



## Nimodipine

Updated: January 11, 2017.

## OVERVIEW

### Introduction

Nimodipine is a second generation calcium channel blocker used in the treatment of cerebral vasospasm after subarachnoid hemorrhage. Nimodipine is not widely used and has not been implicated in causing clinically apparent acute liver injury.

### Background

Nimodipine (nye moe' di preen) belongs to the dihydropyridine class of calcium channel blockers (similar to amlodipine and felodipine) and is used to treat cerebral vasospasm after subarachnoid hemorrhage. Like other calcium channel blockers, nimodipine acts by inhibition of the influx of calcium ions into smooth muscle cells during depolarization which results in vasodilation. Nimodipine has high lipid solubility and was developed specifically to treat cerebral vasospasm. Clinical trials have suggested that nimodipine reduces infarct size and complications after subarachnoid hemorrhage. Nimodipine was approved for use in the United States in 1988 but is not widely used, largely because of its restricted indications. Nimodipine is available in generic forms and under the commercial name Nimotop as capsules of 30 mg. The recommend dose in adults is 60 mg every 4 hours for 21 days starting as soon as possible or within 96 hours of the diagnosis of subarachnoid hemorrhage. Like most calcium channel blockers, nimodipine is generally well tolerated and side effects are largely due to its vasodilating activities and can include headache, dizziness, flushing, fatigue, nausea, diarrhea, peripheral edema, palpitations and rash.

#### Hepatotoxicity, Outcome and Management

Nimodipine has been associated with only rare reports of serum enzyme elevations during therapy. These elevations are usually mild, transient and not associated with symptoms or need for dose modification. Nimodipine is not widely used and has not been linked to instances of clinically apparent liver injury. Thus, hepatotoxicity from nimodipine must be rare, if it occurs at all.

Likelihood score: E (Unlikely cause of clinically apparent liver injury).

The reason why some calcium channel blockers cause liver injury (verapamil, diltiazem, amlodipine) while others (such as nimodipine) do not is not known. Because liver injury from calcium channel blockers is rare, those that are uncommonly used may just not have had enough exposures to manifest idiosyncratic cases of liver injury. Nimodipine is metabolized in the liver largely via CYP 3A4 and is susceptible to drug-drug interactions with agents that induce or inhibit CYP 3A4.

Drug Class: Cardiovascular Agents, [Calcium Channel Blockers](#)

Other Drugs in the Subclass, Calcium Channel Blockers: [Amlodipine](#), [Diltiazem](#), [Felodipine](#), [Isradipine](#), [Nicardipine](#), [Nifedipine](#), [Nisoldipine](#), [Verapamil](#)

## PRODUCT INFORMATION

### REPRESENTATIVE TRADE NAMES

Nimodipine – Generic, Nimotop®

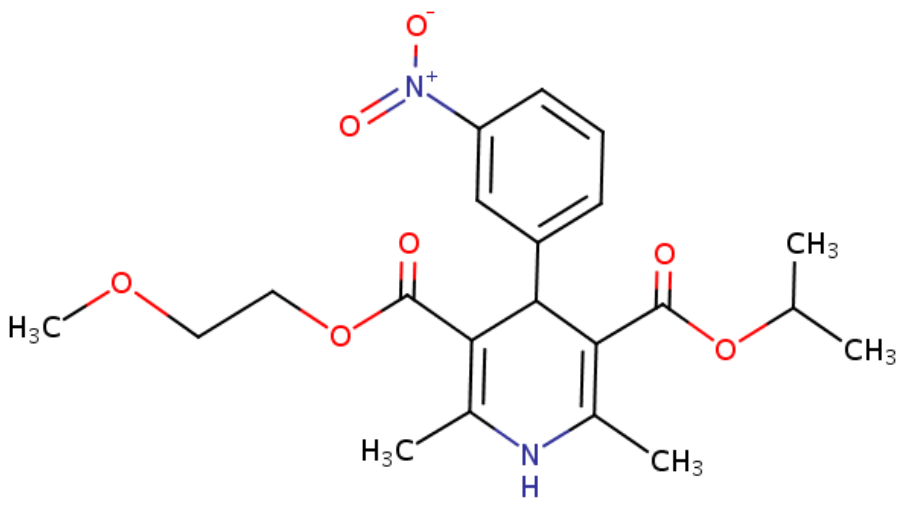
### DRUG CLASS

Cardiovascular Agents

### COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

## CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Nimodipine	66085-59-4	C <sub>21</sub> -H <sub>26</sub> -N <sub>2</sub> -O <sub>7</sub>	 <p>The chemical structure of Nimodipine is a 1,4-dihydropyridine derivative. It features a central dihydropyridine ring with a nitrogen atom at the bottom position. The ring is substituted with two methyl groups (CH<sub>3</sub>) at the 2 and 6 positions. At the 4 position, there is a piperidine ring. The piperidine ring is further substituted with a 4-nitrophenyl group at the 2-position, a propyl 3-methoxypropyl ester group at the 3-position, and an isopropyl ester group at the 4-position. The nitro group is shown with a positive charge on the nitrogen and a negative charge on one of the oxygens.</p>

## REFERENCES

References updated: 11 January 2017

Zimmerman HJ. Calcium channel blockers. Drugs used in cardiovascular disease. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 646-7.

*(Expert review of hepatotoxicity published in 1999; among calcium channel blockers, diltiazem, nifedipine, bepridil and verapamil have been incriminated in instances of hepatic injury; nimodipine is not mentioned).*

De Marzio DH, Navarro VJ. Calcium channel blockers. Hepatotoxicity of cardiovascular and antidiabetic drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 524.

*(Review of hepatotoxicity of calcium channel blockers mentions that diltiazem and verapamil have been implicated in causing cholestatic liver injury; no mention of nimodipine).*

Michel T, Hoffman BB. Calcium channel antagonists. Treatment of myocardial ischemia. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 755-60.

*(Textbook of pharmacology and therapeutics).*

Allen GS, Ahn HS, Preziosi TJ, Battye R, Boone SC, Boone SC, Chou SN, et al. Cerebral arterial spasm--a controlled trial of nimodipine in patients with subarachnoid hemorrhage. N Engl J Med 1983; 308: 619-24. PubMed PMID: 6338383.

*(In a US randomized controlled trial in 125 patients with a subarachnoid hemorrhage treated with oral nimodipine or placebo for 21 days, "there were no side effects from nimodipine").*

Pickard JD, Murray GD, Illingworth R, Shaw MD, Teasdale GM, Foy PM, Humphrey PR, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. BMJ 1989; 298: 636-42. PubMed PMID: 2496789.

*(Among 554 patients with a subarachnoid hemorrhage treated with nimodipine or placebo for 21 days, 4 patients on nimodipine vs 5 on placebo developed hepatobiliary adverse events [jaundice or abnormal liver tests], although "biochemical laboratory tests data were comparable between the two groups").*

Petruk KC, West M, Mohr G, Weir BK, Benoit BG, Gentili F, Disney LB, et al. Nimodipine treatment in poor-grade aneurysm patients. Results of a multicenter double-blind placebo-controlled trial. J Neurosurg 1988; 68: 505-17. PubMed PMID: 3280746.

*(Among 154 patients with subarachnoid hemorrhage treated with oral nimodipine or placebo for 21 days, side effects were similar in the two groups; one patient receiving placebo developed cholestatic hepatitis).*

Langley MS, Sorkin EM. Nimodipine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in cerebrovascular disease. Drugs 1989; 37: 669-99. PubMed PMID: 2663415.

*(Review of pharmacology, mechanism of action, clinical efficacy and tolerability of nimodipine; elevations in serum enzymes occur with intravenous administration of nimodipine, but are uncommon with its oral use).*

Gelmers HJ, Gorter K, de Weerd CJ, Wiezer HJ. A controlled trial of nimodipine in acute ischemic stroke. N Engl J Med 1988; 318: 203-7. PubMed PMID: 3275894.

*(In a randomized controlled trial of nimodipine vs placebo in 186 patients with acute ischemic stroke, side effects were mild; no mention of ALT elevations or liver injury).*

Gelmers HJ. The effects of nimodipine on the clinical course of patients with acute ischemic stroke. Acta Neurol Scand 1984; 69: 232-9. PubMed PMID: 6377803.

*(Among 60 patients with acute ischemic stroke treated with nimodipine or placebo for 4 weeks, side effects were of "minor importance" and of "no clinical relevance").*

Tomassoni D, Lanari A, Silvestrelli G, Traini E, Amenta F. Nimodipine and its use in cerebrovascular disease: evidence from recent preclinical and controlled clinical studies. *Clin Exp Hypertens* 2008; 30: 744-66. PubMed PMID: 19021025.

*(Review of the laboratory and clinical evidence of benefit of nimodipine in cerebrovascular disease; little discussion of side effects and no mention of hepatotoxicity or ALT elevations).*

Chalasanani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology* 2008; 135: 1924-34. PubMed PMID: 18955056.

*(Among 300 cases of drug induced liver disease in the US collected from 2004 to 2008, calcium channel blockers were implicated as a sole agent in 2 cases [1 amlodipine, 1 verapamil: case 1] and as one of several agents in 2 cases [both amlodipine]; no mention of nimodipine).*

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. *Hepatology* 2010; 52: 2065-76. PubMed PMID: 20949552.

*(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but no case was attributed to nimodipine or other calcium channel blockers).*

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology* 2013; 144: 1419-25. PubMed PMID: 23419359.

*(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, none of which were attributed to a calcium channel blocker or other antihypertensive medication).*

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. *Ann Hepatol* 2014; 13: 231-9. PubMed PMID: 24552865.

*(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases; one case was attributed to verapamil, but none were linked to nimodipine or other calcium channel blockers).*

Chalasanani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. *Gastroenterology* 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

*(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 39 [4%] were due to antihypertensive agents including 4 due to calcium channel blockers [amlodipine in 1 and verapamil in 3 instances], but none to nimodipine).*