plasma proteins is approximately 60%, while that of 1,2-dinitroglycerol and 1,3-dinitroglycerol is 60% and 30% respectively. The actively and half-life of the nitroglycerin metabolites is not well characterized. The dinitrates are less potent as vasodilators and the mononitrate is inactive.

Dosage should always be adjusted according to the requirement and response obtained by the individual patient and the severity of the anginal pain.

Adolescents: One NITROCONTIN® Continus tablets 2.6 mg in morning and evening. The tablets should be taken empty stomach.

If the symptoms have not been adequately controlled after a week on this regimen, the dosage should be increased to one 6.4 mg tablet morning and evening.

Children: Not recommended.

Elderly: Normal adult dose. The tablets should be swallowed whole & not chewed.

Contraindications
Allergic reactions to organic nitrates are extremely rare, but they do occur. Nitroglycerin should not be administered to individuals with a known hypersensitivity or idiosyncrasy reaction to nitroglycerin, other organic nitrates, or nitrites or to the excipients of the medicine.

NIHROCONTIN™ Continus tablets should not be used in patients with acute myocardial infarction, marked anaemia, head trauma, cerebral haemorrhage, or closed angle glaucoma.

Sildenafil has been shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitrates or nitric oxide donors is therefore contraindicated.

Warning & Precautions
As with other drugs for the treatment of angina pectoris, abrupt discontinuation of therapy may lead to exacerbation of symptoms. When discontinuing long-term treatment, the dosage should be reduced gradually over several days, and the patient carefully monitored.

Although, tolerance has not been demonstrated to occur in clinical trials with NITROCONTIN™ Continus tablets, the possibility of tolerance to this drug should be considered if symptoms of angina recur on high or more frequent dosing schedules.

The use of any form of nitroglycerin during the early days of acute myocardial infarction requires particular attention to hemodynamic monitoring and clinical status to avoid the hazards of hypotension and tachycardia.

Severe hypotension, particularly with upright posture, may occur even with small doses of nitroglycerin. The drugs, therefore, should be used with caution in subjects who may have volume depletion from diuretic therapy or in patients who have low systolic blood pressure (e.g. below 90 mmHg). Paradoxical tachycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy. Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur.

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory.

Rx
Controlled Release Tablets of Nitroglycerin
NITROCONTIN™ 2.6 / 6.4 CONTINUS® controlled release system

Description
NITROCONTIN™ Continus tablets 2.6 mg or 6.4 mg are flat, beveled, pink, controlled release tablets containing diluted Nitroglycerin USP equivalent to Nitroglycerin 2.6 mg and embossed “NC” on one side and with the symbol MM on the other or diluted Nitroglycerin USP equivalent to Nitrocontin 6.4 mg and embossed “NC 6.4” on one side and MM on the other.

Indication
NITROCONTIN™ Continus tablets are indicated for the management of angina pectoris. The onset of action is not sufficiently rapid for this form to be useful in aborting an acute anginal episode.

Clinical Pharmacology
The principal pharmacologick action of nitroglycerin is relaxation of vascular smooth muscle, producing a vasodilator effect on both peripheral arteres and veins with more prominent effects on the later. Dilation of the post capillary vessels, including large veins, promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure (preload). Arteriolar relaxation reduces systemic vascular resistance and arterial pressure (afterload).

The mechanism by which nitroglycerin relieves angina pectoris is not fully understood. Myocardial oxygen consumption or demand (as measured by the pressure-rate product, tension-time index and stroke-work index) is decreased by both the arterial and venous effects of nitroglycerin, and a more favorable supply-demand ratio is achieved. In coronary circulation, the nitrates redistribute circulating blood flow along collateral channels, improving perfusion to the ischemic myocardium. While large epicardial coronary arteries are also dilated by nitroglycerin, the extent to which this action contributes to relief of exertional angina is unclear.

Therapeutic doses of nitroglycerin reduces systolic, diastolic and mean arterial blood pressures. Effective coronary perfusion pressure is usually maintained, but can be compromised if blood pressure falls excessively or increased heart rate decreased diastolic filling time.

Evaluated central venous and pulmonary capillary wedge pressures, pulmonary vascular resistance and systemic vascular resistance are also reduced by nitroglycerin therapy. Heart rate is usually slightly increased, presumably a reflex response to the fall in blood pressure. Cardiac index may be increased, decreased or unchanged. Patients with elevated left ventricular filling pressure and systemic vascular resistance values in conjunction with a depressed cardiac index are likely to experience an improvement in cardiac index. On the other hand, when filling pressures and cardiac index are normal cardiac index may be slightly reduced by intravenous nitroglycerin.

Nitroglycerin is widely distributed in the body with an apparent volume of distribution of approximately 3L/Kg in adult male subjects, and is rapidly metabolized to dinitrates (1,2 dinitroglycerol and 1,3 dinitroglycerol) and mononitrates, with a short half-life, estimated at 1-4 minutes. A liver reductase enzyme is of primary importance in the metabolism of nitroglycerin to its metabolites. Dinitrates are metabolized to mononitrates and ultimately to glycerols and carbon dioxide. At plasma concentrations between 50 and 500 ng/ml, the binding of nitroglycerin to plasma proteins is approximately 60%, while that of 1,2-dinitroglycerol and 1,3-dinitroglycerol is 60% and 30% respectively. The actively and half-life of the nitroglycerin metabolites is not well characterized. The dinitrates are less potent as vasodilators and the mononitrate is inactive.
Tolerance to the vascular and anti-anginal effects of nitrates has been demonstrated in clinical trials, experience through occupational exposure and in isolated tissue experiments in the laboratory.

In industrial workers who have had long-term exposure to unknown (presumably high) dose of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction and even sudden death have occurred during temporary withdrawal of nitroglycerine from the workers demonstrating the existence of true physical dependence. In various clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of nitroglycerin is not known.

Pregnancy & Lactation: Pregnancy Category C – There is no evidence relating to the safety of nitrate in pregnancy and lactation. Nitrate should not be administered to pregnant women and nursing mothers unless considered essential by the physician.

Children: The safety and effectiveness of NITROCONTIN™ Continus® tablets in children have not been established.

Drug Interactions
Concomitant use of nitrates and alcohol may cause hypertension. Patients receiving antihypertensive drugs, beta-adrenergic blockers, phenothiazine with nitrates should be observed for possible additive hypotensive effects. Marked orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used concomitantly. Dose adjustment of either class of agent may be necessary. Aspirin decreases the clearance and enhances the hemodynamic effects of nitroglycerin. Nitroglycerine may reduce the pharmacologic effects of heparin when used concomitantly.

Nitrates increase the bioavailability of dihydroergotamine with resultant increase in mean standing systolic blood pressure or functional antagonism between these agents, decreasing the antianginal effects.

Nitrates may interfere with the Zlatkis-Zak color reaction causing a false report of decreased serum cholesterol.

Side Effects
Adverse reactions to nitroglycerin are generally dose-related, and almost all of these reactions are the results of nitroglycerin’s activity as a vasodilator. Headache is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Transient episodes of light-headedness, occasionally related to blood pressure changes may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

Allergic reactions to nitroglycerin are also uncommon, and the great majority of those reported have been caused of contact dermatitis or fixed drug eruptions in patients receiving nitroglycerin in ointments or patches. There have been a few reports of genuine anaphylactoid reactions, and these reactions can probably occur in patients receiving nitroglycerin by any route.

Extremely rarely, ordinary doses of organic nitrated have caused methaemoglobinemia in normal-seeming patients. Methaemoglobinemia is so infrequent at these doses that further discussion of its diagnosis and treatment is deferred.

Other adverse reactions occurring in less than 1% of patients are the following: tachycardia, nausea, vomiting, apprehension, restlessness, muscle twitching, retrosternal discomfort, palpitation, dizziness and abdominal pain.

However, such side-effects are virtually absent or substantially diminished with NITROCONTIN™ Continus® tablets therapy due to the controlled release system.

Overdose & Its Treatment
Symptoms of overdosage include vomiting, hypotension, restlessness, syncope, cyanosis and methaemoglobinaemia. Treatment should include gastric lavage, respiratory and circulatory support and attention to circulatory signs and symptoms. In severe cases, oxygen and other symptomatic and supportive respiratory and cardiovascular measures should be provided. Methaemoglobinaemia may also be treated with intravenous methylene blue. Keep unconscious patients horizontal and lower head. Physicians should be aware that tablets in the intestine will release the drug for a period of hours.

Information for The Patient
Daily headaches sometime accompany treatment with nitroglycerine. In patients who get these headaches, the headaches may be a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with nitroglycerin.

Treatment with nitroglycerin may be associated with light-headedness on standing, especially just after rising form a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol.

Physician should discuss with patients the contraindication of nitroglycerin with concurrent Sildenafil.

Pharmaceutical Particulars
Incompatibilities: None reported.

Shelf-life: 24 hours

Storage Precautions: Store at or below 25 C, in a dry place, protected from light. Keep out of reach of children.

Presentation:
Tablets 2.6 mg: Polypropylene bottle of 100 tablets.
Tablets 6.4 mg: Polypropylene bottle of 100 tablets.

Manufactured & Marketed by
MODI-MUNDIPHARMA PVT. LTD.
Mfd at Modipuram – 250 110, U.P. India
Regd Off: 1400, Hembkunt Tower 98, Nehru Place, New Delhi – 110 019, India

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