

# Data Sheet

## DAUNORUBICIN INJECTION

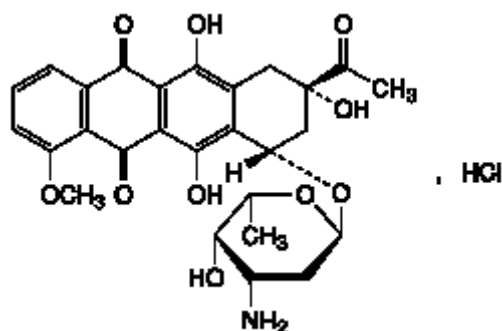
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### NAME OF THE MEDICINE

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Daunorubicin hydrochloride

The structural formula is presented below.



Molecular Formula:  $C_{27}H_{30}ClNO_{10}$

Molecular Weight: 564.0

CAS Number: 23541-50-6

Chemical Name: (8S,10S)-8-Acetyl-10-[(3-amino-2,3,6-trideoxy- $\alpha$ -L-lyxo-hexopyranosyl)oxy]-6,8,11-trihydroxy-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione hydrochloride.

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### DESCRIPTION

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Daunorubicin hydrochloride occurs as a hygroscopic, crystalline, orange-red powder, freely soluble in water and in methanol, slightly soluble in alcohol and practically insoluble in acetone.

Daunorubicin Injection is a sterile, isotonic, preservative free solution containing daunorubicin hydrochloride 2.14 mg/mL (equivalent to 2 mg/mL daunorubicin) and sodium chloride in Water for Injections.

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## PHARMACOLOGY

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**Class of drug:** Cytotoxic anthracycline antibiotic.

### **Mode of action**

Daunorubicin is an antineoplastic antibiotic which is structurally related to doxorubicin. The drug appears to act by inhibiting DNA and DNA-dependent RNA synthesis by forming a complex with DNA with intercalation between base pairs and uncoiling of the helix. Daunorubicin may also inhibit polymerase activity, affect regulation of gene expression, and be involved in free radical damage to DNA.

The drug is not cell cycle-phase specific although maximum cytotoxic activity occurs in the S phase. Daunorubicin also has antibacterial and immunosuppressive properties.

### **Pharmacokinetics**

#### ***Distribution***

Daunorubicin is rapidly and widely distributed in tissues, with highest levels in the heart, kidneys, liver, lungs and spleen. It binds inside the cells to cellular components, mainly nucleic acids.

Daunorubicin does not cross the blood-brain barrier but appears to cross the placenta. It is not known if daunorubicin is present in breast milk.

#### ***Metabolism***

Daunorubicin is extensively metabolised in the liver and other tissues, mainly by cytoplasmic aldo-keto reductases, producing daunorubicinol, the major metabolite, which has antineoplastic activity. Approximately 40% of the drug in the plasma is present as daunorubicinol within 30 minutes and 60% in 4 hours after a dose of daunorubicin. Additional metabolism by reductive cleavage of the glycosidic bond produces aglycones, which have little or no cytotoxic activity and are demethylated and conjugated with sulphate and glucuronide by microsomal enzymes.

Daunorubicin metabolism may be altered in patients with impaired hepatic function.

#### ***Elimination***

Following rapid IV administration, total plasma concentrations of daunorubicin and its metabolites decline in a triphasic manner and plasma concentrations of unchanged daunorubicin decline in a biphasic manner.

The plasma half-life of daunorubicin averages 45 minutes in the initial phase and 18.5 hours in the terminal phase. By 1 hour after administration of daunorubicin, the predominant form of the drug in plasma is the metabolite daunorubicinol, which has an average terminal plasma half-life of 26.7 hours.

Daunorubicin and its metabolites are excreted in the urine and bile, with urinary excretion accounting for 14-23% of the dose. Most urinary excretion of daunorubicin occurs within 3 days. After the first 24 hours, the drug is excreted in urine mainly as daunorubicinol. An estimated 40% of a dose is eliminated by biliary excretion.

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## INDICATIONS

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Daunorubicin Injection is indicated for the treatment of the following:

- Acute lymphocytic (lymphoblastic) leukaemia: Daunorubicin is usually reserved for use in cases shown to be resistant to other drugs. However, combined treatment with daunorubicin, vincristine and a steroid has been used in the early stages of this disease.
- Acute myeloblastic leukaemia: Daunorubicin has been used in all stages, alone or in combination with other cytotoxic agents (e.g. cytarabine).
- Disseminated solid tumours: Daunorubicin has been investigated for use in these tumours and found to be effective in some cases of disseminated neuroblastoma and rhabdomyosarcoma.

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## CONTRAINDICATIONS

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Daunorubicin Injection is contraindicated in:

- Patients with marked myelosuppression induced by previous treatment with other cytotoxic agents or radiotherapy.
- Patients with impaired cardiac function.
- Patients who have previously received the full cumulative dose of daunorubicin and/or doxorubicin.
- Patients with known hypersensitivity to daunorubicin.
- Patients who are pregnant.

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## WARNINGS AND PRECAUTIONS

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***Daunorubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.***

Initial treatment with daunorubicin requires close observation of the patient and extensive laboratory monitoring. It is recommended, therefore, that patients be hospitalised at least during the first phase of treatment. Blood counts and monitoring of parameters of renal and liver function should be performed prior to each treatment with daunorubicin.

Administration of myelosuppressive drugs such as daunorubicin may lead to an increased frequency of infections and haemorrhagic complications. These complications are potentially fatal therefore patients should be instructed to notify the physician if fever, sore throat, or unusual bruising or bleeding occurs.

### ***Cardiac toxicity***

Special attention must be given (by close cardiac monitoring) to the cardiac toxicity exhibited by daunorubicin, especially in infants and children.

Daunorubicin has a cardiotoxic effect, which can be manifested under two distinct sets of circumstances:

Firstly, daily administration of large doses (2 mg/kg or more) will result in transient reversible ECG changes in a proportion of cases. This can be avoided by administering the drug at longer intervals.

Secondly, exceeding the total cumulative dose of 20 mg/kg may result in irreversible cardiac failure. This can occur with very little warning and after only a short period of tachycardia. The cumulative dosage limit appears to be lower in patients previously treated with doxorubicin or in those who have received radiation therapy that encompassed the heart. Pre-existing heart disease, concomitant use of drugs with the ability to suppress cardiac contractility and previous therapy with other anthracyclines are suspected co-factors of increased risk of daunorubicin-induced cardiac toxicity. It has also been suggested, but is not clearly established, that concurrent therapy with cyclophosphamide or some other antineoplastic agents (e.g. dacarbazine, dactinomycin, mitomycin) may increase the risk of daunorubicin-induced cardiotoxicity. In adults, at total cumulative doses less than 550 mg/m<sup>2</sup> (or less than 20 mg/kg body weight), acute congestive cardiac failure is seldom encountered, although rare instances of pericarditis-myocarditis, not dose related, have been reported. There is no absolutely reliable method of predicting the patients in whom acute congestive cardiac failure will develop as a result of daunorubicin therapy. However, certain changes in the electrocardiogram and a decrease in the systolic ejection fraction from pre-treatment baseline may help to recognise those patients at greatest risk. On the basis of the electrocardiogram, a decrease equal to or greater than 30% in limb lead QRS voltage has been associated with a significant risk of drug-induced cardiomyopathy. Therefore, an electrocardiogram and/or determination of systolic ejection fraction should be performed before each course of daunorubicin. In the event that one or the other of these predictive parameters should occur, the benefit of continued therapy must be weighed against the risk of producing cardiac damage. Early clinical diagnosis of drug-induced congestive heart failure appears to be essential for successful treatment with digoxin, diuretics, sodium restriction and bed rest.

Anthracyclines including daunorubicin should not be administered in combination with other cardiotoxic agents (e.g. trastuzumab) unless the patient's cardiac function is closely monitored. Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives may also be at an increased risk of developing cardiotoxicity.

### ***Bone marrow depression***

Bone marrow depression will occur in all patients who receive daunorubicin, the severity being dependent on the dose received and the regenerative capacity of the bone marrow. Myelosuppression is manifested primarily by leucopenia, which is usually severe, and thrombocytopenia. Anaemia may also occur. Leucocyte and platelet nadirs usually occur around days 10-14, with recovery around day 21 following therapy. Haematologic states must be carefully monitored in patients receiving daunorubicin. In a variable proportion of cases, a severe aplasia will develop which must be anticipated in every case by eliminating infection before treatment, by isolating the patient from infection during the treatment and by the use of supportive therapy, including the continuous administration of anti-infective agents, the administration of platelet rich plasma or fresh whole blood transfusion and, under some circumstances, the transfusion of blood or white cells from cases of hyperleucocytic chronic myeloid leukaemia. Therapy with daunorubicin should not be started in patients with pre-existing drug-induced bone marrow depression unless the benefit from such treatment warrants the risk.

### ***Secondary leukaemia***

Secondary leukaemia, with or without a preleukemic phase, has been reported in patients treated with anthracyclines, including daunorubicin. Secondary leukaemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, in combination with radiotherapy, when patients have been heavily pre-treated with cytotoxic drugs, or when doses of the anthracyclines have been escalated. These leukemias can have a 1- to 3-year latency period.

### ***Immunosuppression***

Daunorubicin possesses immunosuppressive properties. Appropriate measures should be taken to prevent secondary infection.

### ***Enhanced toxicity***

Daunorubicin may enhance the toxicity of other cytotoxic agents when administered concurrently and dosage should be suitably reduced.

### ***Hepatic or renal impairment***

Significant hepatic or renal impairment can enhance the toxicity of recommended doses of daunorubicin. Prior to administration, it is recommended that hepatic and renal function be evaluated using conventional clinical laboratory tests. Dosage should be reduced in patients with impaired hepatic or renal function.

Hepatotoxic effects have been reported resulting from daunorubicin treatment. Care should therefore be exercised when treating patients with impaired liver function.

Daunorubicin has been implicated as causing renal failure and should therefore be used with caution when renal damage exists.

### ***Extravasation***

Extravasation of daunorubicin at the site of intravenous administration can cause severe local tissue necrosis.

Rapid destruction of a large number of leukaemia cells may cause a rise in blood uric acid or urea. It is recommended to check the blood uric acid and urea levels three or four times a week during the first week of treatment, for fluids to be pushed, and allopurinol to be used in severe cases to prevent the development of hyperuricaemia.

There is little evidence of neurotoxic effects.

Daunorubicin is potentially mutagenic and carcinogenic.

### ***Alopecia***

Complete alopecia involving beard growth and the scalp, axillary and pubic hair occurs almost always with full doses of daunorubicin. This side-effect may cause distress to patients but is usually reversible, with regrowth of hair, which usually occurs within two to three months from the termination of therapy.

## Use in pregnancy (Australian Category D)

Daunorubicin has shown teratogenic, mutagenic and carcinogenic potential in animals. The drug must be considered as a potential cause of foetal malformations when administered to a pregnant woman.

Daunorubicin should only be used in women of childbearing potential if the expected benefits outweigh the risks of therapy and adequate contraception is used. If the patient becomes pregnant whilst receiving the drug she should be advised of the potential hazard to the foetus.

## Use in lactation

It is not known whether daunorubicin is excreted in breast milk therefore breastfeeding is not recommended during daunorubicin therapy in lactating women. It is recommended that daunorubicin is not administered to mothers who are breastfeeding.

## Interactions with other drugs

**Cyclophosphamide:** The cardiotoxic effects of daunorubicin may be enhanced by concurrent treatment with cyclophosphamide. Daunorubicin may exacerbate cyclophosphamide induced haemorrhagic cystitis. It is recommended that the total dose of daunorubicin not exceed 400 mg/m<sup>2</sup> of body surface area when administered concurrently with cyclophosphamide.

**Doxorubicin:** Previous treatment with doxorubicin increases the risk of daunorubicin induced cardiotoxicity. Daunorubicin should not be administered to patients who have received the complete cumulative dose of doxorubicin.

**Radiotherapy:** Increased radiation toxicities such as skin reactions and mucositis may result from concurrent radiotherapy and daunorubicin therapy.

**Allopurinol, colchicine, probenecid or sulphapyrazone:** Daunorubicin may raise the concentration of uric acid in the blood. Control of hyperuricaemia and gout may require dosage adjustments to be made for antigout medications for better control. Allopurinol may be preferred to prevent or reverse daunorubicin induced hyperuricaemia because of the risk of uric acid nephropathy with uricosuric antigout agents.

**Other bone marrow depressants:** Reduced dosage of daunorubicin may be required.

**Hepatotoxic medications:** Concurrent administration may increase the risk of hepatotoxicity.

**Vaccines, live virus:** Due to its immunosuppressive properties, concurrent use of daunorubicin with a live virus vaccine may potentiate the replication of the vaccine, increase the adverse effects of the vaccine virus, or decrease the patient's antibody response to the virus.

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## ADVERSE EFFECTS

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**Cardiovascular:** Cardiotoxicity as cardiomyopathy, congestive heart failure.

The incidence of cardiotoxicity is more frequent in adults receiving a total cumulative dose over 550 mg/m<sup>2</sup> of body surface area or 20 mg/kg of body weight (450 mg/m<sup>2</sup> in patients who have received concurrent cyclophosphamide or previous chest irradiation, in the elderly, and in patients with a history of cardiac disease or mediastinal radiation).

Children may be more susceptible to the development of cardiomyopathy than adults. However there is little risk with a total dose less than 300 mg/m<sup>2</sup> in children over 2 years of age or at a total dosage of less than 10 mg/m<sup>2</sup> in children younger than 2 years of age with a body surface area of less than 0.5 m<sup>2</sup> of developing cardiomyopathy.

Cardiomyopathy usually appears within 1 to 6 months after initiation of therapy. It may develop suddenly and may not be detected by routine ECG. It may be irreversible and fatal but responds to treatment if detected early.

Although rare, instances of pericarditis-myocarditis, not dose related, have been reported.

**Bone marrow depression:** Myelosuppression is manifested primarily by leucopenia, which is usually severe and thrombocytopenia. Anaemia may also occur. The nadir of leucocytes and platelets usually occurs between 10 and 14 days following drug administration. Recovery usually occurs within 21 days after a dose.

**Neoplasms benign and malignant:** Acute myeloid leukaemia, myelodysplastic syndrome.

**Immunosuppression:** Daunorubicin possesses immunosuppressive properties. Appropriate measures should be taken to prevent secondary infection.

**Hepatic impairment:** Hepatotoxic effects have been reported as resulting from daunorubicin treatment. Care should therefore be exercised when treating patients with impaired liver function.

**Renal impairment:** Daunorubicin has been implicated as causing renal failure and therefore should be used with caution when renal damage exists.

Red colour of urine for 1 to 2 days after administration.

**Gastrointestinal:** Stomatitis usually starts with burning and erythema of the oral mucosa; sores in the mouth and/or lips occur 3 to 7 days after administration, leading to ulceration 7 to 10 days after administration. Oesophagitis may occur in some patients.

Nausea and vomiting are usually mild and transient, occurring soon after administration and lasting 24 to 48 hours.

Diarrhoea and abdominal pain may occur less frequently.

**Dermatological Effects:** Reversible alopecia is common. Other reactions include urticarial rash, contact dermatitis and hyperpigmentation of nail beds and skin.

**Local Effects:** Severe local tissue necrosis, severe cellulitis, thrombophlebitis, or painful induration may be experienced after extravasation.

**Allergic reactions:** Skin rash or itching.

**Other Adverse Effects:** Transient fever and chills occur rarely after administration of daunorubicin, but the drug has been associated with one case of fulminant hyperpyrexia. Transient elevations in serum bilirubin, AST (SGOT), and alkaline phosphatase concentrations have occurred in patients receiving Daunorubicin.

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## DOSAGE AND ADMINISTRATION

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Daunorubicin Injection is intended for intravenous use only and should not be administered by either the intramuscular or the subcutaneous routes, as severe tissue necrosis will result. Daunorubicin must be given into a rapidly flowing intravenous infusion.

The dosage of each individual injection may vary from 0.5 to 3 mg/kg, with the frequency of repetition according to the dose:

- 0.5 to 1 mg/kg repeated at intervals of one or more days;
- 2 mg/kg repeated at intervals of four or more days;
- 2.5 or 3 mg/kg, if used, should only be given at seven to fourteen day intervals.

Dosage must be adjusted to meet individual requirements of each patient, on the basis of clinical response and appearance or severity of toxicity. One injection has sometimes sufficed; commonly three to six injections have been necessary; occasionally up to 10 injections in one series have been used.

When second or subsequent injections are to be given the doses and the time intervals depend on the effect of the previous doses and must be the subject of careful deliberation, examination of the peripheral blood and under some circumstances, of the marrow.

In *acute lymphocytic leukaemia*, doses of 1 mg/kg may be repeated according to tolerance and effect at one to four day intervals.

In *acute myeloblastic leukaemia*, each dose should be about 2 mg/kg, more or less, according to effect, repeated at four to seven day intervals. Doses of over 2 mg/kg should be employed with caution at intervals of one week or longer.

When daunorubicin is administered with other cytotoxic drugs, which have a tendency to depress the marrow, the dosage should be suitably reduced. Examples of combination dosage regimens are as follows:

***Acute lymphocytic leukaemia:*** Prednisolone 100 mg/m<sup>2</sup> daily with vincristine 1.5 mg/m<sup>2</sup> on the first and second days of each week, until remission occurs.

***Acute myeloblastic leukaemia:*** Repeated intermittent courses of daunorubicin and cytosine arabinoside, each course consisting of the intravenous injection of both daunorubicin 1.5 mg/kg and cytarabine 2 mg/kg on the first day, followed by daily cytarabine only for a further four days. It has been reported that an average of two to three such courses at ten day intervals is required to induce remission.

Due to cardiotoxicity, the total lifetime dosage should not exceed 20 mg/kg. The drug is therefore not suitable for maintenance therapy.

## Dose Modifications

**Hepatic Dysfunction:** Dose reductions are recommended in patients with the following serum chemistry values:

- Bilirubin 1.2 to 3 mg/dL:  $\frac{1}{2}$  of recommended starting dose
- Bilirubin > 3 mg/dL:  $\frac{1}{4}$  of recommended starting dose
- Daunorubicin should not be administered to patients with severe hepatic impairment

**Renal Dysfunction:** If serum creatinine is above 3.0 mg/dL, the daunorubicin dose should be reduced by  $\frac{1}{2}$ .

## Administration

It is recommended the injection be added to a free flowing IV infusion of 0.9% sodium chloride or 5% dextrose injection. The tubing should be connected to a butterfly needle, inserted preferably into a large vein. The dose and the size of the vein will determine the rate of administration, which should not be less than 3-5 minutes. Erythematous streaking and facial flushing are indications of too rapid administration.

A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration.

## Instructions to be given to patients

Patients should be advised to immediately report any stinging or burning as these indicate possible extravasations. If this occurs the infusion should be stopped, removed and restarted in another vein.

Daunorubicin may transiently impart a red discolouration to the urine after administration; patients should be advised to expect this.

Complete alopecia is common but reversible on withdrawal of treatment. Patients should be made aware of this adverse effect before commencement of treatment.

Due to the increased frequency of infection as well as haemorrhagic complications resulting from daunorubicin therapy, the patient should be instructed to notify the doctor if fever, sore throat, or unusual bleeding or bruising occurs.

## Incompatibilities

Heparin sodium and aluminium are incompatible with daunorubicin and will precipitate in solution. Incompatibility has also been reported when a daunorubicin hydrochloride solution is mixed with a solution of dexamethasone sodium phosphate, aztreonam, allopurinol sodium, fludarabine and piperacillin/tazobactam. Daunorubicin can be used in combination with other cytotoxic agents, but it is not recommended that it be mixed with other drugs in the same syringe.

## Handling precautions

*Only professionals, who have been trained in the safe use of the preparation of chemotherapeutic agents, should prepare daunorubicin for administration.*

Operations such as transfer to syringes should only be carried out in the designated area. The personnel carrying out these procedures should be adequately protected with clothing, gloves and eye shields.

Pregnant personnel are advised not to handle cytotoxic agents.

Where the solution accidentally contacts skin or mucosa, the affected area should be immediately washed thoroughly with soap and water.

Luer-Lock fitting syringes are recommended.

Items used to dilute daunorubicin, or articles associated with body waste, should be disposed of by placing in a thick polyethylene bag and incinerating at 1100°C.

## Spills and disposal

If spills occur, restrict access to the affected area. Wear two pairs of gloves (latex rubber), a respirator mask, a protective gown and safety glasses. Limit the spread of the spill by covering with absorbent material such as absorbent towel or adsorbent granules. Spills may also be treated with 3M sulphuric acid and 0.3M potassium permanganate (2:1) or 5% sodium hypochlorite. Collect up the towel of absorbent/adsorbent material and other debris from spill and place in a leak proof plastic container labelled accordingly. Cytotoxic waste should be regarded as hazardous or toxic and clearly labelled 'CYTOTOXIC WASTE FOR INCINERATION AT 1100°C'. Waste material should be incinerated for at least one second at 1100°C. Cleanse the remaining spill area with copious amounts of water.

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## OVERDOSAGE

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Clinical features of overdose are likely to be an extension of daunorubicin's pharmacological action. Possible symptoms of toxicity are those listed under **Adverse Effects**.

Acute overdose with daunorubicin will result in severe myelosuppression (mainly leukopenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucositis) and acute cardiac complications.

**Management:** Symptomatic supportive measures should be instituted. Particular attention should be given to prevention and treatment of possible severe haemorrhages or infections secondary to severe, persistent bone marrow depression.

Contact the Poisons Information Centre for advice on the management of an overdose.

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## PRESENTATION AND STORAGE CONDITIONS

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Daunorubicin Injection 20 mg in 10 mL (sterile), Plastic Vial.

Store between 2°C to 8°C. Protect from light.

The expiry date (month/year) is stated on the package after EXP.

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**NAME AND ADDRESS OF SPONSOR**

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Pfizer New Zealand Ltd  
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14 Normanby Road  
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**MEDICINE SCHEDULE**

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Prescription Medicine

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**DATE OF PREPARATION**

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23 February 2011