1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT:

ALLOPURINOL TABLETS 300 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:

Each uncoated tablet contains-

Allopurinol BP……..300 mg

Excipients ……..q.s.

QUANTITATIVE DECLARATION:

Sr. No.	Ingredients	Specification	Label Claim / Tablet (in mg)	Qty. / Tablet (In mg)	Qty. / Batch (In kg)
Dry Mixing					
1.	Allopurinol	BP	300.00	300.000	10.00
2.	Lactose	BP	-	10.00	1.00
3.	Maize Starch	BP	-	25.00	7.5
4.	Purified Talc	BP	-	20.000	3.0
5.	Colloidal Silicon dioxide	BP	-	15.000	1.5
6.	Croscarmellose sodium	BP	-	25.000	2.5
7.	PVPK-30	BP	-	51.000	5.1
8.	Methyl Hydroxybenzoate	BP	-	2.750	0.275
9.	Propyl Hydroxybenzoate	BP	-	2.075	0.2075
10.	Sodium Lauryl Sulphate	BP	-	6.000	0.6
11.	Magnesium Stearate	BP	-	4.000	0.4
12.	Purified Water	BP	-	Q.S.	Q.S.

3. PHARMACEUTICAL FORM

White colored, Round shaped, Biconvex, uncoated tablet having break-line on one side & other side embossing of MCP.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

Allopurinol and its major metabolite, oxipurinol, act by inhibiting the enzyme xanthine oxidase, which catalyses the end stage of the metabolism of purines to uric acid. Allopurinol and its metabolites are excreted by the kidney but the renal handling is such that allopurinol has a plasma half-life of about 1 hour whereas that of oxipurinol exceeds 18 hours. Thus therapeutic effect may be achieved by once-a-day dosage.

1) *Prophylactic management of gout and other conditions of excess body urate:* Allopurinol is used to reduce excessive urate levels (serum is theoretically saturated with urate at a concentration between 0.38-0.42mmol/l). The higher levels seen in practice may be accounted for by: a) the formation of saturated solutions; b) protein binding of urate. Excess body urate may be indicated by hyperuricaemia and/or hyperuricosuria. It may lead to disposition of urate in the tissues or it may be present with no obvious signs or symptoms.

The main clinical manifestations of urate disposition are gouty arthritis, skin tophi and/or renal involvement: Excess body urate is frequently of idiopathic origin but may also be found in association with the following other conditions: neoplastic disease and its treatment; certain enzyme disorders which lead to overproduction of urate and involving: hypoxanthine guanine phosphoribosyl transferase, such as Lesch-Nyhanb syndrome, glucose-6-phosphatase, as in von Gierke's disease or Phosphoribosyl pyrophosphate synthetase; renal failure; renal calculus formation; diuretic therapy and psoriasis.

2) *Calcium renal lithiasis:* Allopurinol is of benefit in the prophylaxis and treatment of calcium renal lithiasis in patients with raised serum or urinary uric acid.

4.2 Dosage and administration

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Creatinine clearance:	Dosage:
Over 20ml/minute	Standard dose
10-20ml/minute	100-200mg daily
Under 10ml/minute	100mg daily or less frequently

Dose recommendations in renal disease: Allopurinol and it metabolites are removed by renal dialysis. If frequent dialysis is required, an alternative schedule of 300-400mg after each dialysis, with none in the interim, should be considered.

4.3 Contraindications:

Hypersensitivity to the active substance or to any of the excipients

• Treatment for an acute attack of gout;

• Prophylactic therapy may be commenced when the acute attack has completely subsided, provided anti-inflammatory agents are also taken.

4.4 Special Warnings and Precautions for Use

Allopurinol should be withdrawn *immediately* when a skin rash or other evidence of sensitivity occurs as this could result in more serious hypersensitivity reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis) (see section 4.8).

Chronic renal impairment

Patients with chronic renal impairment and concomitant diuretic use, in particular thiazides, 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 (see section 4.8).

A reduction in dosage should be considered in the presence of severe renal or hepatic disorders.

Life-threatening cutaneous reactions (Stevens-Johnson syndrome (SJS) and toxic epidermalnecrolysis (TEN)) have been reported with the use of allopurinol.

Patients should be advised of the signs and symptoms and monitored closely for skin reactions.The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.

If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, allopurinol treatment should be discontinued.

The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.

Thyroid disorders

Increased TSH values (>5.5 µIU/mL) were observed in patients on long-term treatment with allopurinol (5.8%) in a long term open label extension study. Caution is required when allopurinol is used in patients with alteration of thyroid function.

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.

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.

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 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.

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 minimised 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.

Lactose intolerance: Allopurinol tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other Medicinal products and other forms of Interaction

6-mercaptopurine and azathioprine: If azathioprine or 6-mercaptopurine is given concurrently with allopurinol, the dose of these agents should only be one quarter of that usually given as inhibition of xanthine oxidase will prolong their activity.

Vidarabine (Adenine Arabinoside): Evidence suggests that the plasma half-life of adenine arabinoside is increased in the presence of allopurinol and hence when these two agents are administered concomitantly, extra vigilance is required to recognize enhanced toxic effects. There is no unequivocal evidence that allopurinol potentiates the activity of other cytotoxic drugs.

Salicylates and uricosuric agents: oxipurinol, 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 oxipurinol. This may decrease the therapeutic activity of Zyloric, but the significance needs to be assessed in each case.

Coumarin anticoagulants: Although there is no evidence that an interaction between allopurinol and the coumarin seen under experimental conditions has any clinical significance, this possibility should be borne in mind when a patient on oral anticoagulants is given allopurinol.

Chlorpropamide: If allopurinol is given concomitantly with chlorpropamide when renal function is poor, there may be an increased risk of prolonged hypoglycemic activity.

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

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

Ampicillin/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 drugs. The cause of the reported association has not been established. However, it is recommended that in patients receiving allopurinol an alternative to ampicillin or amoxicillin is used where available.

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

With administration of allopurinol and cytostatics (e.g. cyclophosphamide, doxorubicin, bleomycin, procarbazine, alkyl halogenides), blood dyscrasias occur more frequently than when these active substances are administered alone. Blood count monitoring should therefore be performed at regular intervals.

Cyclosporine: Reports suggest that the plasma concentration of cyclosporine may be increased during concomitant treatment with allopurinol. The possibility of enhanced cyclosporine 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 2 drugs is generally not recommended. If concomitant use is unavoidable, a dose reduction of didanosine may be required, and patients should be closely monitored.

Aluminium hydroxide: If aluminium hydroxide is taken concomitantly, allopurinol may have an attenuated effect. There should be an interval of at least 3 hours between taking both medicines.

Ace inhibitors: Concurrent use of allopurinol and ACE inhibitors may lead to an increased risk of hematological reactions such as leucopenia, especially if there is pre-existing renal failure.

4.6 Fertility, pregnancy and lactation

Pregnancy

High dose intraperitoneal allopurinol in mice has been associated with foetal abnormalities but extensive animal studies with oral allopurinol have shown none. In human pregnancy, there is no evidence that allopurinol taken orally causes foetal abnormalities; however, as with all drugs, caution should be exercised in the use of allopurinol during pregnancy.

Breast-feeding

Allopurinol and its metabolite oxipurinol is excreted in the human breast milk. Allopurinol during breastfeeding is not recommended.

4.7 Effects on 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.

4.8 Undesirable Effects

These are usually rare and mostly of a minor nature; the incidence is higher in the presence of renal and/or hepatic disorders.

For this product there is no modern clinical documentation which 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 post-marketing 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 (≥1/1000 and <1/100 (≥0.1% and <1%)), Rare (≥1/10,000 and <1/1000 (≥0.01% and <0.1%)), Very rare (<1/10,000 (<0.01%))

Infections and infestations

Very Rare: furunculosis,

Blood and lymphatic system disorders

Very rare: thrombocytopenia, aplastic anaemia, and agranulocytosis

Frequency not known: leucopenia, eosinophilia, hemolytic anaemia

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.

Reports of transient reduction in the number of circulating formed elements of the blood, are usually in association with a renal and/or hepatic disorder reinforcing the need for particular care in this group of patients.

Immune system disorders

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, it may be at any time during treatment, Allopurinol tablets 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.

Uncommon: Hypersensitivity reactions

Very rare: Angioimmunoblastic lymphadenopathy, anaphylaxis

Frequency not known: arthralgia

Associated vasculitis and tissue response may be manifested in various ways including hepatitis, interstitial nephritis and, very rarely, epilepsy. Corticosteroids may be beneficial in overcoming them. When generalized hypersensitivity reactions have occurred, a renal and/or hepatic disorder has usually been present, particularly when the outcome has been fatal.

Metabolism and nutrition disorders

Very rare: diabetes mellitus, hyperlipidemia

Frequency not known: exacerbation of gouty attacks (see section 4.4)

Psychiatric disorders

Very rare: depression,

Nervous system disorders

Very rare: ataxia, coma, headache, neuropathy, paresthesia, paralysis, somnolence, taste perversion

Frequency not known: dizziness

Eye disorders

Very rare: cataract, macular changes, and visual disorders

Ear and labyrinth disorders

Very rare: vertigo

Cardiac disorders

Very rare: angina, bradycardia

Vascular disorders

Very rare: hypertension

Frequency not known: vasculitis

Gastrointestinal disorders

Uncommon: nausea, vomiting

Very rare: changed bowel habit, stomatitis, steatorrhoea, and haematemisis

Frequency not known: diarrhoea, abdominal pain,

Hepatobiliary disorders

Uncommon: asymptomatic increases in liver function tests

Rare: Hepatitis (including hepatic necrosis and granulomatous hepatitis)

Skin and subcutaneous tissue disorders

Common: rash

Very rare: alopecia, angioedema, discoloured hair, fixed drug eruptions.

Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.4).

Frequency not known: skin reaction associated with eosinophilia, urticaria.

Drug Rash with Eosinophilia and Systemic Symptoms has been reported. Some cases have had a fatal outcome.

Skin reactions are the most common reactions and may occur at any time during treatment.

They may be pruritic, maculopapular, sometimes scaly or purpuric, associated with exfoliation, fever, lymphadenopathy, arthralgia and/or eosinophilia resembling Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and/or Lyell's. Allopurinol should be withdrawn *immediately* should such reactions occur.

If desired, after recovery from mild reactions, allopurinol may be reintroduced at a low dose (*eg* 50mg/day) which may be gradually increased. If the rash recurs, allopurinol should be *permanently* withdrawn.

The HLA-B*5801 allele has been has been identified as a genetic risk factor for allopurinol associated SJS/TEN in retrospective, case-control, pharmacogenetic studies in patients of Han Chinese, Japanese and European descent. Up to 20-30% of some Han Chinese, African and Indian populations carry the HLA-B*5801 allele whereas only 1-2% of Northern European, US European and Japanese patients are estimated to be HLA-B*5801 carriers. However, the use of genotyping as a screening tool to make decisions about treatment with allopurinol has not been established.

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*.

Renal and urinary disorders

Very rare: haematuria, uraemia

Frequency not known: nephrolithiasis

Reproductive system and breast disorders

Very rare: gynaecomastia, impotence, infertility

Frequency not known: nocturnal emissions

General disorders and administration site conditions

Very rare: asthenia, fever, general malaise, oedema

4.9 Overdose

No reports of overdosage or acute intoxication are available. Massive absorption of allopurinol may lead to considerable inhibition of xanthine oxidase activity, which should have no untoward effects unless adenine arabinoside, azathioprine or 6-mercaptopurine is being taken concurrently. In this case, the risk of increased activity of these drugs must be recognized.

Symptoms

Nausea, vomiting, diarrhoea, dizziness, headache, somnolence and abdominal pain. Rarely, there may be renal insufficiency and hepatitis.

Treatment

The benefit of gastric decontamination is uncertain. Consider activated charcoal (charcoal dose: 50 g for adults; 1 g/ kg for children) if the patient presents within 1 hour of ingestion of more than 50 mg/kg. If more than 50 mg/kg has been ingested check U&Es and LFTs.

Adequate hydration to maintain optimum diuresis facilitates excretion of allopurinol and its metabolites. Other measures as indicated by the patient's clinical condition.

Haemodialysis is unlikely to be required. Hameodialysis may be considered in patients with severe renal or hepatic impairment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antigout preparations inhibiting uric acid production; ATC code – M04 AA01

Allopurinol is used in the prevention and treatment of gout.

5.2 Pharmacokinetic properties

Allopurinol is absorbed from the GI tract and is reported to have a plasma half-life of about one hour. It is rapidly converted in the body to oxipurinol (alloxanthine) which is also an inhibitor of xanthine oxidase with a reported half-life of 18-30 hours. Allopurinol and oxipurinol are not bound to serum proteins and are excreted mainly in the urine.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Allopurinol, Lactose, Maize starch, Purified Talc, Colloidal Silicon dioxide, Croscarmellose sodium, PVPK 30, Sodium Methyl Paraben, Sodium Propyl Paraben, Purified Water, Magnesium Stearate, Sodium Lauryl Sulphate, Isopropyl Alcohol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 Months

6.4 Special Precautions for Storage

Store at temperature below 30°C in a dry place. Protect from light.

6.6 Nature and Contents of Container

Blister Packs of 2 X 14 Tablets

6.5 Special Precautions for Disposal of a used medicinal product or waste materials derived from such medicinal product and Other Handling of the Product

No special requirements

7. APPLICANT/HOLDER OF CERTIFICATE OG PRODUCT REGISTRATION

MULTICHRIS PHARM & CHEMICAL COMPANY LTD.

13 Qudus Folawoyi Ehi Crescent, Off Ashirigbon Street Isolo, Lagos, Nigeria.

8. DRUG PRODUCT MANUFACTURER

RELAX BIOTECH PVT. LTD.

862/1, G.I.D.C., Makarpura, Vadodara - 390010, INDIA.

9. NAFDAC REGISTRATION NUMBER(S)

B4-8171