

DOCIVYX™ (docetaxel injection)

160 mg/16 mL; 80 mg/8 mL; 20 mg/2 mL (10 mg/mL)

Unique J-Code J9172

Supplied as a solution in a single-dose vial ready to add to the infusion solution

<p>Presentation</p>	<p>Solution ready to add to the infusion solution; No prior dilution with a diluent is required.</p>
<p>How Supplied:</p>	<p>NDC 83831-101-02: Carton containing one (1) single-dose vial of 20 mg/2 mL (10 mg/mL).</p> <p>NDC 83831-102-08: Carton containing one (1) single-dose vial of 80 mg/8 mL (10 mg/mL).</p> <p>NDC 83831-103-16: Carton containing one (1) single-dose vial of 160 mg/16 mL (10 mg/mL)</p>
<p>Reconstitution:</p>	<p>None</p>
<p>Preparation:</p>	<p>DOCIVYX™ Injection (10 mg/mL) requires NO prior dilution with a diluent and is ready to add to the infusion solution. Use only a 21-gauge needle to withdraw DOCIVYX™ from the vial because larger bore needles (e.g., 18 and 19 gauge) may result in stopper coring and rubber particulates.</p> <p>DOCIVYX™ is a hazardous drug. Follow applicable special handling and disposal procedures.</p> <p>Using only a 21-gauge needle, aseptically withdraw the required amount of DOCIVYX™ Injection (10 mg docetaxel/mL) with a calibrated syringe and inject via a single injection (one shot) into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to produce a final concentration of 0.3 mg/mL to 0.74 mg/mL.</p> <p>If a dose greater than 200 mg of DOCIVYX™ is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL DOCIVYX™ is not exceeded.</p> <p>Thoroughly mix the infusion by gentle manual rotation.</p>

As with all parenteral products, DOCIVYX™ should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the DOCIVYX™ final infusion solution is not clear or appears to have precipitation, it should be discarded.

DOCIVYX™ final infusion solution is supersaturated, therefore may crystallize over time. If crystals appear, the solution must no longer be used and shall be discarded.

Infusion Time:

The DOCIVYX™ final infusion solution should be administered intravenously as a 1-hour infusion under ambient room temperature (below 25°C) and lighting conditions

Storage:

Store unopened DOCIVYX™ vials between 2°C and 25°C (36°F and 77°F). Protect from light.

Store final DOCIVYX™ infusion solution (in either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP) between 2°C and 25°C (36°F and 77°F) for up to 6 hours (including the 1-hour intravenous administration). In addition, physical and chemical in-use stability of the infusion solution prepared as recommended has been demonstrated in non-PVC bags up to 48 hours when stored between 2°C and 8°C (36°F and 46°F).

Website and Ordering

Visit **DOCIVYX.com**

AVYXASSIST™
Phone: 866-939-8927

AVYXASSIST™ provides reliable support for eligible patients* prescribed DOCIVYX™:

- Benefit investigation
- Prior authorization requirements
- Appeal process information assistance
- Referrals to 501(c)(3) foundations when applicable
- Free product assistance (uninsured or underinsured), bridge supply (coverage delays)
- Product replacement
- Copay assistance

*For eligibility requirements, please contact a program representative.

References:

1. DOCIVYX™. Package insert. AVYXA™. 2024.
2. *ASP Pricing Files | CMS*. Retrieved March 7, 2024, from <https://www.cms.gov/medicare/payment/all-fee-service-providers/medicare-part-b-drug-average-sales-price/asp-pricing-files>
3. *Hazardous drugs - Overview | Occupational Safety and Health Administration*. Retrieved March 7, 2024, from <https://www.osha.gov/hazardous-drugs>

INDICATIONS AND IMPORTANT SAFETY INFORMATION INCLUDING BOXED 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/m².

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/mm³. 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 AND USAGE

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).

CONTRAINDICATION

DOCIVYX™ is contraindicated in patients with:

- neutrophil counts of <1500 cells/mm³
- a history of severe hypersensitivity reactions to docetaxel. Severe reactions, including anaphylaxis, have occurred.

WARNINGS AND PRECAUTIONS

Toxic Deaths

Breast Cancer

DOCIVYX™ administered at 100 mg/m² 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/m², 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/m² 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/m² dose in the randomized trials. Among patients who experienced treatment-related mortality at the 75 mg/m² 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/mm³. Avoid retreating patients until platelets recover to a level >100,000 cells/mm³.

A 25% reduction in the dose of DOCIVYX™ is recommended during subsequent cycles following severe neutropenia (<500 cells/mm³) lasting 7 days or more, febrile neutropenia, or a grade 4 infection in a DOCIVYX™ cycle.

Neutropenia (<2000 neutrophils/mm³) occurs in virtually all patients given 60 mg/m² to 100 mg/m² of DOCIVYX™ and grade 4 neutropenia (<500 cells/mm³) occurs in 85% of patients given 100 mg/m² and 75% of patients given 60 mg/m². 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/mm³.

Febrile neutropenia occurred in about 12% of patients given 100 mg/m² but was very uncommon in patients given 60 mg/m². 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/m². 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/m². 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/m² delivers 2.0 g/m² of ethanol. For a patient with a BSA of 2.0 m², 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/m² 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/m² were neutropenia <2000 cells/mm³ (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/mm³ (75%, 88%, 86%, respectively), leukopenia <4000 cells/mm³ (96%, 98%, 99%, respectively), leukopenia <1000 cells/mm³ (32%, 47%, 44%, respectively), thrombocytopenia <100,000 cells/mm³ (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 (severe; 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/m² or those with normal liver function tests who were treated with DOCIVYX™ 60 mg/m² were neutropenia <500 cells/mm³ (84%, 94%, and 75% at 100 mg/m² with normal liver function tests, 100 mg/m² with elevated liver function test, and at 60 mg/m² with normal liver function tests, respectively), thrombocytopenia <20,000 cells/mm³ (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/m² or those with normal liver function tests who were treated with DOCIVYX™ 60 mg/m² were neutropenia <2,000 cells/mm³ (98%, 100%, and 95% at 100 mg/m² with normal liver function tests, 100 mg/m² with elevated liver function tests, and at 60 mg/m² with normal liver function tests, respectively), thrombocytopenia <100,000 cells/mm³ (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/m² or those with normal liver function tests who were treated with DOCIVYX™ 60 mg/m² were acute hypersensitivity reaction regardless of premedication (1%, 0%, and 0% at 100 mg/m² with normal liver function tests, 100 mg/m² with elevated liver function test, and at 60 mg/m² 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/m² or those with normal liver function tests who were treated with DOCIVYX™ 60 mg/m² were acute hypersensitivity reaction regardless of premedication (13% ,6%, and 1% at 100 mg/m² with normal liver function tests, 100 mg/m² with elevated liver function test, and at 60 mg/m² 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/m², 75 mg/m² and 100 mg/m² in advanced breast cancer.

The following adverse reactions were associated with increasing docetaxel doses: fluid retention (26%, 38%, and 46% at 60 mg/m², 75 mg/m², and 100 mg/m² 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/m² every 3 weeks in combination with doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² (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/m² every 3 weeks in combination with doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² (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/m² 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/m² 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/m² in combination with cisplatin 75 mg/m² (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/m² in combination with cisplatin 75 mg/m² (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/m² every 3 weeks in combination with prednisone 5 mg orally twice daily (TZ327) 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/m² 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/m² in combination with cisplatin 75 mg/m² and fluorouracil 750 mg/m² 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/m² in combination with cisplatin 75 mg/m² and fluorouracil 750 mg/m² 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/m² in combination with cisplatin 75 mg/m² and fluorouracil 750 mg/m² 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/m² in combination with cisplatin 75 mg/m² and fluorouracil 750 mg/m² 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 $\geq 10\%$ 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 $\geq 10\%$ 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 $> \text{ULN}$ and patients with AST and/or ALT $> 1.5 \times \text{ULN}$ concomitant with alkaline phosphatase $> 2.5 \times \text{ULN}$. The alcohol content of DOCIVYX™ should be taken into account when given to patients with hepatic impairment.

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

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