CIPLORIC Tablets (Allopurinol)

Composition

CIPLORIC 100 Tablets

Each tablet contains:

Allopurinol…100 mg

CIPLORIC 300 Tablets

Each tablet contains:

Allopurinol…300 mg

Dosage Form

Tablet for oral use

Pharmacology

Pharmacodynamics

Allopurinol is a structural analogue of the naturalpurine base, hypoxanthine. Allopurinol and its main metabolite, oxypurinol, lower the level of uric acid in plasma and urine by inhibition of xanthine oxidase, the enzyme catalysing the oxidation of hypoxanthine to xanthine and xanthine to uric acid. In addition to the inhibition of purine catabolism in some but not all hyperuricaemic patients, de novo purine biosynthesis is depressed via feedback inhibition of hypoxanthine-guanine phosphoribosyl transferase. Other metabolites of allopurinol include allopurinol-riboside and oxypurinol-7 riboside. Allopurinol reduces both the serum and urinary uric acid levels by inhibiting the formation of uric acid.

Pharmacokinetics

Absorption

Allopurinol is active when given orally and is rapidly absorbed from the upper gastrointestinal tract. Studies have detected allopurinol in the blood30–60 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 of allopurinol, but fall rapidly and are barely detectable after 6 hours. Peak levels of oxypurinol generally occur 3–5 hours after oral administration of allopurinol and are much more sustained.

Distribution

Allopurinol is negligibly bound by plasma proteins and, therefore, variations in protein binding are

not thought to significantly alter clearance. The apparent volume of distribution of allopurinol is approximately 1.6 litre/kg, which suggests relatively extensive uptake by tissues. Tissue concentrations of allopurinol have not been reported in humans, but it is likely that allopurinol and oxypurinol will be present in the highest concentrations in the liver and intestinal mucosa where xanthine oxidase activity is high.

Metabolism

Oxypurinol is a less potent inhibitor of xanthine oxidase than allopurinol, but the plasma half-life of oxypurinol is far more prolonged. Estimates range from 13 to 30 hours in humans. 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 5-10 mg/litre.

Excretion

Approximately 20% of the ingested allopurinol is excreted in the faeces. Elimination of allopurinol is mainly by metabolic conversion to oxypurinol by xanthine oxidase and aldehyde oxidase, with less than 10% of the unchanged drug excreted in the urine. Allopurinol has a plasma half-life of about 1–2 hours.

Oxypurinol is eliminated unchanged in the urine, but has a long elimination half-life because it undergoes tubular reabsorption. Reported values for the elimination half-life range from 13.6 hours to 29 hours. The large discrepancies in these values may be accounted for by variations in study design and/or creatinine clearance in the patients.

Renal Impairment

Allopurinol and oxipurinol clearance is greatly reduced in patients with poor renal function resulting in higher plasma levels in chronic therapy. Patients with renal impairment, where creatinine clearance values were between 10 and 20ml/min, showed plasma oxipurinol concentrations of approximately 30mg/litre 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 of allopurinol is, therefore, required in patients with renal impairment.

Indications

- Management of patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy).
- Management of patients with leukaemia, lymphoma and malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels. Treatment with allopurinol should be discontinued when the potential for overproduction of uric acid is no longer present.
- Management of patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients. Therapy in such patients should be carefully assessed initially and reassessed periodically to determine in each case that treatment is beneficial and that the benefits outweigh the risks.

Dosage and Administration

Adults

Allopurinol should be introduced at a low dosage, e.g. 100mg/day, to reduce the risk of adverse reactions and increased only if the serum urate response is unsatisfactory. Extra caution should be exercised if renal function is poor. The following dosage schedules are suggested:

- 100–200 mg daily in mild conditions
- 300–600 mg daily in moderately severe conditions
- 700–900 mg daily in severe conditions

If dosage on a mg/kg bodyweight basis is required, 2–10 mg/kg body weight/day should be used.

Paediatric

In children aged below 15 years**,** 10–20 mg/kg bodyweight/day up to a maximum of 400 mg daily. Use in children is rarely indicated, except in malignant conditions (especially leukaemia) and certain enzyme disorders such as Lesch-Nyhan syndrome.

Geriatric

In the absence of specific data, the lowest dosage that produces satisfactory urate reduction should be used. Particular attention should be paid to advice on dosage in renal impairment patients.

Treatment of High Urate Turnover Conditions, e.g. Neoplasia, Lesch-Nyhan Syndrome

It is advisable to correct existing hyperuricaemia and/or hyperuricosuria with allopurinol before starting cytotoxic therapy. It is important to ensure adequate hydration to maintain optimum diuresis and to attempt alkalinization of urine to increase solubility of urinary urate/uric acid. Dosage of allopurinol should be at the lower end of the recommended dosage schedule.

If urate nephropathy or other pathology has compromised renal function, the advice given under Renal Impairment should be followed.

These steps may reduce the risk of xanthine and/or oxipurinol deposition complicating the clinical situation.

Monitoring Advice

The dosage should be adjusted by monitoring serum urate concentrations and urinary urate/uric acid levels at appropriate intervals.

Instructions for Use

Allopurinol may be taken orally once a day after a meal. It is well tolerated, especially after food. Should the daily dosage exceed 300 mg and gastrointestinal intolerance be manifested, a divided doses regimen may be appropriate.

Contraindications

Allopurinol should not be administered to individuals known to be hypersensitive to allopurinol or to any of the components of the formulation.

Warnings and Precautions

General

An increase in acute attacks of gout has been reported during the early stages of administration of allopurinol, even when normal or subnormal serum uric acid levels have been attained. Accordingly, maintenance doses of colchicine generally should be given prophylactically when allopurinol is begun. In addition, it is recommended that the patient start with a low dose of allopurinol (100 mg daily) and increase at weekly intervals by 100 mg until a serum uric acid level of 6 mg/dL or less is attained but without exceeding the maximum recommended dose (800 mg per day). The use of colchicine or anti-inflammatory agents may be required to suppress gouty attacks in some cases. The attacks usually become shorter and less severe after several months of therapy. The mobilization of urates from tissue deposits which cause fluctuations in the serum uric acid levels may be a possible explanation for these episodes. Even with adequate therapy with allopurinol, it may require several months to deplete the uric acid pool sufficiently to achieve control of the acute attacks.

A fluid intake sufficient to yield a daily urinary output of at least 2 litres and the maintenance of a neutral or, preferably, slightlyalkaline urine are desirable to (1) avoid the theoretical possibility of formation of xanthine calculi under the influence of therapy with allopurinol tablets and (2) help prevent renal precipitation of urates in patients receiving concomitant uricosuric agents.

Some patients with pre-existing renal disease or poor urate clearance have shown a rise in BUN during administration of allopurinol tablets. Although the mechanism responsible for this has not been established, patients with impaired renal function should be carefully observed during the early stages of administration of allopurinol tablets and the dosage decreased or the drug withdrawn if increased abnormalities in renal function appear and persist.

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.

Patients with decreased renal function require lower doses of allopurinol than those with normal renal function. Lower than recommended doses should be used to initiate therapy in any patients with decreased renal function and they should be observed closely during the early stages of administration of allopurinol. In patients with severely impaired renal function or decreased urate clearance, the half-life of oxipurinol in the plasma is greatly prolonged. Therefore, a dose of 100 mg per day or 300 mg twice a week, or perhaps less, may be sufficient to maintain adequate xanthine oxidase inhibition to reduce serum urate levels.

Bone marrow depression has been reported in patients receiving allopurinol, most of whom received concomitant drugs with the potential for causing this reaction. This has occurred as early as 6 weeks to as long as 6 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.

Hypersensitivity Syndrome, SJS and TEN

Allopurinol hypersensitivity reactions can manifest in many different ways, including maculopapular exanthema, hypersensitivity syndrome (also known as DRESS) and Stevens-Johnson syndrome/toxic epidermal necrolysis [SJS/TEN]). These reactions are clinical diagnoses, and their clinical presentations remain the basis for decision making. If such reactions occur at any time during treatment, allopurinol should be withdrawn immediately. Re-challenge should not be undertaken in patients with hypersensitivity syndrome and SJS/TEN. Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions.

Chronic Renal Impairment

Patients with chronic renal impairment may be at increased risk of developing hypersensitivity reactions, including SJS/TEN associated with allopurinol. Extra vigilance for the signs of hypersensitivity syndrome or SJS/TEN is required and the patient should be informed of the need to stop treatment immediately and permanently at the first appearance of symptoms.

HLA-B*5801 Allele

The HLA-B*5801 allele has been shown to be associated with the risk of developing allopurinol-related hypersensitivity syndrome and SJS/TEN. The frequency of the HLA-B*5801 allele varies widely between ethnic populations: up to 20% in the Han Chinese population, about 12% in the Korean population, and 1–2% in individuals of Japanese or European origin. The use of genotyping as a screening tool to make decisions about treatment with allopurinol has not been established. If the patient is a known carrier of HLA-B*5801, the use of allopurinol may be considered if the benefits are thought to exceed risks. Extra vigilance for signs of hypersensitivity syndrome or SJS/TEN is required and the patient should be informed of the need to stop treatment immediately at the first appearance of symptoms.

Reduced doses should be used in patients with hepatic or renal impairment. Patients under treatment for hypertension or cardiac insufficiency, e.g. with diuretics or ACE inhibitors, may have some concomitant impairment of renal function and allopurinol should be used with care in this group.

Acute Gouty Attacks

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 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 1month. 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.

Asymptomatic hyperuricaemia per se is generally not considered an indication for use of allopurinol. Fluid and dietary modification with management of the underlying cause may correct the condition.

Xanthine Deposition

In conditions where the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome), the absolute concentration of xanthine in urine could, in rare

cases, rise sufficiently to allow deposition in the urinary tract. This risk may be minimized by adequate hydration to achieve optimal urine dilution.

Impaction of Uric Acid Renal Stones

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

Laboratory Tests

The correct dosage and schedule for maintaining the serum uric acid within the normal range is best determined by using the serum uric acid as an index.

In patients with pre-existing liver disease, periodic liver function tests are recommended during the early stages of therapy.

Allopurinol and its primary active metabolite, oxipurinol, are eliminated by the kidneys; therefore, changes in renal function have a profound effect on dosage. In patients with decreased renal function or who have concurrent illnesses which can affect renal function such as hypertension and diabetes mellitus, periodic laboratory parameters of renal function, particularly BUN and serum creatinine or creatinine clearance, should be performed and the patient's dosage of allopurinol reassessed.

The prothrombin time should be reassessed periodically in the patients receiving dicumarol who are given allopurinol.

Drug Interactions

6-Mercaptopurine and Azathioprine

Azathioprine is metabolized to 6-mercaptopurine, which is inactivated by the action ofxanthine 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.

Vidarabine(Adenine Arabinoside)

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

Salicylates and Uricosuric Agents

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

Chlorpropamide

If allopurinolis 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 have been rare reports of increased effect of warfarin and other coumarin anticoagulants when co-administered with allopurinol; therefore, all patients receiving anticoagulants must be carefully monitored.

Phenytoin

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

Theophylline

Inhibition of the metabolism of the ophylline has been reported. The mechanism of the interaction may be explained by xanthine oxidase being involved in the biotransformation of theophylline in humans. Theophylline levels should be monitored in patients starting or increasing allopurinol therapy.

Ampicillin/Amoxicillin

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

Cyclophosphamide, Doxorubicin, Bleomycin, Procarbazine, Mechloroethamine

Enhanced bone marrow suppression bycyclophosphamide 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 mechloroethamine (chlormethine hydrochloride), allopurinol did not appear to increase the toxic reaction of these cytotoxic agents.

Ciclosporin

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

Didanosine

In healthy volunteers and HIV patients receiving didanosine, plasma didanosine C_{max} and AUC values were approximately doubled with concomitant allopurinol treatment (300 mg daily) without affecting terminal half life. Co-administration of these two drugs is generally not recommended. If concomitant use is unavoidable, a dose reduction of didanosine may be required, and patients should be closely monitored.

Dicumarol

It has been reported that allopurinol prolongs the half-life of the anticoagulant, dicumarol. The

clinical basis of this drug interaction has not been established but should be noted when allopurinol is given to patients already on dicumarol therapy.

Thiazide

The reports that the concomitant use of allopurinol tablets and thiazide diuretics may contribute to the enhancement of allopurinoltoxicity in some patients have been reviewed in an attempt to establish a cause-and-effect relationship and a mechanism of causation. Review of these case reports indicates that the patients were mainly receiving thiazide diuretics for hypertension and that tests to rule out decreased renal function secondary to hypertensive nephropathy were not often performed. In those patients in whom renal impairment was documented, however, the recommendation to lower the dose of allopurinol tablets was not followed. Although a causal mechanism and a cause-and-effect relationship have not been established, current evidence suggests that renal function should be monitored in patients on thiazide diuretics and allopurinol tablets even in the absence of renal failure, and dosage levels should be even more conservatively adjusted in those patients on such combined therapy if diminished renal function is detected.

Tolbutaminde

Tolbutamide's conversion to inactive metabolites has been shown to be catalysed by xanthine oxidase from rat liver. The clinical significance, if any, of these observations is unknown.

Renal Impairment

Since allopurinol and its metabolites are excreted by the kidneys, impaired renal function may lead to retention of the drug and/or its metabolites, with consequent prolongation of plasma half-lives. In severe renal insufficiency, it may be advisable to use less than 100 mg per day or to use single doses of 100mg at longer intervals than a day. If facilities are available to monitor plasma oxipurinol concentrations, the dose should be adjusted to maintain plasmaoxipurinol levels below 100 micromol/litre (15.2 mg/litre). Allopurinol and its metabolites are removed by renal dialysis. If dialysis is required two to three times a week, consideration should be given to an alternative dosage schedule of 300–400 mg allopurinol immediately after each dialysis with none in the interim.

Hepatic Impairment

Reduced doses should be used in patients with hepatic impairment. Periodic liver function tests are recommended during the early stages of therapy.

Pregnancy

Pregnancy Category C

There is inadequate evidence of safety of allopurinolin 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.

Lactation

Reports indicate that allopurinol and oxipurinol are excreted in human breast milk. Concentrations of 1.4mg/litre allopurinoland 53.7 mg/litre oxipurinol have been demonstrated in breast milk from women taking allopurinol300 mg/day. However, there are no data concerning the effects of allopurinol or its metabolites on the breastfed baby.

Paediatric Use

Allopurinol is rarely indicated for use in children with the exception of those with hyperuricaemia secondary to malignancy or to certain rare inborn errors of purine metabolism.

Geriatric Use

In the absence of specific data, the lowest dosage that produces satisfactory urate reduction should be used. Particular attention should be paid to advice on dosage in renal impairment patients**.**

Ability to Drive and Use Machines

Since adverse reactions 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 until they are reasonably certain that allopurinol does not adversely affect performance.

Undesirable Effects

For this product, there is no modern clinical documentation that can be used as support for determining the frequency of undesirable effects. Undesirable effects may vary in their incidence depending on the dose received and also when given in combination with other therapeutic agents.

The frequency categories assigned to the adverse drug reactions below are estimates; for most reactions, suitable data for calculating incidence are not available. Adverse drug reactions identified through postmarketing surveillance were considered to be rare or very rare. The following convention has been used for the classification of frequency:

- Very common:≥1/10 (≥10%)
- Common:≥1/100 and <1/10 (≥1% and <10%)
- Uncommon:≥1/1,000 and <1/100 (≥0.1% and <1%)
- Rare:≥1/10,000 and <1/1,000 (≥0.01% and <0.1%)
- Very rare:<1/10,000 (<0.01%)

Adverse reactions in association with allopurinolare rare in the overall treated population and mostly of a minor nature. The incidence is higher in the presence of renal and/or hepatic disorder.

Infections and Infestations

Very rare: furunculosis

Musculoskeletal

Uncommon: myopathy, arthralgia

Rare: myalgia

Blood and Lymphatic System Disorders

Uncommon: ecchymosis, leucopenia

Very rare: agranulocytosis, aplastic anaemia, thrombocytopenia

Very rare reports have been received of thrombocytopenia, agranulocytosis and aplastic anaemia, particularly in individuals with impaired renal and/or hepatic function, reinforcing the need for particular care in this group of patients.

Immune System Disorders

Uncommon: hypersensitivity reactions, leucocytosis

Rare: aplastic anaemia, eosinophilic fibrohistiocytic lesion of bone marrow, pancytopenia, prothrombin decrease, anaemia, haemolytic anaemia, reticulocytosis, lymphocytosis

Very rare: angioimmunoblastic lymphadenopathy

Serious hypersensitivity reactions, including skin reactions associated with exfoliation, fever, lymphadenopathy, arthralgia and/or eosinophilia (including SJS/TEN), occur rarely. Associated vasculitis and tissue response may be manifested in various ways, including hepatitis, renal impairment and, very rarely, seizures. Very rarely, acute anaphylactic shock has been reported. If such reactions do occur, they may happen at any time during the treatment, and allopurinol should be withdrawn immediately and permanently.

A delayed multi-organ hypersensitivity disorder (known as hypersensitivity syndrome or DRESS) with fever, rashes, vasculitis, lymphadenopathy, pseudo-lymphoma, arthralgia, leucopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts) occurring in various combinations. Other organs may also be affected (e.g. liver, lungs, kidneys, pancreas, myocardium, and colon). If such reactions do occur, they may happen at any time during the treatment, and allopurinol should be withdrawn immediately and permanently.

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

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

Metabolism and Nutrition Disorders

Common: acute gout attacks

Very rare: diabetes mellitus, hyperlipidaemia, hypercalcaemia

Psychiatric Disorders

Very rare: depression

Nervous System Disorders

Uncommon: neuritis, peripheral neuropathy

Rare: optic neuritis, confusion, dizziness, foot drop, decrease in libido, amnesia, tinnitus, insomnia

Very rare: coma, paralysis, ataxia, neuropathy, par aesthesia, somnolence, headache, taste perversion/loss

Eye Disorders

Rare: macular retinitis, iritis, conjunctivitis, amblyopia

Very rare: cataract, visual disorder, macular changes

Ear and Labyrinth Disorders

Very rare: vertigo

Cardiac Disorders

Uncommon: necrotizing angiitis, vasculitis

Rare: pericarditis, peripheral vascular disease, thrombophlebitis, vasodilation

Very rare: angina, bradycardia

Vascular Disorders

Very rare: hypertension

Gastrointestinal Disorders

Common: diarrhoea, alkaline phosphatase increase, SGOT/SGPT increase

Uncommon: vomiting, nausea, hepatic necrosis, granulomatous hepatitis, hepatomegaly, hyperbilirubinaemia, cholestatic jaundice, intermittent abdominal pain, gastritis, dyspepsia

Rare: haemorrhagic pancreatitis, gastrointestinal bleeding, salivary gland swelling, tongue oedema, anorexia.

Very rare: recurrent haematemesis, steatorrhoea, stomatitis, changed bowel habits

In early clinical studies, nausea and vomiting were reported. Further reports suggest that this reaction is not a significant problem and can be avoided by taking allopurinol after meals.

Hepatobiliary Disorders

Uncommon: asymptomatic increases in liver function tests

Rare: hepatitis (including hepatic necrosis and granulomatous hepatitis)

Hepatic dysfunction has been reported without overt evidence of more generalized hypersensitivity.

Skin and Subcutaneous Tissue Disorders

Common: rash, maculopapular rash

Uncommon: vesicular bullous dermatitis, exfoliative dermatitis, eczematoid dermatitis, urticaria, onycholysis, lichen planus, hypersensitivity vasculitis, purpura, pruritus,

Rare: SJS/TEN, facial oedema, sweating, skin oedema

Very rare: angio-oedema, fixed drug eruption, alopecia, discoloured hair

Skin reactions 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, such as SJS/TEN.

Allopurinol should be withdrawn immediately should such reactions occur. After recovery from mild reactions, allopurinol may, if desired, be re-introduced at a small dose (e.g. 50mg/day) and gradually increased. If the rash recurs, Allopurinol should be permanently withdrawn as more severe hypersensitivity may occur.

The clinical diagnosis of SJS/TEN remains the basis for decision-making. If such reactions occur at any time during treatment, allopurinol should be withdrawn immediately and permanently.

Angio-oedema has been reported to occur with and without signs and symptoms of a more generalized hypersensitivity reaction.

Renal and Urinary Disorders

Uncommon: renal failure

Rare: nephritis, primary haematuria, albuminuria

Very rare: haematuria, uraemia

Respiratory

Uncommon: epistaxis

Rare: bronchospasm, asthma, pharyngitis, rhinitis

Reproductive System and Breast Disorders

Rare: impotence

Very rare: male infertility, erectile dysfunction, gynaecomastia

General Disorders and Administration Site Conditions

Uncommon: fever, headache

Very rare: oedema, general malaise, asthenia, fever

Fever has been reported to occur with and without signs and symptoms of a more generalized allopurinol hypersensitivity reaction.

Overdosage

Ingestion of up to 22.5 g allopurinol without adverse effect has been reported. Symptoms and signs, including 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 affecting concomitant medication, especially with 6-mercaptopurine and/orazathioprine. Adequate hydration to maintain optimum diuresis facilitates excretion of allopurinol and its metabolites. If considered necessary, haemodialysis may be used.

In the management of overdosage, there is no specific antidote for allopurinol. There has been no clinical experience in the management of a patient who has taken massive amounts of allopurinol. Both allopurinol and oxipurinol are dialyzable; however, the usefulness of haemodialysis or peritoneal dialysis in the management of an overdose of allopurinol is unknown.

Storage and Handling Instructions

Store below 25°C. Store in the original package.

Packaging Information

CIPLORIC100 is available as a strip pack of 10 tablets

CIPLORIC 300 is available as a strip pack of 10 tablets

KEEP OUT OF THE REACH OF CHILDREN.

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