dosage is recommended.
Neutropenia (< 2000 neutrophils/mm^3) occurs in virtually all patients given 60-100 mg/m^2 of docetaxel and grade 4 neutropenia (< 500 cells/ mm^3) occur in 85 % of patients give 100 mg/m^2 and 75 % of patients given 60 mg/m^2. Frequent monitoring of blood counts is therefore essential so that the dose can be adjusted. Docetaxel should not be administered to patients with baseline neutrophil counts < 1,500 cells/mm^3. Febrile neutropenia may occur in patients given 100 mg/m^2 but is uncommon among patients given 60 mg/m^2.
Breast cancer patients with severe liver impairment (bilirubin > 1.7 times ULN) may develop fatal gastrointestinal bleeding associated with severe drug induced thrombocytopenia. In order to monitor the occurrence of myelotoxicity it is recommended that frequent peripheral blood cell counts be performed on all patients receiving docetaxel. Patients should not be retreated with subsequent cycles of docetaxel until neutrophils recover to a level > 1500 cells/mm^3 and platelets recover to a level > 100000 cells/mm^3. 25 % reduction in dose of docetaxel 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 docetaxel cycle.
Severe fluid retention may occur following docetaxel therapy. Patients should be premedicated with oral corticosteroids prior to each docetaxel 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. moderate to severe fluid retention may occur in breast cancer patients premedicated with 3 day corticosteroids. Patients developing peripheral edema may be treated with standard measures e.g salt restriction, oral diuretic(s).
Severe neurosensory sysmptoms (paresthesia, dysesthesia, pain) may be seen in metastatic breast cancer patients and may result in discontinuation of treatment. When these symptoms occur, the dosage must be adjusted and if symptoms persist, the treatment should be discontinued.
Severe asthenia may be seen in some metastatic breast cancer patients and may lead to treatment discontinuation. Symptoms of fatigue and weakness may last from a few days to several weeks and may be associated with deterioration of performance status in patients with progressive disease.
Patients with combined abnormalities of transaminase and alkaline phosphatase should in general not be treated with docetaxel.

Preganacy and Lactation
Docetaxel may cause fetal harm and might cause maternal toxicity when administered to pregnant women, however there are no adequate and well controlled studies in preganant women using docetaxel. If docetaxel is used during pregnancy or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant during docetaxel therapy. No well documented reports are available whether docetaxel is excreted in human milk. However since many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from docetaxel, mothers should discontinue nursing prior to taking the drug.

ADVERSE REACTION(S)

INFORM DOCTORS ABOUT UNEXPECTED REACTIONS AFTER USE.
Docetaxel is a chemotherapeutic agent and is a cytotoxic compound and so is effectively a biologically damaging drug. As with all chemotherapy, adverse effects are common and many varying side-effects have been documented. Because docetaxel is a cell cycle specific agent, it is cytotoxic to all dividing cells in the body including tumour cells as well as hair follicles, bone marrow and other germ cells.
Haematological adverse effects include Neutropenia, Anaemia, Febrile neutropenia and Thrombocytopenia.

WARNING(S) & PRECAUTION(S)

TAXEWELL® can be non-conditionally used for the treatment of advanced breast cancer, non small cell lung cancer, ovarian cancer, prostate cancer, and squamous cell carcinoma of the head and neck.
TAXEWELL® should be administered under the supervision of a qualified physician experienced in the use of anti-cancer agents and when adequate diagnostic and treatment facilities are readily available for the appropriate management of complications.
Higher incidence of treatment related mortality associated with docetaxel therapy is seen in patients with abnormal liver function, patients receiving higher doses, 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. TAXEWELL® should generally not be given to patients with bilirubin > upper limit of normal (ULN), or to patients with serum glutamic oxaloacetic transaminase (SGOT) and/or serum glutamic pyruvic transaminase (SGPT) > 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 grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Reports suggest that patients with isolated elevations of transaminase > 1.5 x ULN are susceptible to a higher rate of febrile neutropenia grade 4 but may not

have an increased incidence of toxic death. Bilirubin, SGOT or SGPT and alkaline phosphatase values are to be obtained prior to each cycle of TAXEWELL® therapy and reviewed by the treating physician.
TAXEWELL® therapy should not be given to patients with neutrophil counts of < 1500 cells/mm^3. In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed on all patients receiving TAXEWELL®. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis have been reported in patients who receive the recommended 3 day dexamethasone premedication. Hypersensitivity reactions require immediate discontinuation of docetaxel infusion and administration of appropriate therapy. TAXEWELL® must not be given to patients who have a history of severe hypersensitivity reactions to TAXEWELL® or to other drugs formulated with polysorbate 80.
Reports suggest the occurrence of severe fluid retention in 6.5 % of patients despite the use of 3 day dexamethasone premedication regimen. The occurrence 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).
Treatment related acute myeloid leukemia may occur. No studies have been conducted to assess the carcinogenic potential of TAXEWELL®.

DRUG INTERACTION(S)

Drug interactions may be the result of altered pharmacokinetics or pharmacodynamics due to one of the drugs involved. *In vitro* studies report that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit or are metabolized by cytochrome P_{450} 3A4, such as cyclosporine, terfinadine, ketoconazole, erythromycin and troleandomycin. Caution must be exercised with these drugs when treating patients receiving docetaxel.
Clearance of docetaxel in combination therapy with cisplatin is observed to be similar to docetaxel monotherapy. The pharmacokinetic profile of cisplatin in combination therapy with docetaxel is similar to cisplatin monotherapy.
Reports suggest that in patients with hormone refractory metastatic prostate cancer, systemic docetaxel clearance in combination with prednisolone is similar to docetaxel monotherapy.
The co-administration of docetaxel has no effect on the pharmacokinetics of doxorubicin and cyclophosphamide when the there drugs are given in combination compared to co-administration of doxorubicin and cyclophosphamide alone. Doxorubicin and cyclophosphamide has no effect on docetaxel plasma clearance whenthe three drugs are given in combination compared to docetaxel monotherapy. Dexamethasone does not affect protein binding of docetaxel. Cisplatin, dexamethasone, doxorubicin, etoposide and vinblastine are all potentially co-administered with docetaxel and phase II studies report suggest that these do not modify docetaxel plasma binding. Cisplatin is known to have a complex interaction with some CYPs and has in some events been shown to reduce docetaxel clearance by up to 25 %. Anticonvulsants induce some metabolic pathways relevant to docetaxel. CYP_{450} and CYP3A show increased expression in response to the use of anticonvulsants and the metabolism of docetaxel metabolite M4 is processed by these CYPs. A corresponding increase in clearance of M4 by 25 % is observed in patients taking phenytoin and phenobarbital, common anticonvulsants.

Common and/or likely drug-drug combinations and known side effects from drug interactions

Drug Interacting with Docetaxel	Adverse Effects from Interaction
Cisplatin	Increased risk of delayed neuropathy
Cyclosporine, Dalfopristin, Erythromycin, Itraconazole, Ketoconazole, Quinupristin, Terfenadine, Troleandomycin	Increased risk of docetaxel toxicity including anaemia, leucopoenia, thrombocytopenia, fever, diarrhoea
Doxorubicin Hydrochloride	Cholestatic jaundice and pseudomembranous colitis
Doxorubicin Hydrochloride Liposome	Increased doxorubicin exposure
Vaccinations for; Bacillus of Calmette and Guerin, Measles, Mumps, Poliovirus, Rotavirus, Rubella, Smallpox, Typhoid, Varicella, Yellow Fever	Increased risk of infection by live vaccine
Thalidomide	Increased risk of venous thromboembolism

Erythromycin, ketoconazole and cyclosporine are CYP3A4 inhibitors and therefore inhibit the metabolic pathway of docetaxel. When used with anticonvulsants, which induce CYP3A4, an increased dose of docetaxel may be required. Pre-treatment with corticosteroids has been used to decrease hypersensitivity reactions and oedema in response to docetaxel and has shown no effect on the pharmacokinetics of docetaxel. Doxorubicin when combined with docetaxel can result in an increased AUC of docetaxel by 50-70 %. Etoposide has also been shown to decrease docetaxel clearance. Reports testify that prednisone given along with docetaxel led to improved survival, quality of life and pain management in patients with hormone-refractory prostate cancer.

OVERDOSAGE

There is no known antidote for TAXEWELL® (Docetaxel Injection Concentrate) overdosage. In case of overdosage, the patient should be kept in a specialized unit where vital functions can be closely monitored and supportive treatment administered as necessary. 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.

Published reports of docetaxel injection concentrate suggest that patients who received one hour infusion of 150-200 mg/m^2 dose experienced severe neutropenia, mild asthenia, cutaneous reactions and mild paresthesia but recovered without incident.

STORAGE

KEEP OUT OF REACH OF CHILDREN
Unopened vials of TAXEWELL® (Docetaxel Injection Concentrate) are stable until the expiration date indicated on the package when stored between 2-8 °C and protected from light. Freezing does not adversely affect the product.
Reconstituted TAXEWELL® infusion, if stored between 2-8 °C (36-46 °F) is stable for 4 hours however it is recommended that the fully prepared TAXEWELL® infusion (in either 0.9 % sodium chloride intravenous infusion USP/BP or 5 % dextrose Intravenous infusion USP/BP) should be used as soon as possible and maximum within 4 hours (including the 1 hour i.v administration).
It is strictly recommended to avoid the contact of TAXEWELL® with plasticized PVC equipment or devices used to prepare solutions for infusion. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may leach from PVC infusion bags or sets, the final TAXEWELL® dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene lined administration sets.

PRESENTATION

TAXEWELL® (Docetaxel Injection Concentrate IP) is available as single dose vials in 3 strengths as 20, 80, and 120 mg. Each strength of TAXEWELL® is accompanied by a respective sterile, non-pyrogenic, solvent (diluent) vial.
TAXEWELL® 20 mg Combipack contains:
A single dose vial containing 20 mg docetaxel trihydrate IP equivalent to Anhy. Docetaxel and polysorbate 80 (q.s to 0.5 ml).
A 5 ml flint glass vial of solvent for docetaxel injection concentrate containing 95 % v/v alcohol IP (13 % w/v) and Water for injection IP (q.s to 1.5 ml).
Each carton contains 2 vials in combi pack and both vials do not contain any antimicrobial preservatives.
TAXEWELL® 80 mg Combipack contains:
A single dose vial containing 80 mg docetaxel trihydrate IP equivalent to Anhy. Docetaxel and polysorbate 80 (q.s to 2.0 ml).
A 10 ml flint glass vial of solvent for docetaxel injection concentrate containing 95 % v/v alcohol IP (13 % w/v) and Water for injection IP (q.s to 6.0 ml).
Each carton contains 2 vials in combi pack and both vials do not contain any antimicrobial preservatives.
TAXEWELL® 120 mg Combipack contains:
A single dose vial containing 120 mg docetaxel trihydrate IP equivalent to Anhy. Docetaxel and polysorbate 80 (q.s to 3.0 ml).
A 10 ml flint glass vial of solvent for docetaxel injection concentrate containing 95 % v/v alcohol IP (13 % w/v) and Water for injection IP (q.s to 9.0 ml).
Each carton contains 2 vials in combi pack and both vials do not contain any antimicrobial preservatives.

HANDLING AND DISPOSAL

TAXEWELL® is a cytotoxic anticancer drug and as with other potentially toxic compounds, caution should be exercised when handling and preparing TAXEWELL® solutions and hence the use of gloves is recommended.
If either the initial reconstitution or final reconstitution for intravenous infusion of TAXEWELL®, should come into contact with the skin, wash with soap and water immediately and thoroughly. If either the initial reconstitution or final reconstitution for intravenous infusion of TAXEWELL®, should come into contact with the mucosa, wash with cold running water immediately and thoroughly. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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0700DCW

GETWELL

For the use of Registered Medical Practitioner or Hospital or a Laboratory only.

DOCETAXEL Injection Concentrate IP (with solvent)
(Combi-Pack)

TAXEWELL®

Antineoplastic Agent

FOR I.V INFUSION AFTER DILUTION

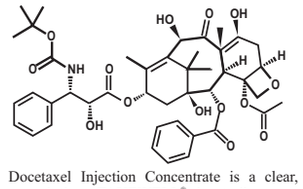
Rx only

WARNING

TAXEWELL® can be non-conditionally used for the treatment of advanced breast cancer, non small cell lung cancer, ovarian cancer, prostate cancer, and squamous cell carcinoma of the head and neck.
TAXEWELL® should be administered under the supervision of a qualified physician experienced in the use of anti-cancer agents and when adequate diagnostic and treatment facilities are readily available for the appropriate management of complications.
TAXEWELL® therapy should not be given to patients with neutrophil counts < 1500 cells/mm^3. In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell count should be performed on all patients receiving TAXEWELL®. Hypersensitivity reactions require immediate discontinuation of docetaxel infusion and administration of appropriate therapy. TAXEWELL® must not be given to patients who have a history of severe hypersensitivity reactions to TAXEWELL® or to other drugs formulated with polysorbate 80.
Treatment related acute myeloid leukemia may occur. No studies have been conducted to assess the carcinogenic potential of TAXEWELL®.

DESCRIPTION

Docetaxel belongs to the chemotherapy drug class; taxane, and is a semi-synthetic analogue of paclitaxel, an extract from the rare Pacific yew tree *Taxus brevifolia*. Due to scarcity of paclitaxel, extensive research was carried out leading to the formulation of docetaxel - an esterified product of 10-deacetyl baccatin III, which is extracted from the renewable and readily available European yew tree. Docetaxel is a semisynthetic derivative of a compound isolated from the renewable and readily available needles of the European yew tree (*Taxus baccata*). It was identified in 1986.
Docetaxel differs from paclitaxel at two positions in its chemical structure. It has a hydroxyl functional group on carbon 10, whereas paclitaxel has an acetate ester, and a tert-butyl carbamate ester exists on the phenylpropionate side chain instead of the benzyl amide in paclitaxel. The carbon 10 functional group change causes docetaxel to be more water soluble than paclitaxel.



TAXEWELL®, Docetaxel Injection Concentrate is a clear, colourless to yellowish viscous solution. TAXEWELL® is sterile, non-pyrogenic and presented is single dose vials containing 20 mg (0.5 ml), 80 mg (2.0 ml) and 120 mg (3.0 ml) anhydrous docetaxel.
TAXEWELL® requires dilution prior to administration, should be stored between 2-8 °C (36-46 °F) and protected from bright light. Freezing does not adversely affect the product.

CHEMISTRY

Docetaxel is chemically (2R, 3S) - N - carboxy - 3 - phenylisoserine, N - *tert* - butyl ester, 13 - ester with 5β - 20 - epoxy - 1, 2α, 4, 7β, 10β, 13α - hexahydroxytax - 11 - en - 9 - one 4 - acetate 2 - benzoate, trihydrate. The molecular formulae and weight of anhydrous docetaxel is $C_{43}H_{53}NO_{14}$ and 807.879 g/mol respectively. Docetaxel is white to almost white powder with a melting point around 232 °C. Docetaxel is practically insoluble in water.

COMPOSITION

Each vial of TAXEWELL® 20 (Docetaxel Injection Concentrate IP 20 mg/0.5 ml) contains	
Docetaxel trihydrate IP eqv. to Anhy. Docetaxel	20 mg
Polysorbate 80 IP	0.5 ml
Each vial of solvent for TAXEWELL® 20 contains	
Alcohol IP (95 % v/v)	13% w/v
(Absolute alcohol content 15.25% V/V)	
Water for Injection IP q.s	1.5 ml
Both vials do not contain any Antimicrobial preservatives	

Each vial of TAXEWELL® 80 (Docetaxel Injection Concentrate IP 80 mg/2.0 ml) contains

Docetaxel trihydrate IP eqv. to Anhy. Docetaxel	80 mg
Polysorbate 80 IP	2.0 ml
Each vial of solvent for TAXEWELL® 80 contains	
Alcohol IP (95 % v/v)	13 % w/v
(Absolute alcohol content 15.25% v/v)	
Water for Injection IP q.s	6.0 ml

Both vials do not contain any antimicrobial preservatives

Each vial of TAXEWELL® 120 (Docetaxel Injection Concentrate IP 120mg/3.0 ml) contains

Docetaxel trihydrate IP eqv. to Anhy. Docetaxel	120 mg
Polysorbate 80 IP	3.0 ml
Each vial of solvent for TAXEWELL® 120 contains	
Alcohol IP (95 % v/v)	13 % w/v
(Absolute alcohol content 15.25% v/v)	
Water for Injection IP q.s	9.0 ml

Both vials do not contain any antimicrobial preservatives

CLINICAL PHARMACOLOGY & MECHANISM OF ACTION

The antitumor activity of TAXEWELL® (docetaxel) is derived from its ability to disrupt the normal process of microtubule assembly and disassembly that is essential for mitotic and interphase cellular functions. Microtubules are cylindrical structures that form the basis of the cellular skeleton and are essential to the reproduction, growth and spread of tumor cells. Normally, as a part of the mitotic process, microtubules are reorganized to form a spindle. Assembly of microtubules from tubulin requires the presence of guanosine triphosphate (GTP). TAXEWELL® binds to ß subunit of the tubulin within the microtubule, promoting polymerization and preventing depolymerization of microtubules in the absence of GTP thus promoting the formation of stable microtubules, which form abnormal bundles that

- Resist physiologic disassembly
- Accumulate within tumor cells
- Inhibit cell proliferation leading to cell death

Both docetaxel and paclitaxel bind to microtubules with a stoichiometry of 1 molecule per tubulin dimmer and binding to the same site, although the affinity of docetaxel is 1.9 fold higher.

PHARMACOKINETICS & PHARMACODYNAMICS

Docetaxel is characterized by a multiphasic plasma kinetic profile, has good tissue distribution and is extensively metabolised in the liver. After intravenous administration, docetaxel is distributed to all tissues and organs except the brain where extremely low levels are found. It is also detected in the foetus, tumour tissue and milk. It is eliminated very rapidly, although at a slower rate from tumour tissue than from normal tissue. It is excreted mainly in the faeces after undergoing hepatic metabolism and excretion. Urinary excretion is very limited. The drug is not markedly absorbed from the gastrointestinal tract. Studies conducted *in vivo* (identification of major metabolites in excreta) and *in vitro* (liver microsome preparations of various species) demonstrate that monooxygenase enzymes, in particular cytochrome P450 3A, play a leading role in docetaxel metabolism while conjugation reactions are very limited. Docetaxel binds strongly to plasma proteins in all the species studied, including humans. Lastly, in man, the metabolic profile of docetaxel is comparable to that of the species used in the toxicity studies.

Pharmacokinetic profile of docetaxel evaluated in phase I cancer patients following intravenous dose of 20-115 mg/m^2 suggest that the pharmacokinetics of docetaxel are dose independent and consistent with 3 compartment model, with mean population α, ß, γ half lives of 4 minutes, 36 minutes and 11.1 hours respectively. Area under the curve (AUC) was dose proportional following 1-2 hour infusion of 70-115 mg/m^2. The approved dosing range of TAXEWELL® is 60 mg/m^2 to 100 mg/m^2. The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is partly due to a relatively slow efflux of docetaxel from the peripheral compartment. Mean values for total body clearance and steady state volume of distribution have been reported to be 21 L/h/m^2 and 113 L respectively. TAXEWELL® plasma concentrations and AUC are found to be directly proportional to dose, although drug clearance is independent of dose or schedule of administration, which is consistent with a linear pharmacokinetic profile. Docetaxel is eliminated in both the urine and feces following oxidative metabolism of the tert-butyl ester group, but fecal excretion is the prominent elimination route. Within 7 days of administration, the urinary and fecal excretion account for approximately 6 and 75 % of the administered radioactivity respectively. It has been experimentally seen that about 80 % of the radioactivity recovered in the feces is excreted during the first 48 hours, as 1 major and 3 minor metabolites with very small amounts (less than 8 %) of unchanged drug.Pharmacokinetics of TAXEWELL® is not influenced by age or gender and the total body clearance is not modified by pre-treatment with dexamethasone. In patients whom clinical chemistry data suggest mild to moderate liver function impairment (SGOT and/or SGPT > 1.5 times the upper limit of normal (ULN) concomitant with alkaline phosphatase > 2.5 times ULN), the total body clearance was observed to be lowered by an average 27 % resulting in 38 % increase in systemic exposure (AUC). This average however includes a substantial range and there is at present no measurement that allows recommendation for dose adjustment in such patients.

Combination therapy of docetaxel with several reference antitumor drugs has

been explored and no synergy has been detected with cisplatin or doxorubicin. Additive effects have been noted with vincristine while synergistic effects have been seen with cyclophosphamide and 5 fluorouracil (5-FU). *In vivo* studies suggest that the I.V administration of docetaxel against tumors grafted in distal sites (generally subcutaneously), several advanced metastatic stage tumors, induced the complete regressions of several advanced grafted murine solid tumors. The activities were dose related and obtained at dosages not toxic for mice. Experimental antitumor activity was also tested against a panel of human tumor xenografts and docetaxel was seen to exert curative activities against ovarian, breast tumors and melanoma. In human cancer xenograft models, capecitabine demonstrated a synergistic effect in combination with docetaxel, which may be related to the upregulation of thymidine phosphorylase by docetaxel.

In vitro studies show that docetaxel is approximately 94 % protein bound, mainly to alpha 1 acid glycoprotein, albumin and lipoproteins. Docetaxel is metabolized by the CYP3A4 isoenzyme and the metabolism can be inhibited by CYP3A4 inhibitors such as ketoconazole, erythromycin, troleandomycin and nifedipine.

Toxicology evaluation of docetaxel in a battery of genotoxic assays *in vitro* and *in vivo show that d*ocetaxel is devoid of mutagenic activity in the bacterial reverse mutation test (Ames test) and in the hypoxanthineguaninephosphoribosyl-transferase (HGPRT) test in Chinese Hamster Ovary cells (CHO-K1). However, in the chromosome aberration test in CHO-K1 cells, docetaxel induced an increase in aneuploid cells but was found to be devoid of any clastogenic activity. In the *in vivo* micronucleus test docetaxel induced an increase in the number of micronucleated polychromatic erythrocytes in bone marrow. The increase in the incidence of micronucleated, aneuploid and polyploidy cells may be related to the pharmacological activity of docetaxel which induces inhibition of microtubule depolymerization.

INDICATION(S)

Breast Cancer

TAXEWELL® is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.

TAXEWELL® 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

TAXEWELL® 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.

TAXEWELL® 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

TAXEWELL® in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.

When used in combination with cisplatin, the recommended dose of TAXEWELL® 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.

DOSAGE(S)

TAXEWELL® **is strictly recommended to be used as I.V infusion only.**

Recommended Dose

Breast Cancer

The recommended dose of TAXEWELL® is 60-100 mg/m^2 administered intravenously over 1 hour every 3 weeks.

In the adjuvant treatment of operable node-positive breast cancer, the recommended TAXEWELL® 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 (NSCLC)

For treatment after failure of prior platinum based chemotherapy, evaluation of TAXEWELL® as monotherapy, 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, TAXEWELL® evaluation in combination with cisplatin has resulted in the recommended dose of 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 hormone refractory metastatic prostate cancer, the recommended dose of TAXEWELL® is 75 mg/m^2 every 3 weeks as a 1 hour intravenous infusion along with continuous administration of prednisone 5 mg (oral) twice daily.

Gastric adenocarcinoma

For gastric adenocarcinoma, the recommended dose of TAXEWELL® is 75 mg/m^2 as hour intravenous infusion, followed by cisplatin 75 mg/m^2, as 1 our intravenous infusion (both on day 1 only), followed by fluorouracil 750 mg/m^2 per day given as 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.

Premedication Regimen

All patients should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg BID) for 3 days starting 1 day prior to TAXEWELL® administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

For hormone refractory metastatic prostate cancer, given the concurrent use of prednisone, the recommended premedication regimen is oral dexamethasone 8 mg at 12 hours, 3 hours and 1 hour before the TAXEWELL® infusion.

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 TAXEWELL® 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 TAXEWELL® therapy may tolerate higher doses. Patients who develop ≥grade 3 peripheral neuropathy should have TAXEWELL® treatment discontinued entirely.

Combination Therapy with TAXEWELL® in the Adjuvant Treatment of Breast Cancer: TAXEWELL® 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 the TAXEWELL® dose reduced to 60 mg/m^2. Patients who experience Grade 3 or 4 stomatitis should have the TAXEWELL® dose decreased to 60 mg/m^2. Patients who experience severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during TAXEWELL® therapy should have the dosage of TAXEWELL® reduced from 75 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 TAXEWELL® 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 TAXEWELL® 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 TAXEWELL® treatment discontinued entirely.

Combination therapy with TAXEWELL® for chemotherapy naive NSCLC: **P**atients who are dosed initially at TAXEWELL® 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 TAXEWELL® 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.

Prostate Cancer

Combination therapy with TAXEWELL® for hormone-refractory metastatic prostate cancer: TAXEWELL® 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 TAXEWELL® therapy should have the dosage of TAXEWELL® reduced from 75 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, the treatment should be discontinued.

Elderly

In general, dose selection for an elderly patient should be done with caution, reflecting the greater frequency of decreased hepatic, renal or cardiac function and concomitant disease or other drug therapy.

Pediatric's

The safety and effectiveness of docetaxel in patients below 16 years of age has not been studied extensively and sufficient data has not been established.

Hepatic Impairment

Patients with bilirubin > ULN, patients with SGOT and/or SGPT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN are not recommended to receive TAXEWELL®.

ADMINISTRATION

TAXEWELL® is a cytotoxic anticancer drug and as with other potentially toxic compounds, caution should be exercised when handling and preparing TAXEWELL® solutions and hence the use of gloves is recommended.

It is strictly recommended that TAXEWELL® must not be mixed with any other medicinal products with the exception of those mentioned in dilution guidelines

below. TAXEWELL® requires two dilutions prior to administration and it is strictly recommended that the following instructions be followed.

Note: Both TAXEWELL® and the solvent vial contains an overfill volume to compensate for liquid loss during preparation. ; this overfill volume ensures that after dilution with the entire content of the accompanying solvent there is an initial reconstituted solution containing not less than 10 mg/ml docetaxel. The table below provides the fill range of the solvent, the approximate extractable volume of solvent when the entire contents of the solvent vial are withdrawn, and the concentration of the initial reconstituted solution for TAXEWELL® 20, 80 and 120 mg.

Dilution guidelines

Initial dilution

TAXEWELL® (Docetaxel Injection Concentrate and diluent) vials should be stored in a refrigerator between 2-8 °C (36-46 °F). Allow the vials to attain the ambient room temperature before use.

Aseptically withdraw the entire contents of the appropriate diluent vial (approximately 1.5 ml for TAXEWELL® 20 mg, 6.0 ml for TAXEWELL® 80 mg and approximately 9.0 ml for TAXEWELL® 120 mg) into a syringe by partially inverting the vial and transferring to an appropriate vial of TAXEWELL® (Docetaxel Injection Concentrate). If the procedure is followed as described above, an initial reconstituted solution of 10 mg docetaxel/ml will result.

Mix the initial reconstituted solution by repeated inversion for at least 45 seconds to ensure proper mixing. Do not shake vigorously.

The initial reconstituted TAXEWELL® solution (10 mg Docetaxel/ml) should be clear; however there may be some foam on top of the solution/air bubbles in the solution due to polysorbate 80. Allow the solution to stand for a few minutes to allow any foam/air bubbles to dissipate. It is not required that all the foam/air bubbles completely dissipate prior to continuing the preparation process.

The initial reconstituted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

Final dilution for infusion

Aseptically withdraw the required amount of initial reconstituted TAXEWELL® solution (10 mg docetaxel/ml) with a calibrated syringe and inject into a 250 ml infusion bag or bottle of either 0.9 % sodium chloride intravenous infusion IP or 5 % dextrose intravenous infusion IP to produce a final concentration of 0.3 to 0.74 mg/ml. If a dose greater than 240 mg of TAXEWELL® is required, use a larger volume of the infusion vehicle ensuring that a concentration of 0.9 mg/ml TAXEWELL® is not exceeded.

Thoroughly mix the infusion by manual rotation.

As with all parenteral products, TAXEWELL® should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the TAXEWELL® initial reconstituted solution or final reconstitution for intravenous infusion is not clear or appears to have precipitation, these should be discarded.

The final TAXEWELL® dilution for infusion should be administered intravenously as 1 hour infusion under ambient room temperature and lighting conditions.

Stability

Diluted TAXEWELL® for infusion use, if stored between 2-8 °C (36-46 °F) is stable for 4 hours however it is recommended that the fully prepared TAXEWELL® infusion (in either 0.9 % sodium chloride intravenous infusion IP or 5 % dextrose Intravenous infusion IP) should be used as soon as possible and maximum within 4 hours (including the 1 hour i.v administration).

Incompatibilities

It is strictly recommended to avoid the contact of TAXEWELL® with plasticized PVC equipment or devices used to prepare solutions for infusion. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may leach from PVC infusion bags or sets, the final TAXEWELL® dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene lined administration sets.

CONTRAINDICATION(S)

TAXEWELL® (Docetaxel Injection Concentrate) is contraindicated in

- patients who have a history of hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80,
- patients with baseline neutrophil counts < 1,500 cells/mm^3,
- pregnant women,
- women who are breast feeding and
- patients with severe liver impairment.

All patients must be premedicated with oral corticosteroids such as dexamethasone 16 mg/day (e.g 8 mg BID) for 3 days, starting 1 day prior to docetaxel therapy to reduce the severity of fluid retention and hypersensitivity reactions. The pretreatment regimen for hormone refractory metastatic prostate cancer is oral dexamethasone 8 mg at 12, 3 and 1 hour before docetaxel therapy.

Patients should be closely observed for hypersensitivity reactions, especially during infusion. Hypersensitivity reactions may occur within a few minutes following initiation of docetaxel infusion. Interruption of therapy is not required if minor reactions such as flushing or localized skin reactions occur. Severe reactions however require immediate discontinuation of docetaxel and aggressive therapy. Localized erythema of the extremities with edema followed by desquamation may be seen. In case of severe skin toxicities an adjustment in