

Cardiovascular Drugs and Therapies

CALCIUM CHANNEL BLOCKING AGENTS - *DIHYDROPYRIDINES*

Generic Name	Amlodipine	Felodipine	Nifedipine	Nifedipine XL	Nimodipine
Trade Name	NORVASC	RENEDIL, PLENDIL	generics immediate release	ADALAT XL	NIMOTOP
Dosage Forms	5 mg, 10 mg tablets	2.5 mg, 5 mg, 10 mg extended release tablets Should not be chewed or crushed	5 mg, 10 mg capsules	20 mg, 30 mg, 60 mg extended release tablets Should not be chewed or crushed	30 mg capsules
Dosing (usual)	Hypertension - initial dose: 5 mg once daily - maximum dose: 10 mg once daily Stable Angina 5-10 mg once daily	Hypertension - initial dose: 2.5-5 mg once daily - maximum dose: 10 mg once daily	Stable Angina & Coronary Spasm: - initial dose: 10 mg tid - maximum dose: 120-180 mg/day	Hypertension - initial dose: 20-30 mg once daily - maximum dose: 90 mg once daily Stable Angina - initial dose: 30 mg once daily - maximum dose: 90 mg once daily	Subarachnoid Hemorrhage (SAH) - usual dose: 60 mg q4h x 21 days after diagnosis of SAH (start therapy within 96 hours of SAH)
Dosage Adjustment	Renal dysfunction: no adjustment Hepatic dysfunction: consider 2.5 mg as initial daily dose for hypertension and 5 mg as initial daily dose for angina	Renal dysfunction: no adjustment Hepatic dysfunction: consider 2.5 mg as initial daily dose	Renal dysfunction: no adjustment Hepatic dysfunction: consider reducing dose by 50-60% in cirrhosis	Renal dysfunction: no adjustment Hepatic dysfunction: 30 mg q4h	Renal dysfunction: no adjustment Hepatic dysfunction: 30 mg q4h

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Generic Name	Amlodipine	Felodipine	Nifedipine	Nifedipine XL	Nimodipine
Special Considerations	<p>Use with caution:</p> <ul style="list-style-type: none"> • in severe aortic stenosis • in hypertrophic cardiomyopathy with outflow tract obstruction 	<p>Use with caution:</p> <ul style="list-style-type: none"> • in severe aortic stenosis • in hypertrophic cardiomyopathy with outflow tract obstruction 	<p>Avoid:</p> <ul style="list-style-type: none"> • in left ventricular dysfunction • immediate release formulation for acute blood pressure reduction or management of myocardial infarction <p>Use with caution:</p> <ul style="list-style-type: none"> • in severe aortic stenosis • in hypertrophic cardiomyopathy with outflow tract obstruction • extended release formulation in patients with known stricture/narrowing of the GI tract - obstruction may occur 		
Bioavailability	60-65% May be taken with or without food	20% Should be taken on an empty stomach	45-75% Rapidly absorbed if administered without food, but may result in vasodilator side effects	86% May be taken with or without food	13% Should be taken on an empty stomach
Onset of Action	6 hours	2-5 hours	20 minutes	2 hours	Peak blood level: 1.5 h
Half-Life	35-50 hours	11-16 hours	2-5 hours	10 hours	8-9 hours
Metabolism/ Elimination	Hepatic: (>90%) via CYP3A4 Inactive metabolites 60% renal 20-25% feces	Hepatic: (major) via CYP 3A4 Intestinal wall (minor) Inactive metabolites 37% renal 10% feces	Hepatic: (extensive) via CYP 3A4 (major), 2D6 (minor) Inactive metabolites 70-80% renal 20% bile/feces		Hepatic: (extensive) via CYP 3A4 Inactive metabolites 80% bile 20% renal

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Generic Name	Amlodipine	Felodipine	Nifedipine	Nifedipine XL	Nimodipine
Drug Interactions^a	↑ cyclosporine levels <u>↑ amlodipine level:</u> grapefruit juice, azole antifungals, erythromycin and other CYP 3A4 inhibitors <u>↓ amlodipine level:</u> rifampin	↓ theophylline action <u>↑ felodipine level:</u> cyclosporine, grapefruit juice, azole antifungals, erythromycin and other CYP 3A4 inhibitors <u>↓ felodipine level:</u> rifampin, carbamazepine	↑ digoxin, phenytoin, theophylline levels ↓ quinidine levels <u>↑ nifedipine level:</u> grapefruit juice, azole antifungals, erythromycin and other CYP 3A4 inhibitors, H ₂ -blockers <u>↓ nifedipine level:</u> rifampin, phenobarbital	may potentiate anti-hypertensive effects of other calcium channel blockers, beta-blockers, or methyl dopa <u>↑ nimodipine level:</u> omeprazole, grapefruit juice, azole antifungals, erythromycin and other CYP 3A4 inhibitors, valproic acid, cimetidine <u>↓ nimodipine level:</u> rifampin	
Unit Cost[*]	\$0.24/5 mg \$0.36/10 mg	\$0.52/ 2.5 mg \$0.56/5 mg \$0.84/10 mg	\$0.37/5 mg \$0.49/10 mg	\$1.27/20 mg \$0.62/30 mg \$0.94/60 mg	\$10.08/30 mg
30 day[#] Patient cost	\$15.60 (5 mg daily) \$11.70 (10 mg daily)	\$17 (2.5 mg daily) \$18 (5 mg daily) \$27 (10 mg)	\$36 (5 mg tid) \$48 (10 mg tid)	\$41.40 (20 mg daily) \$20.10 (30 mg daily) \$30.50 (60 mg daily)	\$ 457 (60 mg every 4 hours for 21 days)
ODB^b	Yes	Yes	Yes	Yes	Yes
MSH^c	Yes	No	Yes	Yes	No
UHN^c	Yes	Yes	Yes	Yes	Yes

* List prices from the Ontario Drug Benefit (ODB) Formulary, Ontario Ministry of Health. Last Updated: 01/04/2011 Version 2.2. All prices represent the generic medication option. IV prices come from distributor database.

30 day patient costs represented by ODB generic price + 8% markup. These prices do not include a dispensing fee, which can range from 4.99 – 11.99. Pricing is based on a typical dosing regimen.

a - Clinically important pharmacokinetic drug interactions; not meant to be all-inclusive. Refer to additional references for more detail.

b - ODB - indicates an item on the Ontario Drug Benefit (ODB) Formulary

c - MSH - indicates an item on the Mount Sinai Hospital Formulary; UHN - indicates an item on the University Hospital Network Formulary

Cardiovascular Drugs

CALCIUM CHANNEL BLOCKING AGENTS - *BENZOTHAZEPINES*

Generic Name	Diltiazem	Diltiazem CD	Diltiazem ER	Diltiazem XC	Diltiazem IV
Trade Name	generics immediate release	CARDIZEM CD	TIAZAC	TIAZAC XC	generics
Dosage Forms	30 mg, 60 mg tablets	120 mg, 180 mg, 240 mg, 300 mg controlled delivery capsules Should not be chewed or crushed	120 mg, 180 mg, 240 mg, 300 mg, 360 mg extended release capsules Should not be chewed or crushed	120 mg, 180 mg, 240 mg, 300 mg, 360 mg extended release tablets Should not be chewed or crushed	25 mg/5 mL, 50 mg/10 mL vials
Dosing (usual)	Chronic Stable or Vasospastic Angina - initial dose: 30 mg qid - maximum dose: 360 mg daily	Hypertension - initial dose: 120-240 mg once daily - maximum dose: 360 mg once daily Stable Angina - initial dose: 120-180 mg once daily - maximum dose: 360 mg once daily	Hypertension - initial dose: 120-240 mg once daily - maximum dose: 360 mg once daily Stable Angina - initial dose: 120-180 mg once daily - maximum dose: 360 mg once daily	Hypertension - initial dose: 180-240 mg qhs - maximum dose: 360 mg qhs Stable Angina - initial dose: 180 mg qhs - maximum dose: 360 mg qhs	Atrial Fibrillation/ Flutter or PSVT* BOLUS: 0.25 mg/kg over 2 min, then 2 nd bolus: 0.35 mg/kg over 2 min prn CONTINUOUS INFUSION: - initial rate of 5-10 mg/h - maximum rate 15 mg/h (infusion >24 h not recommended)
Dosage Adjustment	Renal dysfunction: no adjustment Hepatic dysfunction: consider dose reduction				Use with caution in hepatic dysfunction
Special Considerations	Avoid in: • left ventricular dysfunction • atrial fibrillation or flutter associated with accessory bypass tract (e.g. Wolff-Parkinson-White syndrome) • ventricular tachycardia				
Bioavailability	40-67% Should be taken before meals	40% May be taken with or without food	40% May be taken with or without food	2.5-16% over the first 6 hours May be taken with or without food	100%
Onset of Action	30 minutes	<60 minutes	<60 minutes	Peak blood level: 11-18 hours	3-7 minutes

Cardiovascular Drugs

CALCIUM CHANNEL BLOCKING AGENTS - *BENZOTHIAZEPINES*

Generic Name	Diltiazem	Diltiazem CD	Diltiazem ER	Diltiazem XC	Diltiazem IV
Half-Life	3.5-6 hours	5-8 hours	4-9.5 hours	6-9 hours	3.4-4.9 hours
Metabolism/ Elimination	Active metabolites: desacetyl-diltiazem (25-50% as potent as diltiazem) Hepatic: (extensive) via deacetylation, conjugation, CYP 3A4 (major), 2C8/9, 2D6 35% renal 60-65% feces				
Drug Interactions^a	↑ midazolam, carbamazepine, cyclosporine, digoxin, HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin), lithium, quinidine, tacrolimus levels ↑ <u>diltiazem level</u> : azole antifungals, erythromycin and other CYP 3A4 inhibitors ↓ <u>diltiazem level</u> : rifampin, phenytoin, carbamazepine				
Unit Cost[*]	\$0.19/30 mg \$0.33/60 mg	\$0.36/120 mg \$0.48/180 mg \$0.64/240 mg \$0.80/300 mg	\$0.21/120 mg \$0.29/180 mg \$0.38/240 mg \$0.47/300 mg \$0.58/360 mg	\$0.84/120 mg \$1.11/180 mg \$1.47/240 mg \$1.47/300 mg \$1.47/360 mg	\$23.46 (10ml vial) \$12.65 (5ml vial)
30 day[#] Patient Cost	\$24.60 (30 mg four times a day) \$21.40 (60 mg four times a day)	\$11.70 (120 mg daily) \$15.60 (180 mg daily) \$20.70 (240 mg daily) \$25.90 (300 mg daily)	\$6.80 (120 mg daily) \$9.40 (180 mg daily) \$12.30 (240 mg daily) \$15.20 (300 mg daily) \$18.80 (360 mg daily)	\$36 (120 mg daily) \$47.60 (all other doses daily)	
ODB^b	Yes	Yes	Yes	Yes	No
MSH^c	Yes	Yes	Yes	No	Yes
UHN^c	Yes	Yes	No	No	Yes

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Cardiovascular Drugs

CALCIUM CHANNEL BLOCKING AGENTS - *BENZOTHIAZEPINES*

Cardiovascular Drugs

CALCIUM CHANNEL BLOCKING AGENTS - PHENYLALKYLAMINES

Generic Name	Verapamil	Verapamil SR	Verapamil IV
Trade Name	generics	ISOPTIN SR	generics
Dosage Forms	80 mg, 120 mg tablets	120 mg, 180 mg, 240 mg sustained release tablets May be halved, but should not be chewed or crushed	5 mg/2 mL ampoule
Dosing (usual)	<p>Hypertension</p> <ul style="list-style-type: none"> - initial dose: 40-80 mg tid - maximum dose: 480 mg daily <p>Stable Angina</p> <ul style="list-style-type: none"> - initial dose: 40-80 mg tid - maximum dose: 480 mg daily <p>Atrial Arrhythmia</p> <p>240-320 mg daily (in 3 or 4 divided doses)</p>	<p>Hypertension</p> <ul style="list-style-type: none"> - initial dose: 120-240 mg daily (divided in 1 or 2 doses) - maximum dose: 480 mg daily 	<p>Atrial Fibrillation/ Flutter or PSVT</p> <p>BOLUS: 0.075-0.15 mg/kg over 2 min, then 2nd bolus of 0.15 mg/kg over 2 min prn</p> <ul style="list-style-type: none"> - maximum total dose: 20 mg
Dosage Adjustment	Renal dysfunction: CrCl <10 mL/min - reduce dose to 50-75% of normal dose Hepatic dysfunction: Reduce dose to 20-50% of normal dose		
Special Considerations	<p>Avoid in:</p> <ul style="list-style-type: none"> • left ventricular dysfunction • atrial fibrillation or flutter associated with accessory bypass tract (e.g. Wolff-Parkinson-White syndrome) • ventricular tachycardia 		
Bioavailability	20-35% May be taken with or without food	20-35% Should be taken with food	100%
Onset of Action	<30 minutes	<30 minutes	1-5 minutes
Half-Life	2.8-7.4 hours (4.5-12 hours with repeat dosing) norverapamil: 6-10 hours	6-9 hours	6 ± 4 hours
Metabolism/ Elimination	<p>Hepatic: (65-80%) via CYP 3A4 (major), 1A2, 2B6, 2C8/9, 2C18, 2E1</p> <p>Active metabolites: norverapamil (20% as potent as verapamil)</p> <p style="margin-left: 40px;">70% renal</p> <p style="margin-left: 40px;">9-16% feces</p>		

Cardiovascular Drugs

CALCIUM CHANNEL BLOCKING AGENTS - PHENYLALKYLAMINES

Generic Name	Verapamil	Verapamil SR	Verapamil IV
Drug Interactions^a	↑ lithium neurotoxicity ↑ midazolam, carbamazepine, cyclosporine, digoxin, atorvastatin, lovastatin, simvastatin, quinidine, tacrolimus, theophylline levels ↑ verapamil level: grapefruit juice, azole antifungals, erythromycin and other CYP 3A4 inhibitors ↓ verapamil level: rifampin, phenobarbital		
Unit Cost[*]	\$0.27/80 mg \$0.43/120 mg	\$0.52/180 mg \$0.51/240 mg	\$40.41 (5 mg/2ml vial) \$38.20 (2.5mg/2ml vial)
30 Day[#] Patient Cost	\$26.20 (80 mg tid) \$41.80 (120 mg tid)	\$16.80 (180 mg daily) \$16.50 (240 mg daily)	
ODB^b	Yes	Yes (180 mg, 240 mg)	No
MSH^c	Yes	Yes	Yes
UHN^c	Yes	Yes	Yes

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Cardiovascular Drugs

CALCIUM CHANNEL BLOCKING AGENTS - OTHER

Generic name	Flunarizine
Trade name	generics
Dosage Form	5 mg capsules
Dosing (usual)	Migraine prophylaxis 5-10 mg qhs
Dosage Adjustment	Renal dysfunction: no adjustment Hepatic dysfunction: consider initiating dose at 5 mg qhs
Special Considerations	Avoid in: <ul style="list-style-type: none">• depression• patients with pre-existing extrapyramidal symptoms Not indicated for treatment of acute migraine attacks
Bioavailability	Good; may be taken with or without food
Onset of Action	Peak blood level: 2-4 hours
Half-Life	18-23 days
Metabolism/ Elimination	Hepatic; <0.2% renal; <6% feces
Drug Interactions^a	↑ carbamazepine levels
Unit Cost[*]	\$0.72/5 mg
30 day Patient cost[#]	\$23.30 (5 mg daily)

Non-formulary status at MSH and UHN

a - Clinically important pharmacokinetic drug interactions; not meant to be all-inclusive. Refer to additional references for more detail.

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30 day patient costs represented by ODB generic price + 8% markup. These prices do not include a dispensing fee, which can range from 4.99 – 11.99. Pricing is based on a typical dosing regimen.

REFERENCES

1. e-CPS [Internet]. Ottawa (ON): Canadian Pharmacists Association [cited 2010 Jul].
2. MICROMEDEX® 1.0 (Healthcare Series), 2010.
3. Lexi-Comp's Drug Information Handbook, 13th Edition. Lacy CF, Armstrong LL, Goldman MP, et al. (eds). Hudson, OH: 2005.
4. www.RxFiles.ca [cited 2010 Jul].

Cardiovascular Drugs

CALCIUM CHANNEL BLOCKING AGENTS - OTHER

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Cardiovascular Drugs

CALCIUM CHANNEL BLOCKING AGENTS - OTHER

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The contents of this Handbook are approved and endorsed by the UHN Cardiovascular Subcommittee of the Pharmacy and Therapeutics Committee.

1. Purpose of the Pharmacotherapy Handbook.

Notice to Healthcare Providers:

The Pharmacotherapy Handbook is intended to be used as a tool to aid in the appropriate prescribing and administration of cardiovascular formulary agents.

This information in this Handbook is intended for use by and with experienced physicians and pharmacists. The information is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about Cardiovascular illness and the treatments in question.

Due to the rapidly changing nature of cardiovascular treatments and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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Your comments on the usefulness of the resources contained in the Handbook are welcomed and may be forwarded to Amita Woods, Department of Pharmacy Services (amita.woods@uhn.ca).