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Press Release

Hikma launches Docetaxel Injection, USP

London, 7 May 2021 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, announces it launched Docetaxel Injection, USP through its US affiliate, Hikma Pharmaceuticals USA Inc. The company has launched 20mg/mL and 80mg/4mL doses.

Docetaxel is an antineoplastic agent belonging to the taxoid family and is indicated for the treatment of patients with locally advanced or metastatic cancer, including breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma and head and neck cancer.

According to IQVIA, US sales of Docetaxel Injection, USP, 20mg/mL and 80mg/4mL were approximately $10 million in the 12 months ending March 2021.

Hikma is the third largest US supplier of generic injectable medicines by volume, with a growing portfolio of over 100 products. Today one in every six injectable generic medicines used in US hospitals is a Hikma product.

- ENDS -

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About Hikma
(LSE: HIK) (NASDAQ Dubai: HIK) (OTC: HKMPY) (rated BBB-/stable S&P and BBB-/stable Fitch)

Hikma helps put better health within reach every day for millions of people around the world. For more than 40 years, we've been creating high-quality medicines and making them accessible to the people who need them. Headquartered in the UK, we are a global company with a local presence across the United States (US), the Middle East and North Africa (MENA) and Europe, and we use our unique insight and expertise to transform cutting-edge science into innovative solutions that transform people's lives. We're committed to our customers, and the people they care for, and by thinking creatively and acting practically, we provide them with a broad range of branded and non-branded generic medicines. Together, our 8,600 colleagues are helping to shape a healthier world that enriches all our communities. We are a leading licensing partner, and through our venture capital arm, are helping bring innovative health technologies to people around the world. For more information, please visit: www.hikma.com

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Important Safety Information for Docetaxel Injection, USP, 20mg/mL and 80mg/4mL:

BOXED WARNING

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

Treatment-related mortality associated with docetaxel 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 docetaxel as a single agent at a dose of 100 mg/m^2*[see Warnings and Precautions (5.1)].*

Avoid the use of docetaxel in patients with bilirubin > upper limit of normal (ULN), or to patients with AST and/or ALT >1.5 × ULN concomitant with alkaline phosphatase >2.5 × 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 × ULN also had a higher rate of febrile neutropenia. Measure bilirubin, AST or ALT, alkaline phosphatase prior to each cycle of docetaxel *[see Warnings and Precautions (5.2)]*.

Do not administer docetaxel to patients with neutrophil counts of <1500 cells/mm^3. Monitor blood counts frequently as neutropenia may be severe and result in infection. *[see Warnings and Precautions (5.3)]*.

Do not administer docetaxel to patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80 *[see Contraindications (4)].* Severe hypersensitivity reactions have been reported in patients despite dexamethasone premedication. Hypersensitivity reactions require immediate discontinuation of the docetaxel infusion and administration of appropriate therapy *[see Warnings and Precautions (5.5)].*

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) *[see Warnings and Precautions (5.6)].*

CONTRAINDICATIONS

Docetaxel injection is contraindicated in patients with:

- neutrophil counts of <1500 cells/mm^3 *[see Warnings and Precautions (5.3)]*.
- a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80. Severe reactions, including anaphylaxis, have occurred *[see Warnings and Precautions (5.5)]*.

WARNINGS & PRECAUTIONS

- **Toxic Deaths – Breast Cancer:** Docetaxel administered at 100 mg/m^2 was associated with deaths considered possibly or probably related to treatment of metastatic breast cancer patients, both previously treated and untreated, with normal baseline liver function and with various tumor types who had abnormal baseline liver function. 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.
- **Toxic Deaths – Non-small Cell Lung Cancer:** Docetaxel 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. 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.
- **Hematologic Effects:** Perform frequent peripheral blood cell counts on all patients receiving docetaxel. Hematologic responses, febrile reactions and infections, and rates of septic death for different regimens are dose related. 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 docetaxel 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:** Severe hypersensitivity reactions have been reported in patients premedicated with 3 days of corticosteroids. Severe hypersensitivity reactions require immediate discontinuation of the docetaxel infusion and aggressive therapy. Do not rechallenge patients with a history of severe hypersensitivity reactions with docetaxel. 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. Hypersensitivity reactions may occur within a few minutes following initiation of a docetaxel infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required.
- **Fluid Retention:** Severe fluid retention has been reported following docetaxel therapy. Patients should be premedicated with oral corticosteroids prior to each docetaxel administration to reduce the incidence and severity of fluid retention.
- **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.
- **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. 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 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.
- **Eye Disorders**: Cystoid macular edema (CME) has been reported in patients treated with docetaxel. Patients with impaired vision should undergo a prompt and comprehensive ophthalmologic examination. If CME is diagnosed, docetaxel 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:** Based on findings from animal reproduction studies and its mechanism of action, docetaxel can cause fetal harm when administered to a pregnant woman.
- **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 docetaxel injection 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 docetaxel injection on the ability to drive or use machines immediately after the infusion.
- **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 docetaxel and periodically during treatment. Correction of dehydration and treatment of high uric acid levels are recommended prior to initiation of treatment.

ADVERSE REACTIONS

Most serious adverse reactions:
- Toxic Deaths: see Boxed Warning, Warnings and Precautions
- Hepatic Impairment: see Boxed Warning, Warnings and Precautions
- Hematologic Effects: see Boxed Warning, Warnings and Precautions
- Enterocolitis and Neutropenic Colitis: see Warnings and Precautions

- Hypersensitivity Reactions: see Boxed Warning, Warnings and Precautions
- Fluid Retention: see Boxed Warning, Warnings and Precautions
- Second Primary Malignancies: see Warnings and Precautions
- Cutaneous Reactions: see Warnings and Precautions
- Neurologic Reactions: see Warnings and Precautions
- Eye Disorders: see Warnings and Precautions
- Asthenia: see Warnings and Precautions
- Alcohol Content: see Warnings and Precautions

Most common adverse reactions:

The most common adverse reactions across all docetaxel 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. Adverse reactions are described according to indication. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Responding patients may not experience an improvement in performance status on therapy and may experience worsening. The relationship between changes in performance status, response to therapy, and treatment-related side effects has not been established.

Clinical Trials Experience
Refer to Package Insert for Adverse Reaction information from Clinical Trials Experience for Breast Cancer, Lung Cancer, Prostate Cancer, Gastric Cancer, and Head and Neck Cancer.

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.

DRUG INTERACTIONS

Docetaxel is a CYP3A4 substrate. *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.

In vivo studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of docetaxel and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with docetaxel, close monitoring for toxicity and a docetaxel dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided.

USE IN SPECIFIC POPULATIONS

Pregnancy
Based on findings in animal reproduction studies and its mechanism of action, docetaxel can cause fetal harm when administered to a pregnant woman. 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. Docetaxel contains alcohol which can interfere with neurobehavioral 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. No lactation studies in animals have been conducted. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with docetaxel 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 docetaxel. Docetaxel can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of docetaxel. Based on genetic toxicity findings, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of docetaxel. Based on findings in animal studies, docetaxel may impair fertility in males of reproductive potential.

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

Geriatric Use
In general, 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.

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

DOSAGE AND ADMINISTRATION

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For all indications, toxicities may warrant dosage adjustments. Administer in a facility equipped to manage possible complications (e.g. anaphylaxis).

Breast Cancer

- For locally advanced or metastatic breast cancer after failure of prior chemotherapy, the recommended dose of docetaxel injection is 60 mg/m^2 to 100 mg/m^2 administered intravenously over 1 hour every 3 weeks.
- For the adjuvant treatment of operable node-positive breast cancer, the recommended docetaxel injection dose is 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 courses. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities.

Non-small Cell Lung Cancer

- For treatment after failure of prior platinum-based chemotherapy, docetaxel injection was evaluated as monotherapy, and the recommended dose is 75 mg/m^2 administered intravenously over 1 hour every 3 weeks. A dose of 100 mg/m^2 in patients previously treated with chemotherapy was associated with increased hematologic toxicity, infection, and treatment-related mortality in randomized controlled trials.
- For chemotherapy-naive patients, docetaxel injection was evaluated in combination with cisplatin. The recommended dose of docetaxel injection is 75 mg/m^2 administered intravenously over 1 hour immediately followed by cisplatin 75 mg/m^2 over 30 - 60 minutes every 3 weeks.

Prostate Cancer

- For metastatic castration-resistant prostate cancer, the recommended dose of docetaxel injection is 75 mg/m^2 every 3 weeks as a 1 hour intravenous infusion. Prednisone 5 mg orally twice daily is administered continuously.

Gastric Adenocarcinoma

- For gastric adenocarcinoma, the recommended dose of docetaxel injection is 75 mg/m^2 as a 1 hour intravenous infusion, followed by cisplatin 75 mg/m^2, as a 1 to 3 hour intravenous infusion (both on day 1 only), followed by fluorouracil 750 mg/m^2 per day given as a 24-hour continuous intravenous infusion for 5 days, starting at the end of the cisplatin infusion. Treatment is repeated every three weeks. Patients must receive premedication with antiemetics and appropriate hydration for cisplatin administration.

Head and Neck Cancer

Patients must receive premedication with antiemetics, and appropriate hydration (prior to and after cisplatin administration). Prophylaxis for neutropenic infections should be administered. All patients treated on the docetaxel injection containing arms of the TAX323 and TAX324 studies received prophylactic antibiotics.

Induction Chemotherapy Followed by Radiotherapy (TAX323)

For the induction treatment of locally advanced inoperable SCCHN, the recommended dose of docetaxel injection is 75 mg/m^2 as a 1 hour intravenous infusion followed by cisplatin 75 mg/m^2 intravenously over 1 hour, on day one, followed by fluorouracil as a continuous intravenous infusion at 750 mg/m^2 per day for five days. This regimen is administered every 3 weeks for 4 cycles. Following chemotherapy, patients should receive radiotherapy.

Induction Chemotherapy Followed by Chemoradiotherapy (TAX324)

For the induction treatment of patients with locally advanced (unresectable, low surgical cure, or organ preservation) SCCHN, the recommended dose of docetaxel injection is 75 mg/m^2 as a 1 hour intravenous infusion on day 1, followed by cisplatin 100 mg/m^2 administered as a 30-minute to 3 hour infusion, followed by fluorouracil 1000 mg/m^2/day as a continuous infusion from day 1 to day 4. This regimen is administered every 3 weeks for 3 cycles. Following chemotherapy, patients should receive chemoradiotherapy.

Premedication Regimen

All patients should be premedicated with oral corticosteroids such as dexamethasone prior to docetaxel injection administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

Dosage Adjustments during Treatment

Breast Cancer

Patients who are dosed initially at 100 mg/m^2 and who experience either febrile neutropenia, neutrophils < 500 cells/mm^3 for more than 1 week, or severe or cumulative cutaneous reactions during docetaxel injection therapy should have the dosage adjusted from 100 mg/m^2 to 75 mg/m^2. If the patient continues to experience these

reactions, the dosage should either be decreased from 75 mg/m^2 to 55 mg/m^2 or the treatment should be discontinued. Conversely, patients who are dosed initially at 60 mg/m^2 and who do not experience febrile neutropenia, neutrophils < 500 cells/mm^3 for more than 1 week, severe or cumulative cutaneous reactions, or severe peripheral neuropathy during docetaxel injection therapy may tolerate higher doses. Patients who develop ≥ grade 3 peripheral neuropathy should have docetaxel injection treatment discontinued entirely.

Combination Therapy with Docetaxel Injection in the Adjuvant Treatment of Breast Cancer
Docetaxel injection in combination with doxorubicin and cyclophosphamide should be administered when the neutrophil count is ≥ 1,500 cells/mm^3. Patients who experience febrile neutropenia should receive G-CSF in all subsequent cycles. Patients who continue to experience this reaction should remain on G-CSF and have their docetaxel injection dose reduced to 60 mg/m^2. Patients who experience grade 3 or 4 stomatitis should have their docetaxel injection dose decreased to 60 mg/m^2. Patients who experience severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during docetaxel injection therapy should have their dosage of docetaxel injection reduced from 75 mg/m^2 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, treatment should be discontinued.

Non-small Cell Lung Cancer
Monotherapy with docetaxel injection for NSCLC treatment after failure of prior platinum-based chemotherapy – patients who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions, or other grade 3/4 non-hematological toxicities during docetaxel injection treatment should have treatment withheld until resolution of the toxicity and then resumed at 55 mg/m^2. Patients who develop ≥ grade 3 peripheral neuropathy should have docetaxel injection treatment discontinued entirely.

Combination therapy with docetaxel injection for chemotherapy-naive NSCLC – for patients who are dosed initially at docetaxel 75 mg/m^2 in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy is < 25,000 cells/mm^3, in patients who experience febrile neutropenia, and in patients with serious non-hematologic toxicities, the docetaxel injection dosage in subsequent cycles should be reduced to 65 mg/m^2. In patients who require a further dose reduction, a dose of 50 mg/m^2 is recommended. For cisplatin dosage adjustments, see manufacturers' prescribing information.

Prostate Cancer
Combination therapy with docetaxel injection for metastatic castration-resistant prostate cancer – Docetaxel injection should be administered when the neutrophil count is ≥ 1,500 cells/mm^3. Patients who experience either febrile neutropenia, neutrophils < 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during docetaxel injection therapy should have the dosage of docetaxel injection reduced from 75 mg/m^2 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, the treatment should be discontinued.

Gastric or Head and Neck Cancer
Docetaxel injection in combination with cisplatin and fluorouracil in gastric cancer or head and neck cancer – patients treated with docetaxel injection in combination with cisplatin and fluorouracil must receive antiemetics and appropriate hydration according to current institutional guidelines. In both studies, G-CSF was recommended during the second and/or subsequent cycles in case of febrile neutropenia, or documented infection with neutropenia, or neutropenia lasting more than 7 days. If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs despite G-CSF use, the docetaxel injection dose should be reduced from 75 mg/m^2 to 60 mg/m^2. If subsequent episodes of complicated neutropenia occur the docetaxel injection dose should be reduced from 60 mg/m^2 to 45 mg/m^2. In case of grade 4 thrombocytopenia the docetaxel injection dose should be reduced from 75 mg/m^2 to 60 mg/m^2. Do not retreat patients with subsequent cycles of docetaxel injection until neutrophils recover to a level > 1,500 cells/mm^3 *[see Contraindications (4)].* Avoid retreating patients until platelets recover to a level > 100,000 cells/mm^3. Discontinue treatment if these toxicities persist.

Combination Therapy with Strong CYP384 Inhibitors
Avoid using concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole). There are no clinical data with a dose adjustment in patients receiving strong CYP3A4 inhibitors. Based on extrapolation from a pharmacokinetic study with ketoconazole in 7 patients, consider a 50% docetaxel dose reduction if patients require coadministration of a strong CYP3A4 inhibitor.

Administration Precautions

Docetaxel injection is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing docetaxel injection solutions. The use of gloves is recommended. If Docetaxel injection, initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If Docetaxel injection initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

Contact of the docetaxel injection with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final docetaxel injection dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Preparation and Administration
DO NOT use the two-vial formulation (Injection and diluent) with the one-vial formulation. Docetaxel Injection, USP (20 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 Docetaxel Injection, USP from the vial because larger bore needles (e.g., 18 and 19 gauge) may result in stopper coring and rubber particulates.

1. Docetaxel vials should be stored between 2°C and 25°C (36°F and 77°F). If the vials are stored under refrigeration, allow the appropriate number of vials of Docetaxel Injection, USP vials to stand at room temperature for approximately 5 minutes before use.
2. Using **only** a 21 gauge needle aseptically withdraw the required amount of Docetaxel Injection, USP (20 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 solution or 5% Dextrose solution to produce a final concentration of 0.3 mg/mL to 0.74 mg/mL. If a dose greater than 200 mg of docetaxel injection is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL docetaxel injection is not exceeded.
3. Thoroughly mix the infusion by gentle manual rotation.
4. As with all parenteral products, docetaxel injection should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the docetaxel dilution for intravenous infusion is not clear or appears to have precipitation, it should be discarded.
5. Docetaxel infusion solution is supersaturated, therefore may crystallize over time. If crystals appear, the solution must no longer be used and shall be discarded.

The docetaxel dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature (below 25°C) and lighting conditions.

Stability
Docetaxel final dilution for infusion, if stored between 2°C and 25°C (36°F and 77°F) is stable for 6 hours. Docetaxel final dilution for infusion (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 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).

OVERDOSAGE

There is no known antidote for docetaxel overdosage. In case of overdosage, the patient should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of overdosage include: bone marrow suppression, peripheral neurotoxicity, and mucositis. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

INDICATIONS AND USAGE

Breast Cancer
Docetaxel Injection, USP is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy. Docetaxel Injection, USP 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

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

Prostate Cancer
Docetaxel Injection, USP in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer.

Gastric Adenocarcinoma
Docetaxel Injection, USP 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
Docetaxel Injection, USP 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).

ENDING INFORMATION

Patient Counseling Information should be shared with the patient prior to administration.
For additional information, please refer to the Package Insert for full prescribing information, available on www.hikma.com.

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-233-2001 or the FDA at 1-800-FDA-1088 or **http://www.fda.gov/medwatch**.

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