PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

NANOGIX 100 concentrate for dispersion for infusion

NANOGIX 300 concentrate for dispersion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NANOGIX 100: Each vial contains 100 mg paclitaxel.

NANOGIX 300: Each vial contains 300 mg paclitaxel.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for dispersion for infusion.

Clear, almost colourless to pale yellow slightly viscous solution.

pH (3,0 - 5,0)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NANOGIX is indicated for:

1. The palliative treatment of stage 3 or 4 advanced local carcinoma of the ovary after surgical resection, in combination with cisplatin.
2. The palliative management of metastatic carcinoma of the ovary after failure of first line or subsequent chemotherapy.
3. The treatment of metastatic carcinoma of the breast after failure of combination chemotherapy or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contra-indicated.

4. First line therapy of advanced or metastatic breast cancer in combination with trastuzumab in patients who over-express HER-2 at a 2+ or 3+ level as determined by immunohistochemistry.
5. Palliative treatment of advanced non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy.
6. In combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas.

4.2 Posology and method of administration

Indication 1:

Primary treatment of ovarian carcinoma: A combination regimen consisting of NANOGIX 175 mg/m^2 administered intravenously over 3 hours, followed by cisplatin, given every 3 weeks. Alternatively, a combination regimen consisting of NANOGIX 135 mg/m^2 administered over 24 hours, followed by cisplatin, every 3 weeks. NANOGIX should be administered before cisplatin.

Indication 2 and 3:

Secondary treatment of ovarian carcinoma: NANOGIX at a dose of 175 mg/m^2 administered intravenously over 3 hours every 3 weeks has been reported to be effective in patients with metastatic carcinoma of the ovary or breast after the failure of first line or subsequent chemotherapy.

Indication 4:

Combination, first-line therapy of advanced or metastatic breast cancer:

In combination with trastuzumab, the recommended dose of NANOGIX is 175 mg/m^2 administered intravenously over a period of 3 hours, with a 3 week interval between courses. NANOGIX may be started the day following the first dose of trastuzumab or immediately after the subsequent dose of trastuzumab if the preceding dose of trastuzumab was well tolerated.

Indication 5:

Palliative treatment of advanced non-small cell lung carcinoma: The recommended dose of NANOGIX is 175 mg/m^2 administered over a period of 3 hours; followed by a platinum compound, with a 3 week

interval between courses. NANOGIX should not be re-administered until the neutrophil count is at least 1500/mm^3 and the platelet count is at least 100000/mm^3. Patients who experience severe neutropenia (neutrophil count < 500/mm^3) or moderate to severe peripheral neuropathy should receive a dose reduction of 20 % for subsequent courses (see section 4.8). The incidence and severity of neurotoxicity and haematologic toxicity increases with dose. All patients must be premedicated prior to NANOGIX administration to reduce the risk of severe hypersensitivity reactions.

Such premedications may be corticosteroids, antihistamines, and H_2 antagonists prior to NANOGIX administration, e.g., dexamethasone 20 mg orally approximately 12 and 6 hours before NANOGIX or 20 mg IV approximately 30 to 60 minutes before NANOGIX**,** promethazine 25 mg IV 30 to 60 minutes prior to NANOGIX, and cimetidine 300 mg or ranitidine 50 mg, IV 30 to 60 minutes before NANOGIX**.** NANOGIX should be administered with the provided with 20# needle and a 5 mL luer-lock disposable syringe.

Special populations

Patients with hepatic Impairment: See section 4.4

Dosage adjustment is recommended as shown below:

Degree of Hepatic Impairment

Transaminase levels	Bilirubin Levels [(a)]	Recommended NANOGIX dose[(b)]
24 HOUR INFUSION		
< 2 x ULN and	≤ 0,026 mmol/ L	135 mg/m^2
2 - < 10 x ULN and	≤ 0,026 mmol/L	100 mg/m^2
< 10 x ULN and	0,027 – 0,128 mol/L	50 mg/m^2
≥ 10 x ULN or	> 0,128 mmol/L	Not recommended
3 HOUR INFUSION		
< 10 x ULN and	≤ 1,25 x ULN	175 mg/m^2
< 10 x ULN and	1,26 - 2,0 x ULN	135 mg/m^2
< 10 x ULN and	2,01 - 5,0 x ULN	90 mg/m^2
≥ 10 x ULN or	> 5,0 x ULN	Not recommended

Degree of Hepatic Impairment

Transaminase levels	Bilirubin Levels [a]	Recommended NANOGIX dose[b]

[a] Differences in criteria for bilirubin levels between the 3- and 24- hour infusion are due to differences in clinical trial design.

[b] Dosage recommendations are for the first course of therapy: further dose reduction in subsequent courses should be based on individual tolerance.

ULN = upper limit of normal.

Patients with renal impairment

Adjustment of the starting NANOGIX dose is not required for patients with mild to moderate renal impairment (estimated creatinine clearance ≥ 30 to < 90 mL/min). There are insufficient data available to recommend dose modifications of NANOGIX in patients with severe renal impairment or end stage renal disease (estimated creatinine clearance < 30 mL/min) (see section 5.2).

Paediatric Use

The safety and effectiveness of NANOGIX in children have not been reported. There have been reports of central nervous system toxicity (including death) in a clinical trial in paediatric patients in which NANOGIX was infused intravenously over 3 hours at doses ranging from 350 mg/m^2 to 420 mg/m^2.

Method of administration

Administer reconstituted NANOGIX suspension intravenously using an infusion set incorporating a 15 µm filter. Following administration, it is recommended that the intravenous line be flushed with sodium chloride 9 mg/mL (0,9 %) solution for injection to ensure administration of the complete dose.
For instructions on reconstitution of the medicine before administration, see section 6.6.

4.3 Contraindications

- NANOGIX is contra-indicated in patients who have a history of severe hypersensitivity reactions to the active substance or to any excipients listed in the section 6.1.

- Lactation
- NANOGIX should not be used in patients with baseline neutrophils <1500/mm^3.

4.4. Special warnings and precautions for use

WARNING

Paclitaxel should be administered under the supervision of a medical practitioner experienced in the use of cancer chemotherapeutic medicines. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available. Severe hypersensitivity reactions characterised by dyspnoea, flushing, chest pain and tachycardia and hypotension requiring treatment, angioedema, and generalised urticaria have occurred in patients receiving paclitaxel.

Patients receiving paclitaxel should be pre-treated with corticosteroids, promethazine, and H_2 antagonists to prevent these reactions. (See section 4.2). Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the medicine.
Paclitaxel therapy should not be given to patients with baseline neutrophil counts of less than 1500 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving paclitaxel.

NANOGIX should be administered under the supervision of a medical practitioner experienced in the use of cancer chemotherapeutic medicines. Since severe hypersensitivity reactions may occur, appropriate supportive equipment should be available.

NANOGIX should be administered as a diluted infusion. NANOGIX should be given before cisplatin when used in combination.

Patients should be pre-treated with corticosteroids, antihistamines and H_2 antagonists before receiving NANOGIX. Anaphylaxis and severe hypersensitivity reactions characterised by dyspnoea, flushing, chest pain and tachycardia and hypotension requiring treatment, angioedema and

generalised urticaria have been reported in patients receiving NANOGIX. These reactions are probably histamine-mediated. Fatal reactions have been reported in patients despite pre-treatment. In cases of severe hypersensitivity reactions, NANOGIX infusion should be immediately discontinued, symptomatic therapy should be initiated and the patient should not be rechallenged with NANOGIX. Minor hypersensitivity reactions such as flushing, skin reactions, not requiring treatment do not require interruption of therapy.

Bone marrow suppression (primary neutropenia) is the principal dose-limiting toxicity. Frequent monitoring of blood counts should be instituted during NANOGIX treatment. Patients should not be retreated until neutrophils recover to a level >1 500/mm^3 and platelets recover to a level >100 000/mm^3. In cases of severe neutropenia (< 500 cells/mm^3) during a course of NANOGIX, a 20 % reduction in dose for subsequent courses of therapy is recommended. The incidence of neurotoxicity and the severity of neutropenia increase with dose within a regimen.

Cardiovascular:

Severe cardiac conduction abnormalities have been reported. If patients develop significant conduction abnormalities during NANOGIX administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with NANOGIX. Severe cardiovascular events have been reported more frequently in patients with non-small cell lung carcinoma than breast or ovarian carcinoma.

Hypotension, hypertension and bradycardia have been reported during administration of NANOGIX, but generally do not require treatment. In severe cases NANOGIX infusions may need to be interrupted or discontinued at the discretion of the treating medical practitioner. Frequent vital sign monitoring, particularly during the first hour of NANOGIX infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities. When NANOGIX is used in combination with trastuzumab for treatment of metastatic breast cancer, monitoring of cardiac function is recommended.

Neurologic:

Reported cross-study comparison of neurotoxicity suggests that when NANOGIX is given in combination with cisplatin, the incidence of severe neurotoxicity is more Frequent: at a NANOGIX dose of 175 mg/m^2 given by 3-hour infusion (21 %), than at a dose of 135 mg/m^2 given by 24-hour infusion (3 %).

NANOGIX contains dehydrated alcohol, 100 mg/mL. Consideration should be given to possible central nervous system and other effects of alcohol for all patients. Children may be more sensitive than adults to the effects of alcohol. Although the occurrence of peripheral neuropathy is frequent, the development of moderate to severe symptomatology is unusual and requires a dose reduction of 20 % for all subsequent courses of NANOGIX.

Hepatic:

Patients with hepatic impairment may be at increased risk of toxicity particularly grade III-IV myelosuppression. Dose adjustment is recommended. Patients should be monitored closely for the development of profound myelosuppression. Hepatic necrosis and hepatic encephalopathy leading to death have been reported. Elevations in alkaline phosphatase and AST (SGOT) have been reported.

Injection site reaction:

A specific treatment for extravasation reactions is unknown. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during medicine administration.

Paediatric Use

The safety and effectiveness of NANOGIX in children have not been reported. There have been reports of central nervous system toxicity (including death) in a reported clinical trial in paediatric patients in which NANOGIX was infused intravenously over 3 hours at doses ranging from 350 mg/m^2 to 420 mg/m^2. The toxicity is most likely attributable to the high dose of the ethanol component of the NANOGIX vehicle given over a short infusion time. The use of concomitant anti-histamines may intensify this effect. Although a direct effect of the NANOGIX itself cannot be discounted, the high

doses used in this study (over twice the recommended adult dose) must be considered in assessing the safety of NANOGIX for use in this population.

Pneumonitis

Pneumonitis has been reported in 1 % of patients when NANOGIX was used as monotherapy and in 4 % of patients when NANOGIX was used in combination with gemcitabine. Closely monitor all patients for signs and symptoms of pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with NANOGIX and gemcitabine and promptly initiate appropriate treatment and supportive measures.

CNS metastases

The effectiveness and safety of NANOGIX in patients with central nervous system (CNS) metastases has not been established. CNS metastases are generally not well controlled by systemic chemotherapy.

Gastrointestinal symptoms

If patients experience nausea, vomiting and diarrhoea following the administration of NANOGIX, they may be treated with commonly used anti-emetics and constipating medicines.

Neuropathy

Sensory neuropathy occurs frequently with NANOGIX, although development of severe symptoms is less common. The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose reduction. When NANOGIX is used as monotherapy, if Grade 3 sensory neuropathy develops, treatment should be withheld until resolution to Grade 1 or 2 followed by a dose reduction for all subsequent courses of NANOGIX is recommended. For combination use of NANOGIX and gemcitabine, if Grade 3 or higher peripheral neuropathy develops, withhold NANOGIX; continue treatment with gemcitabine at the same dose. Resume NANOGIX at reduced dose when peripheral neuropathy improves to Grade 0 or 1.

For combination use of NANOGIX and carboplatin, if Grade 3 or higher peripheral neuropathy develops, treatment should be withheld until improvement to Grade 0 or 1 followed by a dose reduction for all subsequent courses of NANOGIX and carboplatin.

Sepsis

Sepsis was reported at a rate of 5 % in patients with or without neutropenia who received NANOGIX in combination with gemcitabine. Complications due to the underlying pancreatic cancer, especially biliary obstruction or presence of biliary stent, were identified as significant contributing factors. If a patient becomes febrile (regardless of neutrophil count), initiate treatment with broad spectrum antibiotics. For febrile neutropenia, withhold NANOGIX and gemcitabine until fever resolves and ANC ≥ 1500 cells/mm^3, then resume treatment at reduced dose levels.

4.5 Interaction with other medicines and other forms of interaction

The recommended regimen of NANOGIX administration for the primary treatment of ovarian carcinoma is for NANOGIX to be given before cisplatin. When NANOGIX is given before cisplatin, the reported safety profile of NANOGIX is consistent with that reported for single medicine use. When NANOGIX was given after cisplatin, a more profound myelosuppression and an approximately 33 % decrease in NANOGIX clearance was reported in patients. It has been reported that medications concomitantly administered with NANOGIX (e.g., corticosteroids, antihistamines, and H_2 antagonists) did not appear to interact adversely; however, possible interactions of NANOGIX with concomitantly administered medications have not been formally investigated.

Based on reported *in vitro* data, there is the possibility of an inhibition of NANOGIX metabolism in patients treated with ketoconazole. As a result, caution should be exercised when treating patients with NANOGIX when they are receiving ketoconazole as concomitant therapy. Plasma levels of doxorubicin and doxorubicinol may be increased when NANOGIX and doxorubicin are used in combination. Sequence effects characterised by more profound neutropenic and stomatitis episodes, have been reported with combination use of NANOGIX and doxorubicin when NANOGIX was administered before doxorubicin and using longer than recommended infusion times.

The metabolism of NANOGIX is catalysed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. In the absence of formal reported clinical interaction studies, caution should be exercised when administering NANOGIX concomitantly with known substrates, inducers (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or inhibitors (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) of these isoenzymes.

NANOGIX is a novel cremophor and albumin-free formulation of NANOGIX and is a composite of nanoparticles of NANOGIX stabilized with polymer and lipid by NanotectonTM Technology. In the absence of cremophor EL and albumin, the risk of hypersensitivity reactions should decrease significantly, and subjects receiving PICN might thus avoid pre-medication. Moreover, as there is no danger of leaching plasticizers from infusion bags or tubing, conventional PVC infusion systems may be safely used, and no in-line filtration is required.

NANOGIX and gemcitabine do not share a common metabolic pathway. NANOGIX clearance is primarily determined by CYP2C8 and CYP3A4 mediated metabolism followed by biliary excretion, while gemcitabine is inactivated by cytidine deaminase followed by urinary excretion. Pharmacokinetic interactions between NANOGIX and gemcitabine have not been evaluated in humans. In a study conducted between NANOGIX and carboplatin, no clinically relevant pharmacokinetic interactions have been reported in non-small cell lung cancer patients. NANOGIX is indicated as monotherapy for breast cancer, in combination with gemcitabine for pancreatic adenocarcinoma, or in combination with carboplatin for non-small cell lung cancer (see section 4.1). NANOGIX should not be used in combination with other anticancer medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy

NANOGIX has been reported to be embryotoxic, fetotoxic and to decrease fertility in animal studies. There is no information reported on the use of NANOGIX in pregnant women. NANOGIX may cause foetal harm when administered to pregnant women. NANOGIX should not be used during pregnancy.

Women of childbearing potential should be advised to avoid becoming pregnant during therapy with NANOGIX, and to inform the treating medical practitioner immediately should this occur.

Contraception in males and females

Women of childbearing potential should use effective contraception during treatment and up to 1 month after receiving treatment with NANOGIX. Male patients treated with NANOGIX are advised to use effective contraception and to avoid fathering a child during and up to six months after treatment.

Breastfeeding

It is not known if NANOGIX is excreted in human milk. Because of potential serious adverse reactions in breastfeeding infants, NANOGIX is contraindicated during lactation. Breastfeeding must be discontinued for the duration of therapy.

Fertility

NANOGIX has been reported to induce infertility in male rats. Based on findings reported in animals, male and female fertility may be compromised. Male patients should seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with NANOGIX.

4.7 Effects on ability to drive and use machines

NANOGIX has been reported to have minor or moderate influence on the ability to drive and use machines. NANOGIX may cause adverse reactions such as tiredness (very Frequent:) and dizziness (Frequent:) that may affect the ability to drive and use machinery. Patients should be advised not to drive and use machines if they feel tired or dizzy.

4.8 Undesirable effects

The frequency and severity of adverse events generally have been reported to be similar between patients receiving NANOGIX for the treatment of ovarian, breast or lung carcinoma. Unless otherwise noted, the following discussion refers to the overall safety of patients with solid tumours treated with

single medicine NANOGIX in reported clinical studies administered as one of two doses (135 or 175 mg/m^2) and one of the two schedules (3 or 24 hours) in the metastatic setting.

Haematologic toxicities: Bone marrow suppression has been reported to be the major dose-limiting toxicity of NANOGIX. Neutropenia, the most important haematologic toxicity, was reported to be dose and schedule dependent and was generally rapidly reversible. Severe neutropenia (< 500 cells/mm^3) has been reported to be more frequent with the 24-hour than with the 3-hour infusion; infusion duration had a greater impact on myelosuppression than dose. Neutropenia did not appear to increase with cumulative exposure and did not appear to be more frequent nor more severe for patients previously treated with radiation therapy.

Infectious episodes have been reported to occur very commonly and were fatal in 1 % of all patients, and included sepsis, pneumonia and peritonitis. Urinary tract infections and upper respiratory tract infections were the most frequently reported infectious complications. The use of supportive therapy, including G-CSF, is recommended for patients who have experienced severe neutropenia.

Twenty percent of the patients were reported to experience a drop in their platelet count below 100000 cells/mm^3 at least once while on treatment; 7 % had a platelet count <50000 cells/mm^3 at the time of their worst nadir. Bleeding episodes were reported in 4 % of all courses and by 14 % of all patients, but most of the haemorrhagic episodes were localised and the frequency of these events were reported to be unrelated to the NANOGIX dose and schedule.

Neurologic: In general, the frequency and severity of neurologic manifestations have been reported to be dose dependent in patients receiving single medicine NANOGIX. The frequency of peripheral neuropathy have been reported to increase with cumulative dose. Paraesthesia commonly occurs in the form of hyperesthesia. Peripheral neuropathy was reported to be the cause of NANOGIX discontinuation in 1 % of all patients. Sensory symptoms have usually improved or resolved within several months of NANOGIX discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contra-indication for NANOGIX therapy.

Less frequent: reports in the literature of abnormal visual evoked potentials in patients have suggested persistent optic nerve damage.Hypersensitivity Reactions (HSR): The frequency and severity of HSR were not affected by the dose or schedule of NANOGIX administration. The most frequent symptoms reported during these severe reactions were dyspnoea, flushing, chest pain and tachycardia.

Abdominal pain: pain in the extremities, diaphoresis, and hypertension were also reported. Minor hypersensitivity reactions, mainly flushing and rash, did not require therapeutic intervention nor did they prevent continuation of NANOGIX therapy.

Injection site reactions: During intravenous administration, injection site reactions have been reported to be usually mild and consisted of localised oedema, pain, erythema, tenderness, and induration; on occasion, extravasation can result in cellulitis. Skin sloughing and/or peeling has been reported, sometimes related to extravasation. Skin discolouration may also occur. These reactions have been reported to be more frequently with the 24-hour infusion than with the 3-hour infusion. In some cases the onset of the injection site reaction was reported to either occur during a prolonged infusion or was delayed by a week to 10 days.

Cardiovascular: Hypotension, during the first 3 hours of infusion, has been reported in 12 % of all patients and 3 % of all courses administered. Bradycardia, during the first 3 hours of infusion, were reported in 3% of all patients and 1 % of all courses. ECG alterations in the form of re-polarisation abnormalities like sinus tachycardia, sinus bradycardia, and premature beats have been reported in clinical studies. Severe cardiac conduction abnormalities have been reported in <1 % of patients during NANOGIX therapy. If patients develop significant conduction abnormalities during NANOGIX administration, appropriate therapy should be administered and continuous electrocardiographic monitoring should be performed during subsequent therapy with NANOGIX.

Gastrointestinal (GI) Toxicity: Mild to moderate nausea/vomiting, diarrhoea and mucositis (also reported as pharyngitis or chelitis) have been reported very Commonby all patients. Mucositis was reported to be schedule dependent and occurred more frequently with the 24-hour than with the 3-hour infusion.

Less frequent: reports of neutropenic enterocolitis (typhlitis), despite the co-administration of GCSF, have been reported in patients treated with NANOGIX alone and in combination with other chemotherapeutic medicines.

The frequency of undesirable effects listed in table below is defined using the following convention: Frequent (≥1/10); (≥1/100, <1/10); less frequent (≥1/1 000, <1/100); (≥1/10 000, <1/1 000).

Breast cancer (NANOGIX administered as monotherapy)

Table: Undesirable effects reported with NANOGIX monotherapy at any dose in reported clinical studies

Infections and infestations	*Frequent*: Infection, urinary tract infection, folliculitis, upper respiratory tract infection, candidiasis, sinusitis *Less frequent*: Oral candidiasis, nasopharyngitis, cellulitis, herpes simplex, viral infection, pneumonia, catheter-related infection, fungal infection, herpes zoster, injection site infection, septic shock
Neoplasms benign, malignant and unspecified (including cysts and polyps)	*Less frequent:* Metastatic pain, tumour necrosis
Blood and lymphatic system disorders	*Frequent:* Neutropenia, anaemia, leukopenia, thrombocytopenia, lymphopenia, bone marrow suppression, myelosuppression, fever, bleeding *Frequent:* Febrile neutropenia

	Less frequent: Acute myeloid leukemia[2], myelodysplastic syndrome[2], Pancytopenia
Immune system disorders	*Less frequent: [1]:* Hypersensitivity, Severe hypersensitivity
Metabolism and nutrition disorders	*Frequent:* Anorexia, dehydration, decreased appetite, hypokalaemia *Less Frequent:* Hypophosphataemia, fluid retention, hypoalbuminaemia, polydipsia, hyperglycaemia, hypocalcaemia, hypoglycaemia, hyponatraemia
Psychiatric disorders	*Frequent:* Insomnia, depression, anxiety *Less Frequent:* Restlessness
Nervous system disorders	*Frequent:* Peripheral neuropathy, neuropathy, hypoaesthesia, paraesthesia, peripheral sensory neuropathy, headache, dysgeusia, dizziness, peripheral motor neuropathy, ataxia, sensory disturbance, somnolence *Less Frequent:* Polyneuropathy, areflexia, dyskinesia, hyporeflexia, neuralgia, sensory loss, syncope, postural dizziness, neuropathic pain, tremor
Ear and labyrinth disorders	*Frequent*: Vertigo *Less Frequent:*: Ear pain, tinnitus
Cardiac disorders	*Frequent:* abnormal ECG, Tachycardia, arrhythmia, supraventricular tachycardia *Less frequent:* bradycardia, cardiac arrest, left ventricular dysfunction, congestive heart failure, atrioventricular block[2]
Vascular disorders	*Frequent:* Flushing, hot flushes, hypertension, lymphoedema *Less frequent:* Hypotension, peripheral coldness, orthostatic hypotension, thrombophlebitis, thrombosis

Respiratory, thoracic and mediastinal disorders	*Frequent:* Interstitial pneumonitis[2], dyspnoea, epistaxis, pharyngolaryngeal pain, cough, rhinitis, rhinorrhoea *Less frequent:* Productive cough, exertional dyspnoea, sinus congestion, decreased breath sounds, pleural effusion, allergic rhinitis, hoarseness, nasal congestion, nasal dryness, wheezing, pulmonary embolism, pulmonary thromboembolism
Gastrointestinal disorders	*Frequent:* Nausea, diarrhoea, vomiting, constipation, stomatitis, mucosal inflammation, abdominal pain, abdominal distension, upper abdominal pain, dyspepsia, gastrooesophageal reflux disease, oral hypoaesthesia *Less frequent:* Dysphagia, flatulence, glossodynia, dry mouth, gingival pain, loose stools, oesophagitis, lower abdominal pain, mouth ulceration, oral pain, rectal haemorrhage
Hepatobiliary disorders	*Less frequent:* Hepatomegaly
Skin and subcutaneous tissue disorders	*Frequent:* Alopecia, rash, nail disorder, pruritus, dry skin, erythema, nail pigmentation/discolouration, skin hyperpigmentation, onycholysis, nail changes *Less frequent:* Nail bed tenderness, urticaria, skin pain, photosensitivity reaction, pigmentation disorder, pruritic rash, skin disorder, hyperhidrosis, onychomadesis, erythematous rash, generalised rash, dermatitis, night sweats, maculo-papular rash, vitiligo, hypotrichosis, nail discomfort, generalized pruritus, macular rash, papular rash, skin lesion, swollen face, Stevens-Johnson syndrome[2], toxic epidermal necrolysis[2]

Musculoskeletal and connective tissue disorders	*Frequent:* Arthralgia, myalgia, pain in extremity, bone pain, back pain, muscle cramps, limb pain *Less frequent:* Chest wall pain, muscular weakness, neck pain, groin pain, muscle spasms, musculoskeletal pain, flank pain, limb discomfort, muscle weakness
Renal and urinary disorders	*Less frequent:* Dysuria, pollakiuria, haematuria, nocturia, polyuria, urinary incontinence
Reproductive system and breast disorders	*Less frequent:* Breast pain
General disorders and administration site conditions	*Frequent:* Fatigue, asthenia, pyrexia, peripheral oedema, mucosal inflammation, pain, rigors, oedema, weakness, decreased performance status, chest pain, influenza-like illness, malaise, lethargy, hyperpyrexia *Less frequent:* Chest discomfort, abnormal gait, swelling, injection site reaction (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis), extravasation
Investigations	*Frequent:* Decreased weight, increased alanine aminotransferase, increased aspartate aminotransferase, decreased haematocrit, decreased red blood cell count, increased body temperature, increased gamma-glutamyltransferase, increased blood alkaline phosphatase *Less frequent:* Increased blood pressure, increased weight, increased blood lactate dehydrogenase, increased blood creatinine, increased blood glucose, increased blood phosphorus, decreased blood potassium, increased bilirubin
Injury, poisoning and procedural complications	*Less frequent:* Contusion, radiation recall phenomenon, radiation pneumonitis

MedDRA = Medical Dictionary for Regulatory Activities.

SMQ = Standardized MedDRA Query; SMQ is a grouping of several MedDRA preferred terms to capture a medical concept.

[1] The frequency of hypersensitivity reactions is calculated based on one definitely related case in a population of 789 patients.

[2] The frequency of pneumonitis is calculated based on pooled data in 1310 patients in reported clinical trials receiving NANOGIX monotherapy for breast cancer and for other indications using MedDRA SMQ Interstitial lung disease.

Pancreatic adenocarcinoma (NANOGIX administered in combination with gemcitabine)

Table: Adverse reactions reported with NANOGIX in combination with gemcitabine

System organ class	***Adverse drug reaction***
Infections and infestations	*Frequent:* Sepsis, pneumonia, oral candidiasis
Blood and lymphatic system disorders	*Frequent:* Neutropenia, anaemia, thrombocytopenia, pancytopenia *Less frequent:* Thrombotic thrombocytopenic purpura
Metabolism and nutrition disorders	*Frequent:* Dehydration, decreased appetite, hypokalaemia
Psychiatric disorders	Frequent: Insomnia, depression, anxiety
Nervous system disorders	*Frequent:* Peripheral neuropathy[1], dysgeusia, headache, dizziness *Less frequent:* VIIth nerve paralysis
Eye disorders	*Frequent:* Lacrimation increased *Less frequent:* Cystoid macular oedema
Cardiac disorders	*Frequent:* Cardiac failure congestive, tachycardia
Vascular disorders	*Frequent:* Hypotension, hypertension

Respiratory, thoracic and mediastinal disorders	*Frequent:* Dyspnoea, epistaxis, cough, pneumonitis[2], nasal congestion *Less frequent:* Dry throat, nasal dryness
Gastrointestinal disorders	*Frequent:* Nausea, diarrhoea, vomiting, constipation, abdominal pain, abdominal pain upper, Stomatitis, intestinal obstruction, colitis, dry mouth
Hepatobiliary disorders	*Frequent:* Cholangitis
Skin and subcutaneous tissue disorders	*Frequent:* Alopecia, rash, pruritus, dry skin, nail disorder, flushing
Musculoskeletal and connective tissue disorders	*Frequent:* Pain in extremity, arthralgia, myalgia, muscular weakness, bone pain
Renal and urinary disorders	*Frequent:* Acute renal failure *Less Frequent:* Haemolytic uraemic syndrome
General disorders and administration site conditions	*Frequent:* Fatigue, oedema peripheral, pyrexia, asthenia, chills, infusion site reaction
Investigations	*Frequent:* Weight decreased, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, blood creatinine increased

MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA Query (a grouping of several

MedDRA preferred terms to capture a medical concept).

[1] Peripheral neuropathy evaluated using the SMQ (broad scope).

[2] Pneumonitis is evaluated using the SMQ interstitial lung disease (broad scope)

In this phase III randomized, controlled, open-label trial, adverse reactions resulting in death within 30 days of the last dose of study drug were reported for 4 % of patients receiving Abraxane in combination with gemcitabine and for 4% of patients receiving gemcitabine monotherapy.

Table: Additional undesirable effects reported during post-marketing surveillance

Infections and infestations:	Pneumonia, sepsis, neutropenic sepsis
Blood and the lymphatic system disorders:	Acute myeloid leukemia, myelodysplastic syndrome
Immune system disorders:	Anaphylactic reactions (with fatal outcome), anaphylactic shock
Metabolism and nutrition disorders:	Anorexia
Psychiatric disorders:	Confusional state
Nervous system disorders:	Motor neuropathy (with resultant distal weakness), autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal seizures, convulsions, encephalopathy, dizziness, headache, ataxia
Eye disorders:	Reversible optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended, photopsia, visual floaters, cystoid macular oedema
Ear and labyrinth disorders:	Hearing loss, tinnitus, vertigo, ototoxicity
Cardiac disorders:	Atrial fibrillation, supraventricular tachycardia, atrioventricular block
Vascular disorders:	Shock
Respiratory, thoracic and mediastinal disorders:	Dyspnoea, pleural effusion, respiratory failure, interstitial pneumonia, lung fibrosis, pulmonary embolism, cough
Gastrointestinal disorders:	Bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis, mesenteric thrombosis,

	pseudomembranous colitis, oesophagitis, constipation, ascites
Hepato-biliary disorders:	Hepatic necrosis (with fatal outcome), hepatic encephalopathy (with fatal outcome)
Skin and subcutaneous tissue disorders:	Pruritus, rash, erythema, phlebitis, cellulitis, skin exfoliation, necrosis and fibrosis, radiation recall, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet), scleroderma, palmar plantar erythrodysaesthesiae
General disorders and administration site conditions:	Asthenia, malaise, pyrexia, dehydration, oedema
Investigations:	Increase in blood creatinine

Table: Undesirable effects reported with NANOGIX in combination with carboplatin

Infections and infestations	*Frequent:* Pneumonia, bronchitis, upper respiratory tract infection, urinary tract infection *Less frequent:* Sepsis, oral candidiasis
Blood and the lymphatic system disorders[1]	*Frequent:* Neutropenia[1], thrombocytopenia[1], anaemia[1], leukopenia[1], febrile neutropenia, lymphopenia *Less frequent:* Pancytopenia
Immune system disorders:	*Less frequent:* Drug hypersensitivity, hypersensitivity
Metabolism and nutrition disorders:	*Frequent:* Decreased appetite, dehydration
Psychiatric disorders:	*Frequent:* Insomnia

Nervous system disorders:	*Frequent:* Peripheral neuropathy[2], dysgeusia, headache, dizziness
Eye disorders:	*Frequent:* Vision blurred
Vascular disorders:	*Frequent:* Hypotension, hypertension *Less frequent:* Flushing
Respiratory, thoracic and mediastinal disorders:	*Frequent:* Dyspnoea, haemoptysis, epistaxis, cough, pneumonitis[3]
Gastrointestinal disorders:	*Frequent:* Diarrhoea, vomiting, nausea, constipation, stomatitis, dyspepsia, abdominal pain, dysphagia
Hepato-biliary disorders:	*Frequent:* Hyperbilirubinaemia
Skin and subcutaneous tissue disorders:	*Frequent:* Rash, alopecia, pruritus, nail disorder *Less frequent:* Skin exfoliation, dermatitis allergic, urticaria
Musculoskeletal and connective tissue disorders	*Frequent:* Arthralgia, myalgia, back pain, pain in extremity, musculoskeletal pain
General disorders and administration site conditions:	*Frequent:* Fatigue, asthenia, oedema peripheral, pyrexia, chest pain *Less frequent:* Mucosal inflammation, infusion site extravasation, infusion site inflammation, infusion site rash
Investigations:	*Frequent:* Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, weight decreased

MedDRA = Medical Dictionary for Regulatory Activities: SMQ = Standardized MedDRA Query

[1] Based on laboratory assessments: maximal degree of myelosuppression (treated population)

[2] Peripheral neuropathy is evaluated using the SMQ neuropathy (broad scope)

[3] Pneumonitis is evaluated using the SMQ interstitial lung disease (broad scope)

NANOGIX and cisplatin:

Reported cross-study comparison of neurotoxicity suggests that when NANOGIX is given in combinations with cisplatin, the incidence of severe neurotoxicity is more Frequent: at a NANOGIX dose of 175 mg/m^2 given by 3-hour infusion (21 %) than at a dose of 135 mg/m^2 given by 24-hour infusion (3 %).

NANOGIX and Radiotherapy:

Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.

NANOGIX and trastuzumab:

When administered as a 3-hour infusion in combination with trastuzumab for the first line treatment of patients with metastatic breast cancer, the following events (regardless of relationship to NANOGIX or trastuzumab) have been reported more frequently than with single medicine NANOGIX: heart failure, infection, chills, fever, cough, rash, arthralgia, tachycardia, diarrhoea, hypertonia, epistaxis, acne, herpes simplex, accidental injury, insomnia, rhinitis, sinusitis and injection site reaction. Some of these frequency differences may be due to the increased number and duration of treatments with NANOGIX/trastuzumab combination vs. single medicine NANOGIX.

Administration of trastuzumab in combination with NANOGIX in patients previously treated with anthracyclines have been reported to result in an increased frequency and severity of cardiac dysfunction in comparison with patients treated with NANOGIX single medicine and rarely has been associated with death. In most cases, patients responded to appropriate medical treatment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications:

https:www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

There is no antidote reported for paclitaxel overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Overdoses in paediatric patients may be associated with acute ethanol toxicity.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A 26 Cytostatic Agents

ATC code: L01CD01

Paclitaxel is an antimicrotubule medicine that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. This stability results in the inhibition of the normal dynamic reorganisation of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, Paclitaxel induces abnormal arrays or bundles of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

5.2 Pharmacokinetic properties

Following intravenous administration, paclitaxel exhibits a biphasic decline in plasma concentrations. The initial rapid decline represents distribution to the peripheral compartment and elimination; the later phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment. In patients treated with doses of 135 and 175 mg/m^2 given as 3 and 24 hour infusions, mean terminal half-life has ranged from 3,0 to 52,7 hours. Mean values for total body clearance ranged from 11,6 to 24 L/h/m^2. Mean steady state volume of distribution has ranged from 198 to 688 L/m^2, indicating extensive extravascular distribution and/or tissue binding.

The pharmacokinetics of paclitaxel have been reported to be non-linear. There is a disproportionately large increase reported in C_{max} and AUC with increasing dose, accompanied by an apparent dose related decrease in total body clearance. These findings have been most readily reported in patients in whom high plasma concentrations of paclitaxel are achieved. Saturable processes in distribution and elimination/metabolism may account for these findings.

No evidence of accumulation of paclitaxel with multiple treatment courses have been reported. Reported in vitro studies of binding to human serum proteins, using NANOGIX concentrations ranging from 0,1 to 50 µg/mL, indicate that, on average, 89 % of paclitaxel is bound. The presence of cimetidine, ranitidine, dexamethasone or diphenhydramine did not affect protein binding of paclitaxel. The disposition of paclitaxel has not been fully elucidated in humans. After intravenous administration of paclitaxel, mean values of cumulative urinary recovery of unchanged paclitaxel have been reported to range from 1,3 to 12,6 % of the dose, indicating extensive non-renal clearance. Hepatic metabolism and biliary clearance may be the principal mechanism for disposition of paclitaxel.

Paclitaxel has been reported to be metabolised primarily by cytochrome P450 enzymes. Hydroxylated metabolites have been reported to be the principal metabolites. The formation of 6α-hydroxy paclitaxel, 3'-p-hydroxy paclitaxel and 6α, 3'-p-dihydroxy paclitaxel is catalysed by CYP2C8, 3A4 and both 2C8 and 3A4 respectively.

The effect of the renal or hepatic dysfunction on the disposition of paclitaxel has not been reported. The clearance of paclitaxel was reported to be not affected by cimetidine pre-treatment. Ketoconazole may inhibit the metabolism of paclitaxel. Plasma levels of doxorubicin and doxorubicinol may be increased when paclitaxel and doxorubicin are used in combination.

5.3 Preclinical safety data

Based on the published literature, paclitaxel is a potentially carcinogenic and genotoxic medicine at clinical doses, based upon its pharmacodynamic mechanism of action. Paclitaxel has been reported to be clastogenic in vitro (chromosome aberrations in human lymphocytes) and in vivo (micronucleus test in mice). Paclitaxel has been reported to be genotoxic in vivo (micronucleus test in mice), but it did not induce mutagenicity in the Ames test or the Chinese hamster ovary/hypoxanthine-guanine phosphoribosyl transferase (CHO/HGPRT) gene mutation assay.

Paclitaxel at doses below the human therapeutic dose was reported to be associated with low fertility when administered prior and during mating in male and female rats and foetal toxicity in rats.

Paclitaxel has been reported to be non-reversible, toxic effects on the male reproductive organs at clinically relevant exposure levels.

Paclitaxel and/or its metabolites has been reported to be excreted into the milk of lactating rats. Following intravenous administration of radiolabelled paclitaxel to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk was reported to be higher than in plasma and declined in parallel with the plasma concentrations.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Caprylic acid (octanoic acid)

dehydrated alcohol

polyethylene glycol (400)

povidone (K-12)

sodium cholesteryl sulphate.

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

2 years.

Unopened product

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C - 8 °C in the original carton, protected from light.

Chemical and physical in-use stability has been demonstrated for 8 hours at 25 °C in the original carton, protected from light.

Admixture stability

Chemical and physical in-use stability has been demonstrated for 8 hours at 25 °C and up to 24 hours when stored at 2°- 8°C.

This reinforces the 8 h recommended in-use stability of the NANOGIX at room temperature and 24 h when stored at 2°- 8°C.

However, from a microbiological point of view, unless the method of reconstituting and filling of the infusion bags precludes the risks of microbial contamination, the product should be used immediately after reconstitution and filling of the infusion bags.

If not used immediately, in-use storage times and conditions are the responsibility of the user.
The total combined storage time of reconstituted medicine in the vial and in the infusion bag when refrigerated and protected from light is 24 hours. This may be followed by storage in the infusion bag for 8 hours below 25 °C, protected from light. The total combined storage time of reconstituted medicine in the vial and in the infusion bag when refrigerated and protected from light is 24 hours. This may be followed by storage in the infusion bag for 8 hours below 25 °C, protected from light.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the vial in the outer carton in order to protect it from the light.

For storage conditions after dilution, see section 6.3.

6.5 Nature and contents of container

NANOGIX 100: Type I clear, colourless 2 mL glass vial containing 100 mg of NANOGIX.

NANOGIX 300: Type I clear, colourless 5 mL glass vial containing 300 mg of NANOGIX.

Pack size: 1 vial.

6.6 Special precautions for disposal other handling

Preparation and administration precautions

NANOGIX is a cytotoxic anticancer medicine and, as with other potentially toxic compounds, caution should be exercised in handling NANOGIX. The use of gloves, goggles and protective clothing is recommended. If the suspension contacts the skin, the skin should be washed immediately and thoroughly with soap and water. If it contacts mucous membranes, the membranes should be flushed thoroughly with water. NANOGIX should only be prepared and administered by personnel

appropriately trained in the handling of cytotoxic medicines. Pregnant staff should not handle NANOGIX.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during administration of the medicine. Limiting the infusion of NANOGIX to 30 minutes, as directed, reduces the likelihood of infusion-related reactions.

Reconstitution and administration of the medicine

NANOGIX should be diluted with appropriate volume of 5 % m/v Dextrose injection, NANOGIX should not be diluted with any other diluents other than 5 % m/v Dextrose injection. Use of recommended luer lock syringe and 20G needle for NANOGIX provides ease of product withdrawal, and dilution. Dilution of NANOGIX in 5 % m/v Dextrose injection must be performed with shaking. All aseptic precautions shall be taken during dilution and intravenous administration.

1. Calculate the exact total dosing volume of NANOGIX and 5 % dextrose injection to obtain the NANOGIX suspension of 5 mg/mL required for the intravenous infusion.

Volume of NANOGIX (mL): Total dose (mg)/110 (mg/mL).

Volume of 5 % dextrose injection (mL): (Total dose (mg)/5 (mg/mL)) – Volume of NANOGIX (mL)

2. Take calculated volume of 5 % dextrose injection in the sterile infusion bag [plasticised polyvinyl chloride (PVC) containers, PVC or non-PVC type intravenous bag].

3. Aseptically withdraw the calculated volume of NANOGIX from vials, into the luer lock syringe.

4. Hold 5 % dextrose injection infusion bag in slanted position, see following figure.

5. Aseptically inject NANOGIX volume into infusion bag within two minutes with gentle shaking. The use of specialised DEHP-free solution containers or administration sets is not necessary to prepare or administer NANOGIX dilutions. Do not mix or dilute with other medicines.

6. Gently shake the infusion bag after injection. If concentrate is visible in the injection/infusion port, port should be gently squeeze and infusion bag should be gently shaken again to ensure complete resuspension prior to use. If foaming occurs, stand solution for at least 15 minutes until foam subsides.

Each mL of the diluted formulation will contain 5 mg/mL NANOGIX.

Visually inspect the diluted NANOGIX suspension in the intravenous bag prior to administration. The diluted suspension should be white translucent to milky and homogenous without visible particulates. Discard the diluted suspension if particulate matter is observed.

Discard any unused portion.

Disposal:

All items used for reconstitution, administration or otherwise coming into contact with **NANOGIX** should undergo disposal according to local guidelines for the handling of cytotoxic compounds.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill Ext.1

Roodepoort

Johannesburg

8. REGISTRATION NUMBER(S)

NANOGIX 100: 54/26/0454

NANOGIX 300: 54/26/0455

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 February 2024

10. DATE OF REVISION OF THE TEXT

Ranbaxy Pharmaceuticals(Pty) Ltd	**Injection Concentrate for Nanodispersion, 10 % w/w,100 mg & 300 mg**
Paclitaxel	**Paclitaxel USP**