

NEW ZEALAND DATA SHEET

Allopurinol Sandoz[®]

Allopurinol Ph Eur, tablets, 100 mg and 300 mg

Presentation

100 mg

White, round, plain, uncoated tablets, scored on one side. Each tablet contains allopurinol 100 mg.

300 mg

White to off-white, 17 mm x 7 mm oblong, biconvex plain, uncoated tablets with a breaking notch on both sides. Each tablet contains allopurinol 300 mg.

Uses

Actions

Allopurinol is used to decrease uric acid concentrations in plasma and/or urine when hyperuricaemia is clinically significant.

Pharmacotherapeutic group

M04AA01 - Preparations inhibiting uric acid production, allopurinol.

Mechanism of action

Allopurinol inhibits xanthine oxidase, the enzyme which catalyses the oxidation of hypoxanthine to xanthine, and of xanthine to urate/uric acid.

Pharmacodynamic effects

Allopurinol and its main metabolite oxypurinol lower the level of uric acid in plasma and urine in two ways: the inhibition of xanthine oxidase reduces the amount of hypoxanthine and xanthine converted to urate/uric acid; this action, in some but not all hyperuricaemic patients, makes more hypoxanthine and xanthine available for reutilisation in the purine metabolic cycle, which in turn, depresses overall *de novo* purine biosynthesis via feedback inhibition of hypoxanthine-guanine phosphoribosyltransferase.

With the lowered urate/uric acid levels in serum and urine produced by allopurinol there are also increased levels of the substrates hypoxanthine and xanthine. Plasma concentrations of these oxypurines are only slightly increased and the rate and extent of their renal clearance is greater than that of uric acid. In the absence of allopurinol, normal urinary output of oxypurines is almost solely in the form of uric acid. After administration of allopurinol, it is composed of hypoxanthine, xanthine and uric acid, each with different solubility properties. Consequently, the concentration of uric acid in plasma is reduced without exposing the urinary tract to an excessive load of urate/uric acid, thus decreasing the risk of crystalluria. By lowering the uric acid concentration in the plasma below its limits of solubility, allopurinol facilitates dissolution of tophi. Although the levels of hypoxanthine and xanthine are increased, the risk of their deposition is less than that of uric acid as they are more soluble and are rapidly cleared by the kidney. However to avoid xanthine stones being deposited, it is advisable to maintain a high fluid intake and a neutral or alkaline urinary pH, especially if initial uric acid concentrations are high and the patient is symptomatic.

Reduction of the urate concentrations in body fluids by allopurinol permits mobilisation and dissolution of urate deposits anywhere in the body, the commonest sites being those in the skin, bones, joints and kidney interstitial tissue. Therapeutic effects therefore include: the resolution of skin tophi and the healing of urate sinuses; eventual reduction in the frequency of attacks of acute gouty arthritis,

improvement in joint mobility; reduction of the urate load to be excreted via the kidney; prevention and treatment of acute uric acid nephropathy; and, in the long-term, reduced risk of renal impairment by urate/uric acid and prevention and dissolution of uric acid renal stones.

Onset and duration of action

Serum urate concentrations usually begin to decline slowly within 48 to 72 hours reaching a plateau after 1 to 3 weeks of therapy. However, in patients with tophaceous gout or those who are undersecretors of uric acid, a decline in serum urate levels may be delayed for the first few months.

Pharmacokinetics

Absorption

Allopurinol is active when given orally and is rapidly absorbed from the upper gastrointestinal tract. Studies have detected allopurinol in the blood 30 to 60 minutes after dosing. Estimates of bioavailability vary from 67% to 90%. Peak plasma levels of allopurinol generally occur approximately 1.5 hours after oral administration, but fall rapidly and are barely detectable after six hours. Peak plasma levels of oxypurinol generally occur three to five hours after oral administration of allopurinol and are much more sustained.

Distribution

The apparent volume of distribution of allopurinol is approximately 1.6 litres/kg which suggests relatively extensive uptake by tissues. Allopurinol is uniformly distributed in total tissue water with the exclusion of the brain, where concentrations of the drugs are approximately 50% of those of other tissues. Within muscles, small amounts of allopurinol and oxypurinol crystals have been found. Allopurinol is negligibly bound by plasma proteins and therefore variations in protein binding are not thought to significantly alter clearance. Allopurinol and oxypurinol are present in breast milk.

Biotransformation

Allopurinol is rapidly converted in the body to the pharmacologically active principal metabolite oxypurinol and other metabolites including allopurinol riboside and oxypurinol-7-ribose. Peak plasma levels generally occur at 1.5 hours and 4.5 hours for allopurinol and oxypurinol respectively. Oxypurinol is also an inhibitor of xanthine oxidase.

Elimination

Elimination of allopurinol is mainly by metabolic conversion to oxypurinol by xanthine oxidase and aldehyde oxidase, with less than 10% of the unchanged medicine and 70% as oxypurinol excreted in the urine. Approximately 20% of the ingested allopurinol is excreted unchanged in the faeces.

Because of its rapid oxidation to oxypurinol and a renal clearance rate approximately that of glomerular filtration rate, allopurinol has a plasma half-life of about one to two hours. Little allopurinol is found in the urine six hours after administration. Oxypurinol, however, has a longer plasma half-life (approximately 15.0 hours) and therefore effective inhibition of xanthine oxidase is maintained over a 24 hour period with a single daily dose of allopurinol. Patients with normal renal function will gradually accumulate oxypurinol until a steady-state plasma oxypurinol concentration is reached. Such patients, taking 300 mg of allopurinol per day will generally have plasma oxypurinol concentrations of 5 to 10 mg/l. Whereas allopurinol is cleared essentially by glomerular filtration, oxypurinol is reabsorbed in the kidney tubules in a manner similar to the reabsorption of uric acid.

The renal clearance of hypoxanthine and xanthine is at least ten times greater than that of uric acid. The increased xanthine and hypoxanthine in the urine have not been accompanied by problems of nephrolithiasis.

Special patient considerations

Patients with renal impairment:

Allopurinol and oxypurinol clearance is greatly reduced in patients with poor renal function resulting in higher plasma levels in chronic therapy. Patients presenting renal impairment, where creatinine clearance values were between 10 and 20 ml/min, showed plasma oxypurinol concentrations of

approximately 30 mg/l after prolonged treatment with 300 mg allopurinol per day. This is approximately the concentration which would be achieved by doses of 600 mg/day in those with normal renal function. A reduction in the dose is therefore required in patients with renal impairment.

Elderly patients:

Pharmacokinetics in elderly are not likely to be altered other than due to deterioration in renal function.

Indications

Allopurinol is mainly used in the management of primary gout or secondary hyperuricaemia associated with chronic gout. It is not, however, used to treat an acute attack of gout as it has no analgesic, anti-inflammatory or uricosuric activity and may prolong the attack. If changing therapy from a uricosuric agent alone, the dose should be reduced gradually while allopurinol is introduced. In severe cases of chronic gout, allopurinol can be used together with a uricosuric agent unless the latter is contra-indicated.

Uric acid nephropathy.

Recurrent uric acid stone formation.

Certain enzyme disorders or blood disorders which lead to overproduction of urate (e.g. Lesch-Nyhan syndrome; haemolytic anaemia).

Hyperuricaemia associated with malignancy and cytotoxic therapy which result in a high cell turnover rate.

The prevention and treatment of calcium oxalate/phosphate renal stones in the presence of high uric acid levels of the blood and/or urine.

Dosage and administration

Allopurinol Sandoz may be taken once daily after a meal. It is normally well tolerated, especially after food. Should the total daily dose exceed 300 mg and/or gastrointestinal intolerance be manifested, a divided doses regimen may be appropriate. The dosage should be adjusted by monitoring serum urate concentrations and urinary urate/uric acid levels at appropriate intervals.

Adults

The average daily dose is 2 to 10 mg/kg body weight, or 100 to 200 mg for mild conditions, 300 to 600 mg for moderately severe conditions and 700 to 900 mg for severe conditions.

Initiating therapy

Allopurinol may increase the frequency of acute attacks during the first few months of therapy; it is therefore recommended that low doses be given initially and slowly increased, and that anti-inflammatory agents or colchicine should be given concomitantly during this period as prophylactic cover. In patients with good renal function, doses of 100 mg should be given and increased by 50 mg to 100 mg at weekly intervals until serum urate levels of 0.6 mg per ml are achieved.

Hyperuricaemia of malignancy or cancer therapy

Therapy should be initiated 2 to 3 days prior to cytotoxic therapy after which maintenance doses are given according to response. Adequate hydration is essential throughout.

Children

The average daily dose is 10 to 20 mg/kg body weight up to a maximum of 400 mg daily. Use in children is rarely indicated, except in malignant conditions and certain enzyme disorders.

Use in the elderly

The lowest dose, which produces satisfactory urate reduction, should be used. Special attention to dosage is necessary if there is overt renal dysfunction.

Use in renal dysfunction

The excretion of allopurinol and its metabolites is prolonged so dosage reductions are recommended. Doses of 100 to 200 mg daily should be used if creatinine clearance is between 10 to 20 ml/min. and not more than 100 mg per day should be used if clearance is less. These doses may be halved or reduced even further when initiating therapy and then slowly increased depending on response.

Contraindications

Known hypersensitivity to allopurinol, its metabolites, or to any of the inactive ingredients listed in [Further information](#).

Allopurinol should not be given concomitantly with iron salts to patients with idiopathic haemochromatosis, nor should it be given to the immediate relatives of such patients.

Warnings and precautions

Warnings

Allopurinol must be withdrawn immediately and permanently at the first signs of intolerance especially when a skin rash or other allergic response occurs. In some instances a skin rash may be followed by more severe hypersensitivity reactions such as exfoliative, urticarial, and purpuric lesions as well as Stevens-Johnson syndrome (erythema multiforme exudativum), and/or generalised vasculitis, irreversible hepatotoxicity, and on rare occasions death.

Precautions

Mild asymptomatic hyperuricaemia per se is generally not considered an indication for allopurinol treatment. Fluid and dietary modification with management of the underlying cause may correct the condition. In general, allopurinol should only be considered if serum urate concentrations exceed 0.8 to 0.9 mg/ml with an aim of reducing levels to 0.6 mg/ml.

Allopurinol treatment should not be started until an acute attack of gout has completely subsided, as further attacks may be precipitated. In the early stages of treatment with allopurinol, as with other uricosuric agents, an acute attack of gouty arthritis may be precipitated. Therefore it is advisable to give prophylaxis with a suitable anti-inflammatory agent or colchicine for at least one month. The literature should be consulted for details of appropriate dosage and precautions and warnings.

If acute attacks develop in patients receiving allopurinol, treatment should continue at the same dosage while the acute attack is treated with a suitable anti-inflammatory agent.

In conditions where the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) the concentration of xanthine in urine could approach saturation leading to stone formation in the urinary tract. This risk may be minimised by adequate fluid intake to achieve optimal urine dilution.

Adequate therapy with allopurinol will lead to dissolution of large uric acid renal pelvic stones, with the remote possibility of impaction in the ureter.

The occurrence of hypersensitivity reactions to allopurinol may be increased in patients with decreased renal function receiving thiazides and allopurinol concurrently. For this reason, in this clinical setting, such combinations should be administered with caution and patients should be observed closely.

Bone marrow depression has been reported in patients receiving allopurinol, most of whom received concomitant medicines with the potential for causing this effect. This has occurred as early as six weeks to as long as six years after the initiation of therapy of allopurinol. Rarely a patient may develop varying degrees of bone marrow depression, affecting one or more cell lines, while receiving allopurinol alone.

Allopurinol's primary action in treating gout is to inhibit the enzyme, xanthine oxidase. Xanthine oxidase may be involved in the reduction and clearance of hepatically stored iron. Some rodent studies have found increased iron storage in animals treated with allopurinol, while others have not. A study in 28 healthy volunteers found no change in hepatic iron storage with allopurinol treatment. There are no human studies which have investigated the safety of administering allopurinol to patients with haemochromatosis. Administration of allopurinol to patients with abnormal iron storage, including haemochromatosis, should be undertaken with caution.

Dosage reduction should be considered for patients with hepatic or renal impairment.

Some patients with pre-existing renal disease or poor urate clearance have shown a rise in serum urea during administration of allopurinol. Although the mechanism responsible for this has not been established, patients with impaired renal function should be carefully observed during the early stages of allopurinol administration and dosage decreased or the medicine withdrawn if increased abnormalities in renal function appear and persist. Patients under treatment for hypertension or cardiac insufficiency, for example with diuretics or ACE inhibitors, may have some concomitant impairment of renal function and allopurinol should be used with care in this group.

Renal failure in association with administration of allopurinol has been observed among patients with hyperuricaemia secondary to neoplastic diseases. Concurrent conditions such as multiple myeloma and congestive myocardial disease were present among those patients whose renal dysfunction increased after allopurinol was begun. Renal failure is also frequently associated with gouty nephropathy and rarely with hypersensitivity reactions associated with allopurinol. Albuminuria has been observed among patients who developed clinical gout following chronic glomerulonephritis and chronic pyelonephritis.

A few cases of reversible clinical hepatotoxicity have been noted in patients taking allopurinol, and in some patients asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed. If anorexia, weight loss or pruritus develop in patients on allopurinol, evaluation of liver function should be part of their diagnostic workup. In patients with pre-existing liver disease, periodic liver function tests are recommended during the early stages of therapy.

Pregnancy and lactation

Use in pregnancy

Assigned Category B2 by the Australian Drug Evaluation Committee. This category includes medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.

There is inadequate evidence of safety of allopurinol in human pregnancy, although it has been in wide use for many years without apparent ill consequence. Use in pregnancy only when there is no safer alternative and when the disease itself carries risk for the mother or unborn child.

Use in lactation

Reports indicate that all allopurinol and oxypurinol are excreted in human breast milk. Concentrations of 1.4 mg/litre allopurinol and 53.7 mg/litre oxypurinol have been demonstrated in breast milk from a woman taking allopurinol 300 mg/day. However, there are no data concerning the effects of allopurinol or its metabolites on the breast-fed infant. Allopurinol should be used with caution during breast feeding as there is a theoretical risk to the infant of allergic sensitisation.

Effects on ability to drive and use machines

This medicine is likely to produce minor or moderate adverse effects. Since adverse effects such as somnolence, vertigo and ataxia have been reported in patients receiving allopurinol, patients should exercise caution before driving, using machinery or participating in dangerous activities where alertness is mandatory until they are reasonably certain that allopurinol does not adversely affect performance.

Other

Preclinical safety data

Mutagenicity

Evidence from biochemical and other cytological investigations strongly suggests that allopurinol has no deleterious effects on DNA at any stage of the cell cycle and is not mutagenic. Cytogenetic studies show that allopurinol does not induce chromosome aberrations in human blood cells *in vitro* at concentrations up to 100 mcg/ml and *in vivo* at doses up to 60 mg/day for a mean period of 40 months. Allopurinol does not produce nitroso compounds *in vitro* or affect lymphocyte transformation *in vitro*.

Carcinogenicity

No evidence of carcinogenicity has been found in mice and rats treated with allopurinol for up to two years.

Teratogenicity

One study of mice receiving intraperitoneal doses of 50 or 100 mg/kg on days 10 and 13 of gestation resulted in foetal abnormalities, however in a similar study in rats at 120 mg/kg on day 12 of gestation no abnormalities were observed. Extensive studies of high oral doses of allopurinol of up to 100 mg/kg/day in mice, up to 200 mg/kg/day in rats and up to 150 mg/kg/day in rabbits during days 8 to 16 of the gestation produced no teratogenic effects. An *in vitro* study using foetal mouse salivary glands in culture to detect embryotoxicity indicated that allopurinol would not be expected to cause embryotoxicity without also causing maternal toxicity.

Adverse effects

Adverse effects in association with allopurinol are rare in the overall treated population and are mostly of a minor nature. The incidence is higher in the presence of renal and/or hepatic disorders.

Adverse effects are usually reversed by the reduction of dosage or complete withdrawal of allopurinol. Taking allopurinol after meals may minimise gastrointestinal disturbances. Where allergic reactions occur, allopurinol should be withdrawn immediately.

Skin reactions

These are the most common reactions and may occur at any time during treatment. They may be pruritic, maculopapular, sometimes scaly, sometimes purpuric and rarely exfoliative. Severe skin reactions resembling Stevens-Johnson and/or Lyell syndrome associated with exfoliation and toxic epidermal necrolysis occur rarely. Skin reactions may be delayed and rarely have been followed by severe hypersensitivity reactions which may be fatal. For this reason, allopurinol should be withdrawn immediately should such reactions occur. After recovery from mild reactions, allopurinol may, if desired, be reintroduced at a small doses (e.g. 50 mg/day) and gradually increased. If the rash recurs, allopurinol should be permanently withdrawn.

Generalised hypersensitivity

Hypersensitivity reactions characterised by pruritus, fever, chills, lymphadenopathy, arthralgia, leucopenia or leucocytosis and/or eosinophilia, have occurred occasionally. Associated vasculitis and tissue response may be manifested in various ways including hepatitis, interstitial nephritis and, very rarely, epilepsy. If such reactions do occur, it may be at any time during treatment. In all cases, allopurinol should be withdrawn immediately and permanently.

Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions. When generalised hypersensitivity reactions have occurred, concomitant thiazide diuretic treatment, a renal and/or hepatic disorder has usually been present particularly when the outcome has been fatal.

Angioimmunoblastic lymphadenopathy

Angioimmunoblastic lymphadenopathy has been described rarely following biopsy of a generalised lymphadenopathy. It appears to be reversible on withdrawal of allopurinol.

Hepatic function

Rare reports of hepatic dysfunction ranging from asymptomatic rises in liver function tests to hepatitis including hepatic necrosis and granulomatous hepatitis, without overt evidence of more generalised hypersensitivity, have been described. Granulomatous hepatitis appears to be reversible on withdrawal of allopurinol.

Gastrointestinal

In early clinical studies, nausea and vomiting were reported. Diarrhoea, abdominal pain, gastritis and dyspepsia have also been reported. Further reports suggest that these reactions are not a significant problem and can be avoided by taking allopurinol after meals. Recurrent haematemesis has been reported as an extremely rare event, as has steatorrhoea.

Haematological

Bone marrow depression has been reported in patients during allopurinol therapy. However most patients were also receiving other medicines with myelosuppressive potential concomitantly. There have been occasional reports of transient reduction in the numbers of circulating formed elements of the blood, usually in association with impaired renal and/or hepatic function. Adverse effects such as leukocytosis, leukopenia, eosinophilia, thrombocytopenia, granulocytopenia, agranulocytosis and aplastic anaemia, have occurred very rarely. The clinical significance has yet to be demonstrated.

Miscellaneous

The following complaints have been reported occasionally: fever, general malaise, asthenia, headache, vertigo, ataxia, somnolence, coma, depression, paralysis, paraesthesia, neuropathy, peripheral neuritis, drowsiness, confusion, visual disorder, cataract, macular changes, taste perversion, stomatitis, changed bowel habit, infertility, impotence, diabetes mellitus, hyperlipidaemia, furunculosis, alopecia, discoloured hair, angina, hypertension, bradycardia, oedema, uraemia, haematuria, angioedema, gynaecomastia.

There have been incidences of xanthine stone deposition and of impaction of partly dissolved renal uric acid stones in the ureter. Adequate hydration is important especially in patients with significant hyperuricaemia and tophaceous deposits. Alkalinisation of the urine will further reduce crystalluria.

On initiating therapy, patients may experience an increase in acute gouty attacks (refer to [Dosage and Administration](#)).

Interactions

6-mercaptopurine and azathioprine

Azathioprine is metabolised to 6-mercaptopurine which is inactivated by the action of xanthine oxidase. When 6-mercaptopurine or azathioprine is given concurrently with allopurinol, only one-quarter of the usual dose of 6-mercaptopurine or azathioprine should be given because inhibition of xanthine oxidase will prolong their activity.

Ampicillin and amoxicillin

An increase in the frequency of skin rash has been reported among patients receiving ampicillin or amoxicillin concurrently with allopurinol compared to patients who are not receiving both medicines. The cause of the reported association has not been established. However, it is recommended that for patients receiving allopurinol an alternative to ampicillin or amoxicillin is used where available.

Angiotensin Converting Enzyme inhibitors:

Isolated reports indicate that concurrent administration of captopril and allopurinol may predispose to hypersensitivity reactions e.g. Stevens-Johnson syndrome. Patients on the combination should be monitored and if a reaction occurs, use of the medicines discontinued.

Chlorpropamide

If allopurinol is given concomitantly with chlorpropamide when renal function is poor, there may be an increased risk of prolonged hypoglycaemic activity because allopurinol and chlorpropamide may compete for excretion in the renal tubule.

Coumarin anticoagulants

There is no evidence that interaction between allopurinol and the coumarins seen under experimental conditions has any clinical significance. However, all patients receiving anticoagulants must be carefully monitored.

Cyclophosphamide, doxorubicin, bleomycin, procarbazine, mechlorethamine

Enhanced bone marrow suppression by cyclophosphamide and other cytotoxic agents has been reported among patients with neoplastic disease (other than leukaemia), in the presence of allopurinol. However, in a well controlled study of patients treated with cyclophosphamide, doxorubicin, bleomycin, procarbazine and/or mechlorethamine (mustine hydrochloride) allopurinol did not appear to increase the toxic reaction of these cytotoxic agents.

Cyclosporin

Reports suggest that the plasma concentration of cyclosporin may be increased during concomitant treatment with allopurinol. The possibility of enhanced cyclosporin toxicity should be considered if the drugs are co-administered.

Diuretics

Thiazide diuretics may increase the risk of serious allopurinol toxicity, including hypersensitivity reactions and the combination should be monitored, especially if renal function is compromised.

Phenytoin

Allopurinol may inhibit hepatic oxidation of phenytoin but the clinical significance has not been demonstrated.

Salicylates and uricosuric agents

Oxypurinol, the major metabolite of allopurinol and itself therapeutically active, is excreted by the kidney in a similar way to urate. Hence drugs with uricosuric activity such as probenecid or large doses of salicylate may accelerate the excretion of oxypurinol. This may decrease the therapeutic activity of allopurinol, but the significance needs to be assessed in each case.

Theophylline

Experimental studies of the effect of allopurinol on theophylline metabolism have produced contradictory findings. Inhibition of theophylline metabolism has been reported in normal subjects given relatively high doses of allopurinol (300 mg twice daily) under experimental conditions. The mechanism of the interaction may be explained by xanthine oxidase being involved in the biotransformation of theophylline in humans. To avoid toxicity, theophylline levels should be monitored in patients starting or increasing allopurinol therapy.

Vidarabine (adenine arabinoside)

Evidence suggests that the plasma half-life of vidarabine is increased in the presence of allopurinol. When the two medicines are used concomitantly, extra vigilance is necessary to recognise enhanced toxic effects.

Overdosage

Signs and symptoms

Ingestion of up to 22.5 g allopurinol without adverse effect has been reported. Nausea, vomiting, diarrhoea and dizziness have been reported in a patient who ingested 20 g allopurinol. Recovery followed general supportive measures. Massive absorption of allopurinol may lead to considerable inhibition of xanthine oxidase activity, which should have no untoward effects unless 6-mercaptopurine and/or azathioprine is being taken concomitantly.

Management

The patient should be monitored and receive normal supportive measures. Adequate hydration to maintain optimum diuresis facilitates excretion of allopurinol and its metabolites. Haemodialysis may be used if necessary.

Pharmaceutical precautions

Instructions for use/handling

Nil.

Incompatibilities

None known.

Special precautions for storage

Store at or below 25°C.

Medicine classification

Prescription Medicine.

Package quantities

Allopurinol Sandoz 100 mg - Bottles of 200 and 250 tablets.
Allopurinol Sandoz 300 mg - Bottles of 30 and 60 tablets.

Further information

Instructions to patients

Wherever possible a high fluid intake sufficient to yield a daily urinary output of 2 litres and the maintenance of a neutral or alkaline urine are desirable in hyperuricaemic patients whether or not they are on allopurinol therapy. Allopurinol is better tolerated if taken after meals. Due to the occasional occurrence of drowsiness, patients should be alerted to the need for due precautions when engaging in activities where alertness is mandatory.

List of excipients

Microcrystalline cellulose, cellulose, povidone, crospovidone, macrogol 4000, talc, magnesium stearate.

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Date of preparation

01 February 2011