SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nitrocontin 2.6
(Controlled Release Tablets of Nitroglycerin)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:

NAME OF INGREDIENT (S)	Reference Standard	Quantity (mg/tablet)	Function	Label Claim
ACTIVE INGREDIENT(S)				
Nitroglycerin Diluted (10%)	USP	29.90*	Active	2.6 mg
INACTIVE INGREDIENT(S)				
Lactose	BP/ Ph.Eur.	106.40	Binder	-
Hydroxyethyl Cellulose (Natrosol 250 HX)	BP/ Ph.Eur.	15.00	Drug Release controlling agent	-
Cetostearyl Alcohol (Kolliwax CSA 50)	BP/ Ph.Eur.	45.00	Drug Release controlling agent	-
Purified Talc	BP/Ph.Eur.	5.00	Antiadherent	-
Magnesium Stearate	BP/Ph.Eur.	2.00	Lubricant	-
Purified Water	BP/Ph.Eur.	0.050** ml	Solvent	-
Erythrosine Lake	IH	0.60	Colour	
Weight of the tablet		203.90mg		

*Includes 15% overage.
**Not present in final weight.

3. PHARMACEUTICAL FORM

Controlled release tablets
Description: Pink, round, flat, bevelled edges, uncoated tablets engraved with 'MM' logo on one of the facet and 'NC' on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nitrocontin Continus tablets are indicated for the management of angina pectoris.

4.2 Posology and method of administration

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

Adults: One Nitrocontin Continus tablet 2.6 mg in morning and evening. The tablet 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 and not chewed.

4.3 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.

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

Concomitant intake of nitric oxide donors and phosphodiesterase type 5 inhibitors (e.g Sildenafil, tadalfil and verdenafil) enhances the hypotensive effect. Therefore, the concomitant use of above drugs is contraindicated. If a patient treated with sildenafil, tadalfil or verdenafil needs a rapidly effective nitrate (e.g in case of an acute angina pectoris attack) he/she must be hospitalized immediately.

4.4 Special warnings and precautions for use

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.

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 drug, 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 nitrates may occur.
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.

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

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 nitroglycerin from the workers demonstrating the existence of true physical dependence. In various clinical trials in angina patients, there are reports of angina 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.
Contains lactose as an excipient, should not be used in patients with lactose intolerance.

4.5 Interactions with other medicinal products and other forms of interactions

Concomitant use of nitrates and alcohol may cause hypotension. Patients receiving antihypertensive drugs, beta adrenergic blockers, phenothiazines 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 enhance the hemodynamic effects of nitroglycerin. Nitroglycerin 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 colour reaction causing a false report of decreased serum cholesterol.

4.6 Pregnancy and lactation

Pregnancy Category C- There is no evidence relating to the safety of nitrates in pregnancy and lactation. Nitrates 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.

4.7 Effects on ability to drive and use machines
Not Applicable

4.8 Undesirable effects

Adverse reactions to nitroglycerin are generally dose-related, and almost all of these reactions are the result 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 cases 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 nitrates have caused methaemoglobinaemia in normal-seeming patients. Methaemoglobinaemia 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.

4.9 Overdose

Symptoms of overdosage include vomiting, hypotension, restlessness, syncope, cyanosis and methaemoglobinaemia.
Treatment of overdosage
Treatment should include gastric lavage, respiratory and circulatory support 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.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The principal pharmacologic action of nitroglycerin is relaxation of vascular smooth muscle, producing a vasodilator effect on both peripheral arteries and veins with more prominent effects on the latter. 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 artierial 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 ischaemic 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 reduce systolic, diastolic and mean arterial blood pressure, effective coronary perfusion pressure is usually maintained, but can be compromised if blood pressure falls excessively or increased heart rate decreases diastolic filling time.

Elevated 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.

5.2 Pharmacokinetic properties

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 µg/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 activity and half-life of the nitroglycerin metabolites is not well characterized. The dinitrates are less potent as vasodilators and the mononitrate is inactive.

5.3 Preclinical Safety Data

Nitroglycerine is well established drug for its safety and tolerability as reported in published literature.

6.0 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1. Lactose
2. Hydroxyethyl Cellulose (Natrosol 250 HX)
3. Cetostearyl alcohol (Kolliwax CSA 50)
4. Purified Talc
5. Magnesium Stearate
6. Erythrosine Lake
7. Purified Water

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

24 months

6.4 Special precautions for storage

Store at or below 30^{o} C, in a dry place, protected from light.

6.5 Nature and contents of container

25 tablets of Nitrocontin 2.6mg are packed in a Polypropylene bottle (with polypropylene body and LDPE Cap) along with a pink coloured LDPE spacer. The body colour of bottle is pink with a white cap.

6.6 Special precautions for disposal

No special requirements.

7.0 Name and address of marketing authorization holder

Manufactured by:
Modi-Mundipharma Pvt. Ltd.
Modipuram – 250 110,
U.P., India
Phone: +91-121-2576214-17
Fax: +91-121-2575517

Registered by:
Modi-Mundipharma Pvt. Ltd.
1400, Modi Tower,
98, Nehru Place,
New Delhi – 110019, India.
Phone: +91-11-42504555
Fax: +91-11-26451659
E-mail: mithu.sen@winmedicare

8.0 Marketing authorization number

Rwanda FDA-HMP-MA-0657

9.0 Date of first authorization/renewal of the authorization

02/12/2023

10.0 Date of (partial) revision of the text

December 2023