

Product Summary

1. Trade Name of the Medicinal Product

Rheumox 600

2. Qualitative and Quantitative Composition

Rheumox tablets contain 600mg of the active ingredient azapropazone dihydrate.

3. Pharmaceutical Form

Rheumox 600: Pale orange, film coated, capsule shaped tablets. One side scored with a breakline and the other engraved 'WYETH' or 'FW281', containing azapropazone dihydrate 600mg. This product also contains sunset yellow (E110) and quinoline yellow (E104).

Clinical Particulars

4.1. Therapeutic Indications

Rheumox is a non-steroidal anti-inflammatory analgesic agent indicated in the treatment of rheumatoid arthritis, ankylosing spondylitis and attacks of acute gouty arthritis in patients for whom other therapy has been ineffective.

Rheumox should be used in suitable low-risk patients (see contraindications, precautions and warnings).

4.2 Posology and Method of Administration

Route of administration: Oral.

The lowest effective dose of Rheumox should be used for the shortest duration.

Dosage recommendations for Rheumox are lower for patients older than 60 years and for patients of any age who have reduced renal function. Rheumox is contraindicated in severe renal insufficiency. If any abnormality is suspected renal function should be investigated before commencing treatment with Rheumox.

Rheumatoid arthritis and ankylosing spondylitis

Adults under 60 years with adequate renal function

Rheumox 600 Tablets:	One 600mg tablet night and morning.
Rheumox 300mg Capsules	One 300mg capsule four times daily or two 300mg capsules night and morning

Adults over 60 years:

Rheumox 300mg One 300mg capsule twice daily
Capsules

Adults of any age with reduced renal function

Please follow dosage instructions for adults over 60 years, given above.

Acute Gout

Adults under 60 years with adequate renal function 1800mg per day in divided doses until the acute symptoms subside, normally by the fourth day, after which 1200mg per day in divided doses is taken until symptoms have resolved. If symptoms persist then appropriate alternative therapy for chronic gout should be considered. In treating acute gout, it is good practice to ensure that the patient increases their fluid intake.

Adults over 60 years: Rheumox is not recommended in acute gout in patients with a creatinine clearance of less than 60ml per minute.

1800mg in divided doses during the first 24 hours followed by 1200mg per day in divided doses. A maximum maintenance dose of 600mg per day in divided doses should be achieved as early as possible preferably by the fourth day. Treatment with Rheumox should only be continued until the acute symptoms resolve. If symptoms persist then appropriate alternative therapy for chronic gout should be considered. In treating acute gout, it is good practice to ensure that the patient increases their fluid intake.

Adults of any age with reduced renal function: Please follow dosage instructions for adults over 60 years, given above.

Children Not recommended.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

4.3 Contra-indications

- i Use in patients with a history or evidence of peptic ulceration or ulcerative colitis.
- ii Use in patients with severe renal insufficiency.
- iii Rheumox should not be given to patients known to be hypersensitive to this drug or to other non-steroidal anti-inflammatory drugs (NSAIDs).
- iv Use in patients with a history or evidence of blood dyscrasia.
- v Use in patients with severe hepatic insufficiency.

- vi Rheumox significantly potentiates the action of warfarin in many patients and must not be used with this or other oral anticoagulants.
- vii Rheumox increases the plasma concentration of phenytoin and should not be given to patients taking this drug.
- vii Rheumox should not be given to patients taking methotrexate.
 - i
- ix Rheumox, as with other Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) should not be used in patients suffering from porphyria.
- x Rheumox should not be given to patients with Severe heart failure.

4.4 Special Warnings and Precautions for Use

- i. Rheumox should only be considered for use in rheumatoid arthritis, ankylosing spondylitis and attacks of acute gouty arthritis in patients for whom other therapy has been ineffective.
- ii. Azapropazone should not be used in patients who are at a high risk of developing serious adverse events known to be associated with NSAID therapy, for example, patients who are suffering from gastrointestinal, severe renal or heart disease, or who are taking diuretics. This would include elderly patients and particularly those who already have or are suspected to have any of these conditions. In addition, patients who are on long-term therapy or multiple therapies should be carefully evaluated before treatment with Rheumox is initiated.
- iii. Serious gastrointestinal adverse effects such as bleeding, ulceration and perforation can occur at any time with or without warning symptoms in patients treated with Rheumox. Although this applies to all patients elderly or debilitated patients are less able to tolerate serious ulceration or bleeding events. If any sign of gastrointestinal bleeding occurs, Rheumox should be stopped immediately.
- iv. Azapropazone is excreted unchanged mainly by the kidney and should therefore be used with caution in older patients and in adults with any reduced renal function. NSAIDs in general inhibit renal prostaglandin synthesis and in patients with reduced renal function this action may result in overt renal decompensation. In such cases, the reduced dosage recommendations for the treatment of adults over 60 year's should be followed. If any abnormality is suspected, renal function should be fully investigated before commencing therapy with Rheumox. See also contraindications.
- v. A large number of photosensitivity reactions have been reported in association with Rheumox. Patients taking azapropazone should be advised to avoid direct exposure to sunlight or to use sunblock preparations.

vi. Rheumox can cause fluid retention. It should therefore be used with caution in patients with fluid retention, hypertension or heart failure.

vii. If abnormal liver function tests occur, persist or worsen, or if clinical signs and symptoms indicate the development of liver disease, Rheumox should be discontinued.

viii. Inhibition of renal lithium clearance by Rheumox has not been reported but the possibility of this occurring should be borne in mind.

ix. Rheumox may precipitate bronchospasm in patients with bronchial asthma or allergic disease.

x. The concomitant administration of corticosteroids with Rheumox may increase the risk of gastrointestinal bleeding and ulceration.

xi. Patients on long-term treatment with Rheumox should be carefully monitored and regularly reviewed. Haematological effects associated with chronic NSAID therapy should be borne in mind.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for Azapropazone.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Azapropazone after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

4.5. Interactions with other Medicaments and other forms of Interaction

i. Consult the section 'Contraindications' with phenytoin, warfarin and methotrexate.

ii. Since azapropazone is highly protein bound, it may possibly displace other protein bound drugs. It may therefore interfere with the blood sugar lowering effect of oral hypoglycaemic agents. Concurrent use of these drugs is not recommended.

iii. Concomitant use with azapropazone of lithium or digoxin may cause an increase in serum levels of these compounds. Concomitant use of cimetidine may cause an increase in azapropazone and decrease in cimetidine plasma levels respectively.

4.6. Pregnancy and Lactation

Animal reproduction studies did not result in fetal abnormalities but safety in human pregnancy cannot be assumed and its use should be avoided in pregnancy whenever possible. Azapropazone is excreted in small quantities in breast milk and should not therefore be used in breast feeding women.

4.7. Effects on Ability to Drive and Use Machines

None stated (presumed to be safe or unlikely to produce any effect)

4.8 Undesirable Effects

See also contraindication, precautions and warnings.

i. Serious gastrointestinal events including bleeding, gastric and duodenal ulceration, perforation and haemorrhage have been reported. Epidemiological studies show that these reactions occur more frequently than for other NSAIDs. In addition diarrhoea, dyspepsia, nausea, vomiting, melaena, and stomatitis have also been reported.

ii. Blood disorders including thrombocytopenia, pancytopenia, neutropenia and leucopenia have been reported. Anaemia and haemolytic anaemia have also been reported and some patients may develop a positive direct Coombs test without haemolytic anaemia. Rheumox should be discontinued in the presence of haemolytic anaemia or a positive direct Coombs test.

iii. NSAIDs have been reported to cause nephrotoxicity in various forms and their use can lead to interstitial nephritis, nephrotic syndrome and renal failure. Renal impairment and renal failure have been reported in association with Rheumox.

iv. Oedema and angioneurotic oedema.

v. Occasional central nervous system effects including dizziness, headache and fatigue

vi. Skin rashes including a high frequency of photosensitivity reactions.

vii. Allergic alveolitis, pulmonary fibrosis and fibrosing alveolitis has been reported rarely and if this occurs, Rheumox should be discontinued. Many NSAIDs may precipitate bronchospasm in patients with bronchial asthma or allergic disease, and this has been reported in association with Rheumox.

viii. Hepatic side effects including jaundice and hepatitis have been reported rarely.

Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

4.9. Overdose

If overdosage should occur, two specific courses of action are suggested on theoretical grounds. Since Rheumox is poorly soluble in gastric juice, stomach lavage should recover any gastric residue of the drug, provided of course that it is done early enough. Since Rheumox is predominantly excreted by the kidney, forced alkaline diuresis is theoretically indicated.

In addition to the above mentioned treatment, patients should be managed with symptomatic and Supportive care.

Pharmacological Properties

5.1. Pharmacodynamic Properties

Azapropazone is a non-steroidal anti-inflammatory agent with anti-inflammatory analgesic and antipyretic activity established by standard animal pharmacology tests and confirmed via clinical studies and use in man. In addition, this active ingredient is hyperuricaemic, reducing serum urate by enhancing urate excretion.

5.2. Pharmacokinetic Properties

Rheumox 600 and Rheumox capsules are immediate release preparations containing the active ingredient azapropazone dihydrate. Human pharmacokinetic studies with azapropazone have demonstrated rapid absorption following oral dosing with the attainment of maximum plasma levels at approximately 4 hours post dosing.

Azapropazone is reported to be highly bound to plasma proteins following absorption and in animal studies its distribution throughout body tissues is related to plasma concentration. Only low concentrations are reported in the brain and fatty tissues thus confirming the low lipophilic activity of azapropazone.

Metabolic studies have demonstrated that azapropazone is not extensively metabolised and is excreted primarily as unchanged azapropazone by the kidney.

5.3. Preclinical Safety Data

The oral LD₅₀ of azapropazone in rats was 4200 mg/kg. This value is equivalent to 150 times the maximum recommended human dose.

When administered to animals at the maximum tolerated daily doses, azapropazone did not exhibit a carcinogenic effect.

Pharmaceutical Particulars

6.1. List of Excipients

Rheumox 600: maize starch, gelatin, magnesium stearate, sepiFilm (PEG300, cellulose), and sepisperse orange (propylene glycol, titanium dioxide E171, sunset yellow E110, quinoline yellow E104).

6.2. Incompatibilities

None stated.

6.3. Shelf Life

Rheumox 600	blister packs - 42 months amber glass bottles - 42 months
-------------	--

6.4. Special Precautions for Storage

Protect from light.

6.5. Nature and Contents of Container

Rheumox 600:
Screw cap amber glass bottles (pack size 6, 28, 56, 100, 112 and 500)
PVC/aluminium foil blisters (pack size 4, 14, 28, 56 and 112)

6.6. Instruction for Use/Handling

None stated.

Administrative Data

7. Marketing Authorisation Holder

Goldshield Pharmaceuticals Limited
NLA Tower
12-16 Addiscombe Road
Croydon
Surrey
CRO OXT

8. Marketing Authorization Number

PL 12762/0022

9. Date of First Authorisation/Renewal of Authorisation

01 February 1998

10 DATE OF REVISION OF THE TEXT

12/04/2007