000 cells/mm^3 (96% all tumor types with normal liver function tests, 96% all tumor types with elevated liver function tests, 99% breast cancer with normal liver function tests, respectively), neutropenia <500 cells/mm^3 (75%, 88%, 86%, respectively), leukopenia <4000 cells/mm^3 (96%, 98%, 99%, respectively), leukopenia <1000 cells/mm^3 (32%, 47%, 44%, respectively), thrombocytopenia <100,000 cells/mm^3 (8%, 25%, 9%, respectively), anemia <11 g/dL (90%, 92%, 94%, respectively), anemia <8 g/dL (9%, 31%, 8%, respectively), severe febrile neutropenia (11%, 26%, 12%,

respectively), infections (severe; 6%, 16%, 6%, respectively), infections (any; 22%, 33%, 22%, respectively), fever in the absence of infection (severe; 2%, 8%, 2%, respectively), fever in the absence of infection (any; 31%, 41%, 35%, respectively), hypersensitivity reactions regardless of premedication (severe; 4%, 10%, 3%, respectively), hypersensitivity reactions regardless of premedication (any; 21%, 20%, 18%, respectively), hypersensitivity reactions with 3-day premedication (sever; 2%, 0%, 2%, respectively), hypersensitivity reactions with 3-day premedication (any; 15%, 33%, 15%, respectively), fluid retention regardless of premedication (severe; 7%, 8%, 9%, respectively), fluid retention regardless of premedication (any; 47%, 39%, 60%, respectively, fluid retention with 3-day premedication (severe; 7%, 33%, 7%, respectively), fluid retention with 3-day premedication (any; 64%, 67%, 64%, respectively), neurosensory (severe; 4%, 0%, 6%, respectively), neurosensory (any; 49%, 34%, 58%, respectively), cutaneous (severe; 5%, 10%, 5%, respectively), cutaneous (any; 48%, 54%, 47%, respectively), nail changes (severe; 3%, 5%, 4%, respectively), nail changes (any; 31%, 23%, 41%, respectively), gastrointestinal (severe; 5%, 5%, 6%, respectively), nausea (39%, 38%, 42%, respectively), vomiting (22%, 23%, 23%, respectively), diarrhea (39%, 33%, 43%, respectively), stomatitis (severe; 6%, 13%, 7%, respectively), stomatitis (any; 42%, 49%, 52%, respectively), alopecia (76%, 62%, 74%, respectively), asthenia (severe; 13%, 25%, 15%, respectively), asthenia (any; 62%, 53%, 66%, respectively), myalgia (severe; 2%, 2%, 2%, respectively), myalgia (any; 19%, 16%, 21%, respectively), arthralgia (9%, 7%, 8%, respectively), and infusion site reactions (4%, 3%, 4%, respectively). Septic death (2%, 5%, 1%, respectively) and non-septic death (1%, 7%, 1%, respectively) also occurred.

Monotherapy with DOCIVYX for locally advanced or metastatic breast cancer after failure of prior chemotherapy

Hematologic adverse reactions (Grade 3/4) occurring in breast cancer patients previously treated with chemotherapy with normal or elevated liver function tests who were treated with DOCIVYX 100 mg/m^2 or those with normal liver function tests who were treated with DOCIVYX 60 mg/m^2 were neutropenia <500 cells/mm^3 (84%, 94%, and 75% at 100 mg/m^2 with normal liver function tests, 100 mg/m^2 with elevated liver function test, and at 60 mg/m^2 with normal liver function tests, respectively), thrombocytopenia <20,000 cells/mm^3 (1%, 17%, 1%, respectively), infection (7%, 33%, 0%, respectively), febrile neutropenia by patient (12%, 33%, 0%, respectively), and febrile neutropenia by course (2%, 9%, 0%, respectively).

Hematologic adverse reactions (any) occurring in breast cancer patients previously treated with chemotherapy with normal or elevated liver function tests who were treated with DOCIVYX 100 mg/m^2 or those with normal liver function tests who were treated with DOCIVYX 60 mg/m^2 were neutropenia <2,000 cells/mm^3 (98%, 100%, and 95% at 100 mg/m^2 with normal liver function tests, 100 mg/m^2 with elevated liver function tests, and at 60 mg/m^2 with normal liver function tests, respectively), thrombocytopenia

<100,000 cells/mm^3 (11%, 44%, 14%, respectively), anemia <11 g/dL (95%, 94%, 65%, respectively), and infection (23%, 39%, 1%, respectively).

Severe non-hematologic adverse reactions occurring in breast cancer patients previously treated with chemotherapy with normal or elevated liver function tests who were treated with DOCIVYX 100 mg/m^2 or those with normal liver function tests who were treated with DOCIVYX 60 mg/m^2 were acute hypersensitivity reaction regardless of premedication (1%, 0%, and 0% at 100 mg/m^2 with normal liver function tests, 100 mg/m^2 with elevated liver function test, and at 60 mg/m^2 with normal liver function tests, respectively), fluid retention regardless of premedication (8%, 17%, 0%, respectively), neurosensory (6%, 0%, 0%, respectively), cutaneous (5%, 17%, 0%, respectively), asthenia (17%, 22%, 0%, respectively), diarrhea (6%, 11%, NA, respectively), and stomatitis (8%, 39%, 1%, respectively).

Non-hematologic adverse reactions (any) occurring in breast cancer patients previously treated with chemotherapy with normal or elevated liver function tests who were treated with DOCIVYX 100 mg/m^2 or those with normal liver function tests who were treated with DOCIVYX 60 mg/m^2 were acute hypersensitivity reaction regardless of premedication (13% ,6%, and 1% at 100 mg/m^2 with normal liver function tests, 100 mg/m^2 with elevated liver function test, and at 60 mg/m^2 with normal liver function tests, respectively), fluid retention regardless of premedication (56%,61%,13, respectively), neurosensory (57%,50%,20%, respectively), myalgia (23%,33%,3%, respectively), cutaneous (45%,61%,31%, respectively), asthenia (65%,44%,66%, respectively), diarrhea (42%,28%,NA, respectively), and stomatitis (53%,67%,19%, respectively).

Septic death (2%,6%,1%, respectively), and non-septic death (1%,11%,0%, respectively) also occurred.

Monotherapy trial (TAX313) comparing DOCIVYX 60 mg/m^2, 75 mg/m^2 and 100 mg/m^2 in advanced breast cancer

The following adverse reactions were associated with increasing docetaxel doses: fluid retention (26%, 38%, and 46% at 60 mg/m^2, 75 mg/m^2, and 100 mg/m^2, respectively), thrombocytopenia (7%,11%,12%, respectively), neutropenia (92%, 94%, 97% respectively), febrile neutropenia (5%,7%,14%, respectively), treatment-related grade 3 or 4 infection (2%, 3%, 7%, respectively) and anemia (87%, 94%, 97%, respectively).

Combination therapy with DOCIVYX in the adjuvant treatment of breast cancer

Adverse reactions (Grade 3/4) occurring in patients with breast cancer who were treated with DOCIVYX 75 mg/m^2 every 3 weeks in combination with doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 (TAX316) were anemia (4%), neutropenia (66%), fever in the absence of infection (1%), infection (4%), thrombocytopenia (2%),

hypersensitivity reactions (1%), fluid retention (1%), neuro-cortical (1%), syncope (1%), skin toxicity (1%), nausea (5%), stomatitis (7%), vomiting (4%), diarrhea (4%), constipation (1%), taste perversion (1%), anorexia (2%), abdominal pain (1%), vasodilation (1%), asthenia (11%), myalgia (1%), and arthralgia (1%).

Adverse reactions (any) occurring in patients with breast cancer who were treated with DOCIVYX 75 mg/m^2 every 3 weeks in combination with doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 (TAX316) were anemia (92%), neutropenia (71%), fever in the absence of infection (47%), infection (39%), thrombocytopenia (39%), febrile neutropenia (25%), neutropenic infection (12%), hypersensitivity reactions (13%), lymphedema (4%), fluid retention (35%), peripheral edema (27%), weight gain (13%), neuropathy sensory (26%), neuro-cortical (5%), neuropathy motor (4%), neuro-cerebellar (2%), syncope (2%), alopecia (98%), skin toxicity (27%), nail disorders (19%), nausea (81%), stomatitis (69%), vomiting (45%), diarrhea (35%), constipation (34%), taste perversion (28%), anorexia (22%), abdominal pain (11%), amenorrhea (62%), cough (14%), cardiac dysrhythmias (8%), vasodilation (27%), hypotension (2%), phlebitis (1%), asthenia (81%), myalgia (27%), arthralgia (19%), lacrimation disorder (11%), and conjunctivitis (5%).

Monotherapy with DOCIVYX for unresectable, locally advanced or metastatic non-small cell lung cancer (NSCLC) previously treated with platinum-based chemotherapy

Adverse reactions (Grade 3/4 or severe) occurring in patients with locally advanced or metastatic NSCLC and a history of prior treatment with platinum-based chemotherapy who were treated with DOCIVYX 75 mg/m^2 monotherapy were neutropenia (65%), leukopenia (49%), thrombocytopenia (3%), anemia (9%), febrile neutropenia (6%), infection (10%), hypersensitivity reactions (3%), fluid retention (3%), neurosensory (2%), neuromotor (5%), skin (1%), nausea (5%), vomiting (3%), diarrhea (3%), asthenia (18%), stomatitis (2%), pulmonary (21%), nail disorder (1%), taste perversion (1%), and treatment related mortality (3%).

Adverse reactions (any) occurring in patients with locally advanced or metastatic NSCLC and a history of prior treatment with platinum-based chemotherapy who were treated with DOCIVYX 75 mg/m^2 monotherapy were neutropenia (84%), leukopenia (84%), thrombocytopenia (8%), anemia (91%), infection (34%), hypersensitivity reactions (6%), fluid retention (34%), neurosensory (23%), neuromotor (16%), skin (20%), nausea (34%), vomiting (22%), diarrhea (23%), alopecia (56%), asthenia (53%), stomatitis (26%), pulmonary (41%), nail disorder (11%), myalgia (6%), arthralgia (3%), and taste perversion (6%).

Combination therapy with DOCIVYX in chemotherapy-naïve advanced unresectable or metastatic NSCLC

Adverse reactions (Grade 3/4 or severe) occurring in patients with unresectable stage IIIB or IV NSCLC and no history of prior chemotherapy who were treated with DOCIVYX 75 mg/m^2 in combination with cisplatin 75 mg/m^2 (TAX326) were neutropenia (74%), thrombocytopenia (3%), anemia (7%), infection (8%), fever in the absence of infection (<1%), hypersensitivity reaction (3%), fluid retention (2%), pleural effusion (2%), peripheral edema (<1%), weight gain (<1%), neurosensory (4%), neuromotor (3%), skin (<1%), nausea (10%), vomiting (8%), diarrhea (7%), anorexia (5%), stomatitis (2%), alopecia (<1%), asthenia (12%), nail disorders (<1%), and myalgia (<1%).

Adverse reactions (any) occurring in patients with advanced unresectable or metastatic NSCLC and no history of prior chemotherapy who were treated with DOCIVYX 75 mg/m^2 in combination with cisplatin 75 mg/m^2 (TAX326) were neutropenia (91%), febrile neutropenia (5%), thrombocytopenia (15%), anemia (89%), infection (35%), fever in the absence of infection (33%), hypersensitivity reaction (12%), fluid retention (54%), pleural effusion (23%), peripheral edema (34%), weight gain (15%), neurosensory (47%), neuromotor (19%), skin reaction (16%), nausea (72%), vomiting (55%), diarrhea (47%), anorexia (42%), stomatitis (24%), alopecia (75%), asthenia (74%), nail disorders (14%), and myalgia (18%).

Combination therapy with DOCIVYX in patients with castration-resistant prostate cancer (CRPC)

Adverse reactions (Grade 3/4) occurring in patients with CRPC who were treated with DOCIVYX 75 mg/m^2 every 3 weeks in combination with prednisone 5 mg orally twice daily (TZX327) were anemia (5%), neutropenia (32%), thrombocytopenia (1%), infection (6%), allergic reactions (1%), fluid retention (1%), neuropathy sensory (2%), neuropathy motor (2%), nausea (3%), diarrhea (2%), stomatitis/pharyngitis (1%), vomiting (2%), anorexia (1%), dyspnea (3%), fatigue (5%), tearing (1%), and arthralgia (1%).

Adverse reactions (any) occurring in patients with CRPC who were treated with DOCIVYX 75 mg/m^2 every 3 weeks in combination with prednisone 5 mg orally twice daily (TZX327) were anemia (67%), neutropenia (41%), thrombocytopenia (3%), febrile neutropenia (3%), infection (32%), epistaxis (6%), allergic reactions (8%), fluid retention (24%), weight gain (8%), peripheral edema (18%), neuropathy sensory (30%), neuropathy motor (7%), rash or desquamation (6%), alopecia (65%), nail changes (30%), nausea (41%), diarrhea (32%), stomatitis/pharyngitis (20%), taste disturbance (18%), vomiting (17%), anorexia (17%), cough (12%), dyspnea (15%), cardiac left ventricular function (10%), fatigue (53%), myalgia (15%), tearing (10%), and arthralgia (8%).

Combination therapy with DOCIVYX in gastric adenocarcinoma

Adverse reactions (Grade 3/4) occurring in patients with advanced gastric adenocarcinoma and no history of prior chemotherapy for advanced disease who were treated with DOCIVYX 75 mg/m^2 in combination with cisplatin 75 mg/m^2 and fluorouracil 750 mg/m^2 include anemia (18%), neutropenia (82%), fever in the absence of infection (2%), thrombocytopenia (8%), infection (16%), allergic reactions (2%), lethargy (21%), neurosensory (8%), neuromotor (3%), dizziness (5%), alopecia (5%), rash/itch (1%), nausea (16%), vomiting (15%), anorexia (13%), stomatitis (21%), diarrhea (20%), constipation (2%), esophagitis/dysphagia/odynophagia (2%), gastrointestinal pain/cramping (2%), and cardiac dysrhythmias (2%).

Adverse reactions (any) occurring in patients with advanced gastric adenocarcinoma and no history of prior chemotherapy for advanced disease who were treated with DOCIVYX 75 mg/m^2 in combination with cisplatin 75 mg/m^2 and fluorouracil 750 mg/m^2 were anemia (97%), neutropenia (96%), fever in the absence of infection (36%), thrombocytopenia (26%), infection (29%), febrile neutropenia (16%), neutropenic infection (16%), allergic reactions (10%), fluid retention (15%), edema (13%), lethargy (63%), neurosensory (38%), neuromotor (9%), dizziness (16%), alopecia (67%), rash/itch (12%), nail changes (8%), skin desquamation (2%), nausea (73%), vomiting (67%), anorexia (51%), stomatitis (59%), diarrhea (78%), constipation (25%), esophagitis/dysphagia/odynophagia (16%), gastrointestinal pain/cramping (11%), cardiac dysrhythmias (5%), myocardial ischemia (1%), tearing (8%), and altered hearing (6%).

Combination therapy with DOCIVYX in head and neck cancer

Adverse reactions (Grade 3/4) occurring in patients with squamous cell carcinoma of the head and neck (SCCHN) who received induction chemotherapy with DOCIVYX 75 mg/m^2 in combination with cisplatin 75 mg/m^2 and fluorouracil 750 mg/m^2 followed by radiotherapy (TAX323) or chemoradiotherapy (TAX 324), were neutropenia (76%, 84% with combination therapy followed by radiotherapy [TAX323] or chemoradiotherapy [TAX324], respectively), anemia (9%, 12%, respectively), thrombocytopenia (5%, 4%, respectively), infection (9%, 6%, respectively), cancer pain (5%, 9%, respectively), lethargy (3%, 5%, respectively), fever in the absence of infection (1%, 4%, respectively), myalgia (1%, 0%, respectively), weight loss (1%, 2%, respectively), fluid retention (0%,1%, respectively), edema (0%, 1%, respectively), dizziness (0%, 4%, respectively), neurosensory (1%, 1%, respectively), altered hearing (0%, 1%, respectively), neuromotor (1%, 0%, respectively), alopecia (11%, 4%, respectively), desquamation (1%, 0%, respectively), nausea (1%, 14%, respectively), stomatitis (4%, 21%, respectively), vomiting (1%, 8%, respectively), diarrhea (3%, 7%, respectively), constipation (1%, 1%, respectively), anorexia (1%, 12%, respectively), esophagitis/dysphagia/odynophagia (1%, 13%, respectively), gastrointestinal pain/cramping (1%,5%, respectively), heartburn (0%, 2%, respectively), gastrointestinal bleeding (2%, 1%, respectively), cardiac

dysrhythmia (2%, 3%, respectively), venous (2%, 2%, respectively), and ischemia myocardial (2%, 1%, respectively).

Adverse reactions (any) occurring in patients with SCCHN who received induction chemotherapy with DOCIVYX 75 mg/m^2 in combination with cisplatin 75 mg/m^2 and fluorouracil 750 mg/m^2 followed by radiotherapy (TAX323) or chemoradiotherapy (TAX 324), respectively, were neutropenia (93%, 95% with combination therapy followed by radiotherapy [TAX323] or chemoradiotherapy [TAX324], respectively), anemia (89%, 90%, respectively), thrombocytopenia (24%, 28%, respectively), infection (27%, 23%, respectively), febrile neutropenia (5%, 12%, respectively), neutropenic infection (14%, 12%, respectively), cancer pain (21%, 17%, respectively), lethargy (41%, 61%, respectively), fever in the absence of infection (32%, 30%, respectively), myalgia (10%, 7%, respectively), weight loss (21%, 14%, respectively), allergy (6%, 2%, respectively), fluid retention (20%, 13%, respectively), edema (13%, 12%, respectively), weight gain (6%, 0%, respectively), dizziness (2%, 16%, respectively), neurosensory (18%, 14%, respectively), altered hearing (6%, 13%, respectively), neuromotor (2%, 9%, respectively), alopecia (81%, 68%, respectively), rash/itch (12%, 20%, respectively), dry skin (6%, 5%, respectively), desquamation (4%, 2%, respectively) nausea (47%, 77%, respectively), stomatitis (43%, 66%, respectively), vomiting (26%, 56%, respectively), diarrhea (33%, 48%, respectively), constipation (17%, 27%, respectively), anorexia (16%, 40%, respectively), esophagitis/dysphagia/odynophagia (13%, 25%, respectively), taste, sense of smell altered (10%, 20%, respectively), gastrointestinal pain/cramping (8%, 15%, respectively), heartburn (6%, 13%, respectively), gastrointestinal bleeding (4%, 5%, respectively), cardiac dysrhythmia (2%, 6%, respectively), venous (3%, 4%, respectively), ischemia myocardial (2%, 2%, respectively), tearing (2%, 2%, respectively), and conjunctivitis (1%, 1%, respectively).

Postmarketing Experience
The following adverse reactions have been identified from clinical trials and/or postmarketing surveillance. Because these reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a whole: diffuse pain, chest pain, radiation recall phenomenon, injection site recall reaction (recurrence of skin reaction at a site of previous extravasation following administration of docetaxel at a different site) at the site of previous extravasation.

Cardiovascular: atrial fibrillation, deep vein thrombosis, ECG abnormalities, thrombophlebitis, pulmonary embolism, syncope, tachycardia, myocardial infarction. Ventricular arrhythmia, including ventricular tachycardia, in patients treated with docetaxel in combination regimens including doxorubicin, 5-fluorouracil and/or cyclophosphamide may be associated with fatal outcome.

Cutaneous: cutaneous lupus erythematosus, bullous eruptions such as erythema multiforme and severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome, toxic epidermal necrolysis and acute generalized exanthematous pustulosis, scleroderma-like changes (usually preceded by peripheral lymphedema), severe palmar-plantar erythrodysesthesia, and permanent alopecia.

Gastrointestinal: enterocolitis, including colitis, ischemic colitis, and neutropenic enterocolitis, which may be fatal. Abdominal pain, anorexia, constipation, duodenal ulcer, esophagitis, gastrointestinal hemorrhage, gastrointestinal perforation, intestinal obstruction, ileus, and dehydration as a consequence of gastrointestinal events.

Hearing: ototoxicity, hearing disorders and/or hearing loss, including during use with other ototoxic drugs.

Hematologic: bleeding episodes, disseminated intravascular coagulation (DIC), often in association with sepsis or multiorgan failure.

Hepatic: hepatitis, sometimes fatal, primarily in patients with pre-existing liver disorders.

Hypersensitivity: anaphylactic shock with fatal outcome in patients who received premedication. Severe hypersensitivity reactions with fatal outcome with docetaxel in patients who previously experienced hypersensitivity reactions to paclitaxel.

Metabolism and nutrition disorders: electrolyte imbalance, including hyponatremia, hypokalemia, hypomagnesemia, and hypocalcemia. Tumor lysis syndrome, sometimes fatal.

Neurologic: confusion, seizures or transient loss of consciousness, sometimes appearing during the infusion of the drug.

Ophthalmologic: conjunctivitis, lacrimation or lacrimation with or without conjunctivitis, cystoid macular edema (CME). Excessive tearing which may be attributable to lacrimal duct obstruction. Transient visual disturbances (flashes, flashing lights, scotomata), typically occurring during drug infusion and reversible upon discontinuation of the infusion, in association with hypersensitivity reactions.

Respiratory: dyspnea, acute pulmonary edema, acute respiratory distress syndrome/pneumonitis, interstitial lung disease, interstitial pneumonia, respiratory failure, and pulmonary fibrosis, which may be fatal. Radiation pneumonitis in patients receiving concomitant radiotherapy.

Renal: renal insufficiency and renal failure, the majority of cases were associated with concomitant nephrotoxic drugs.

Second primary malignancies: second primary malignancies, including AML, MDS, NHL, and renal cancer.

Musculoskeletal disorder: myositis.

USE IN SPECIFIC POPULATIONS

Pregnancy
Available data from case reports in the literature and pharmacovigilance with docetaxel use in pregnant women are not sufficient to inform the drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Based on findings in animal studies and its mechanism of action, DOCIVYX can cause fetal harm when administered to a pregnant woman. DOCIVYX contains alcohol which is associated with fetal harm including central nervous system abnormalities, behavioral disorders, and impaired intellectual development.

Lactation
There is no information regarding the presence of docetaxel in human milk, or on its effects on milk production or the breastfed child. Advise women not to breastfeed during treatment with DOCIVYX and for 1 week after the last dose.

Females and Males of Reproductive Potential
Verify pregnancy status in females of reproductive potential prior to initiating DOCIVYX. Advise females of reproductive potential to use effective contraception during treatment and for 2 months after the last dose of DOCIVYX. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the last dose of DOCIVYX. Based on findings in animal studies, DOCIVYX may impair fertility in males of reproductive potential.

Pediatric Use
The alcohol content of DOCIVYX should be taken into account when given to pediatric patients. The efficacy of DOCIVYX in pediatric patients as monotherapy or in combination has not been established. The overall safety profile of DOCIVYX in pediatric patients receiving monotherapy or TCF was consistent with the known safety profile in adults.

Geriatric Use
Dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in elderly patients.

Non-small Cell Lung Cancer

Patients ≥65 years of age with non-small cell lung cancer treated with DOCIVYX plus cisplatin were more likely to experience diarrhea (55%), infections (42%), peripheral edema (39%) and stomatitis (28%) compared to patients less than the age of 65 administered the same treatment (43%, 31%, 31% and 21%, respectively). In patients ≥ 65 years of age treated with DOCIVYX+cisplatin, diarrhea (55%), peripheral edema (39%) and stomatitis (28%) were observed more frequently than in the vinorelbine+cisplatin group (diarrhea 24%, peripheral edema 20%, stomatitis 20%). When DOCIVYX was combined with carboplatin for the treatment of chemotherapy-naive, advanced non-small cell lung carcinoma, patients ≥65 years (28%) experienced higher frequency of infection compared to similar patients treated with DOCIVYX+cisplatin, and a higher frequency of diarrhea, infection and peripheral edema than elderly patients treated with vinorelbine+cisplatin.

Prostate Cancer

In patients ≥65 years of age with prostate cancer treated with DOCIVYX every three weeks plus prednisone, the following treatment-emergent adverse reactions occurred at rates ≥10% higher compared to younger patients: anemia (71% vs 59%), infection (37% vs 24%), nail changes (34% vs 23%), anorexia (21% vs 10%), weight loss (15% vs 5%), respectively.

Breast Cancer and Head and Neck Cancer

The number of patients ≥65 years of age with breast cancer patients who received DOCIVYX in combination with doxorubicin and cyclophosphamide and the number of head and neck cancer patients who received DOCIVYX in combination with cisplatin and fluorouracil were not sufficient to determine whether elderly and younger patients responded differently.

Gastric Cancer

The number of patients ≥65 years of age with gastric cancer treated with DOCIVYX in combination with cisplatin and fluorouracil was not sufficient to determine whether they respond differently from younger patients. However, the incidence of serious adverse reactions was higher in patients ≥65 years of age compared to younger patients. The incidence of the following adverse reactions (all grades, regardless of relationship): lethargy, stomatitis, diarrhea, dizziness, edema, febrile neutropenia/neutropenic infection occurred at rates ≥10% higher in patients who were 65 years of age or older compared to younger patients. Elderly patients treated with TCF should be closely monitored.

Hepatic Impairment

Avoid DOCIVYX in patients with bilirubin >ULN and patients with AST and/or ALT >1.5 × ULN concomitant with alkaline phosphatase >2.5 × ULN. The alcohol content of DOCIVYX should be taken into account when given to patients with hepatic impairment.

Please see the full Prescribing information for safety information, including BOXED WARNING, and dosing guidelines.

To report SUSPECTED ADVERSE REACTIONS, contact Avyxa Pharma, LLC at 1-888-520-0954 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.