NYSA™

[PIROXICAM BETA-CYCLODEXTRIN TABLETS]

Tablets 20mg

DESCRIPTION

NYSA (Piroxicam beta-cyclodextrin), is the first non-steroidal anti-inflammatory agent, which also possesses analgesic and antipyretic properties, in which the active substance is complexed with the cyclic oligosaccharide cyclodextrin, which acts as an artificial receptor. The beta-cyclodextrin acts like a molecular-size capsule that envelopes the poorly soluble piroxicam and improves its solubility and speeds absorption. This offers the potential advantages of a more rapid onset of effect and better tolerability due to reduced contact time with the GI mucosa.

Chemically piroxicam is described as 4-hydroxy-2-methyl-N-(2-pyridinyl)-2H-1, 2-Benzothiazine-3-carboxamide-1, 1-dioxide as a complex with beta-cyclodextrin and the molecular formula is $(C_{15}H_{13}N_3O_4S)_2$-$(C_{42}H_{70}O_{35})_5$.

QUALITATIVE & QUANTITATIVE COMPOSITION

NYSA (Piroxicam beta-cyclodextrin) is available for oral administration as:

NYSA Tablets 20mg
Each tablet contains:
Piroxicam beta-cyclodextrin 191.2mg equivalent to
Piroxicam USP … 20mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Piroxicam an NSAID complex with cyclodextrin, possess analgesic and antipyretic properties, the complex allows single molecule of NSAID to be released adjacent to the gastrointestinal mucosa, instead of crystals. Since the time contact with gastric mucosa is reduced, the risk of direct contact gastric irritation is also reduced.

Pharmacokinetics

Piroxicam beta-cyclodextrin dissociates in the gastrointestinal tract to piroxicam and beta-cyclodextrin. Piroxicam absorption from piroxicam beta-cyclodextrin is more rapid than that of unmodified piroxicam. Piroxicam is well absorbed from the gastrointestinal tract peak plasma concentrations of piroxicam are reached 30 to 60 minutes after an oral dose. beta-cyclodextrin is not absorbed but is metabolized in the colon to various sugars. Piroxicam is 99% bound to plasma proteins. Piroxicam has a long plasma elimination half life of about 50 hours. Because of this steady state conditions are not reached for 7 to 12 days, it is metabolized in the liver by hydroxylation and conjugation with glucuronic acid and excreted mainly in the urine with smaller amounts in faeces. Enterohepatic recycling occurs. Less than 5% of the dose is excreted unchanged in the urine and faeces.

THERAPEUTIC INDICATIONS

NYSA (Piroxicam beta-cyclodextrin) is indicated for a variety of acute painful conditions requiring anti-inflammatory and analgesic activity, including rheumatoid arthritis, juvenile idiopathic arthritis, osteo-arthritis (arthrosis, degenerative joint disease), ankylosing spondylitis, musculoskeletal and joint disorders, gout, in soft-tissue disorders and in post-operative pain.

DOSAGE AND ADMINISTRATION

In rheumatic disorders a usual initial dose of NYSA (Piroxicam beta-cyclodextrin) is 20mg daily as a single dose. Daily maintenance doses may vary between 10mg and 30mg given in single or divided doses. In acute musculoskeletal conditions an initial dose of 40mg daily may be given for 2 days followed by 20mg daily for a total of 1 to 2 weeks. NYSA (Piroxicam beta-cyclodextrin) is also used in acute gout, the usual dose being 40mg daily for 5 to 7 days. In the treatment of post operative pain following dental or minor surgery, the dose is 20mg daily. Higher doses of 40mg daily for the first 2 days are recommended following orthopaedic surgery.

The dose may be reduced to 10mg daily in elderly patients.

For children (over 6 years) the dosage for juvenile idiopathic arthritis is given in the table below:

Weight	Dosage
15kg	5mg daily
16-25kg	10mg
26-45kg	15mg
Over 46kg	20mg

ADVERSE REACTIONS

Very common: nausea, epigastric distress, abdominal pain and discomfort, flatulence, constipation and diarrhoea. Other possible reactions are hypersensitivity signs, such as skin rash, headache, vertigo, asthenia, blood chemistry modifications, and increase in blood urea.

Less common: vomiting, allergic oedema of the face and hands, blurred vision, tinnitus, aplastic anaemia, leucopoenia, eosinophilia, pancytopenia, thrombocytopenia, increase in parameters of liver functions, jaundice, acute renal insufficiency, water retention that may occur in the form of oedema (mainly ankle oedema), or cardiocirculatory disorders (hypertension, congestive heart failure). Sporadic cases of gastric ulcer with perforation, Stevens-Johnson's syndrome, Lyell's syndrome-, agranulocytosis, bladder disorders, shock and warning symptoms, acute heart failure. Stomatitis, alopecia and nail growth disorders have been reported.

Rare: Gastric ulcers and haemorrhages may also occur.

CONTRAINDICATIONS

Piroxicam should not be used in the following:

- Known hypersensitivity to the drug.
- Gastroduodenal ulcer, gastritis, dyspepsia, severe hepatic or renal disturbances, severe heart failure, severe hypertension, severe blood alterations or hemorrhagic diathesis.
- Piroxicam must not be administered to patients in whom acetylsalicylic acid or other NSAIDs induce the symptoms of asthma, rhinitis or urticaria.
- Ascertained or suspected pregnancy, during lactation and in children.

WARNINGS

CHMP Advice
The CHMP has recommended restrictions on the use of piroxicam because of the increased risk of gastrointestinal side effects and serious skin reactions. The CHMP has advised that:

- Piroxicam should be initiated only by physicians experienced in treating inflammatory or degnerative rheumatic diseases.
- Piroxicam should not be used as first-line treatment.
- In adults, use of piroxicam should be limited to the symptomatic relief of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.
- Piroxicam dose should not exceed 20mg daily.
- Piroxicam should no longer be used for the treatment of acute painful and inflammatory conditions.
- Treatment should be reviewed 2 weeks after initiating piroxicam and periodically thereafter.
- Concomitant administration of a gastro-protective agent should be considered.

Note: Topical preparations containing piroxicam are not affected by these restrictions.

PRECAUTIONS

General:

- NSAIDs inhibit the synthesis of renal prostaglandin which plays a supportive role in the maintenance of renal perfusion in patients whose renal blood flow and blood volume are decreased. Particular caution must be taken in

patients at greatest risk of this complication include those with impaired hepatic or renal function, with heart failure, taking diuretics or the elderly. Such patients should be carefully monitored while receiving NSAID therapy.

– Blood urea nitrogen elevation has been observed in some patients. The rise in blood urea nitrogen as a rule is not associated with elevations in serum creatinine. As with other NSAIDs, it is recommended that piroxicam be given under close supervision in patients with a history of impaired renal function and periodic renal function tests carried out. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with piroxicam. Although such reactions are rare, if abnormal liver function tests persist or worsen, if clinical signs consistent with hepatic disease develop or if systemic manifestations occur (e.g. eosinophilia, rash) piroxicam should be discontinued.

Gastrointestinal tract:
Serious gastrointestinal toxicity such as bleeding, ulceration and perforation can occur anytime with or without warning symptoms, in patients treated chronically with NSAID therapy. Piroxicam must be used under strict medical control in patients with a medical history of disturbances in the upper gastrointestinal tract.

Asthma:
Piroxicam should be used with caution in patients with asthma because bronchial smooth muscle spasm may be aggravated by prostaglandin inhibition.

Hypertension:
As with other NSAIDs, piroxicam should be given under close supervision to patients with hypertension as the antihypertensive effect of thiazide diuretics and β-blocking agents is antagonized by NSAIDs.

Effects on ability to drive or use machinery:
Patients experiencing dizziness or other central nervous system disturbance should refrain from driving a vehicle or operating machinery.

Compromised Cardiac function:
Edema, mainly ankle edema, has been reported during piroxicam treatment; as with other non-steroidal anti-inflammatory agents, piroxicam should be used with caution in patients with compromised cardiac function.

Bleeding time:
Piroxicam, like other NSAIDs, decreases platelet aggregation and prolongs bleeding; this should be remembered when hematological tests are carried out and when patients undergo concomitant treatment with drugs that inhibit platelet aggregation, and in patients undergoing surgery or with hemorrhagic disorders.

Masking infection:
As with other NSAIDs, anti-inflammatory, antipyretic and analgesic effects of piroxicam may mask the signs of infection (pain, fever, etc.).

Ophthalmologic Monitoring:
Adverse ophthalmologic effects have been observed with NSAIDs. Patients who develop visual disturbances during treatment with piroxicam should have an ophthalmologic examination.

Pregnancy:
Piroxicam should not be used in pregnant women or those likely to become pregnant unless the expected benefits outweigh the potential risk.

Nursing Mothers:
Piroxicam appeared in breast milk in a concentration approximately 1 to 3% of that reached in maternal plasma. Piroxicam is not recommended for breastfeeding mothers unless the expected benefits outweigh any potential risk, as clinical safety has not been demonstrated.

Pediatric Use:
The use of piroxicam in children under 12 years is not recommended as safety and efficacy in this age group are not established.

Drug Interactions:
Warfarin: The concurrent use of non-steroidal anti-inflammatory drugs and warfarin has been associated with severe, sometimes fatal hemorrhage. Piroxicam should be used in combination with warfarin only if absolutely necessary and patients taking this combination of drugs should be closely monitored.

Protein bound drugs: Piroxicam is highly protein bound and therefore might be expected to displace other protein bound drugs. The physician should closely monitor dosage requirements of coumarin anticoagulants and other drugs that are highly protein bound when these are administered concomitantly with piroxicam. Such drugs include hydantoins, sulphonamides and sulfonylureas. Bleeding has been reported rarely when piroxicam, as well as other NSAIDs, have been administered to patients on coumarin type anticoagulants.

Methotrexate: Extreme care should also be exercised in giving methotrexate to patients on piroxicam therapy, because lethal interactions have been reported between NSAIDs and methotrexate.

Aspirin and other NSAIDs: Administration of piroxicam and aspirin reduced the plasma levels of piroxicam to about 80% of the normal value.
The use of piroxicam with aspirin or its concurrent use with other NSAIDs increases the potential for adverse reactions and therefore concomitant use of two or more NSAIDs is not recommended.

Plasma lithium concentrations: NSAIDs including piroxicam have been shown to decrease the renal clearance and increase steady state plasma concentrations of lithium. Plasma lithium concentrations should be monitored when initiating, adjusting or discontinuing concurrent piroxicam.

Diuretics: Piroxicam may cause sodium, potassium and fluid retention and may interfere with the natriuretic action of diuretic drugs causing a reduction in diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs. These properties should be kept in mind when treating patients with compromised cardiac function of hypertension, to avoid a possible worsening of these conditions.

Anti-hypertensives: There may be a reduction in the effect of anti-hypertensives.

Cardiac Glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycosides.

Quinolone Antibiotics: Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Mifepristone: In common with other NSAIDs, piroxicam should be avoided for at least 8 to 12 days following mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Cyclosporine: NSAIDs may increase cyclosporine nephrotoxicity as a result of their effect on renal prostaglandins.

Corticosteroids: There is increased risk of gastrointestinal bleeding with corticosteroids.

Aminoglycosides: Reduction in renal function in susceptible individuals, decreased elimination of aminoglycosides and increased plasma concentrations have been reported.

Oral Hypoglycemic Agents: Inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycemia is known to occur with oral hypoglycemic agents.

STORAGE
Store below 30°C.
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
NYSA (Piroxicam beta-cyclodextrin) Tablets 20mg are available in blister packs of 20 Tablets.

Keep out of reach of children.

To be sold on prescription of a medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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