Patient Profile 3: Hypertension in AIS

Patient history and presentation

- 39-year-old male with sudden onset of left-sided weakness and slurred speech
- Symptoms started 2.5 hours prior to ED arrival. Wife witnessed onset
- Brought to the ED by ambulance
- Code Stroke activated by EMS alert from the field; stroke team present prior to ambulance arrival
- Medical history includes:
  - Hypertension
  - Hypercholesterolemia—wife states he refused medication and has been noncompliant with dietary measures
  - Current medication: lisinopril 10 mg; but hasn’t refilled his prescription in 3 months

Abbreviations: AIS, acute ischemic stroke; ED, emergency department; EMS, emergency medical services.

Not an actual patient. Patient symptoms may vary; individual clinical evaluation should be done to determine the best course of therapy.
Patient Profile 3: Hypertension in AIS

Patient history and presentation
- 39-year-old male
- Sudden onset of left-sided weakness and slurred speech witnessed by wife (2.5 hours prior to ED)
- History of hypertension and hypercholesterolemia
- Noncompliant with dietary measures and medication (lisinopril 10 mg)

Initial examinations performed
- ABCD exam performed and BP assessed at ambulance entrance to the ED
- Neurologic exam performed en route to noncontrast CT scan
- Vitals taken

Abbreviations: ABCD, airway, breathing, circulation, and disability; BP, blood pressure; CT, computed tomography; ED, emergency department.

Not an actual patient. Patient symptoms may vary; individual clinical evaluation should be done to determine the best course of therapy.
**Patient Profile 3: Hypertension in AIS**

**Patient history and presentation**
- 39-year-old male
- Sudden onset of left-sided weakness and slurred speech witnessed by wife (2.5 hours prior to ED)
- History of hypertension and hypercholesterolemia
- Noncompliant with dietary measures and medication (lisinopril 10 mg)

**Physical exam results**
- BP=206/98 mm Hg
- MAP=134 mm Hg
- HR=86 bpm, regular
- RR=16 breaths/minute
- Afebrile

**Neurologic exam results**
- Awake, oriented to time, place, person
- Left hemiparesis (face, arm, leg)
- Dysarthria; speech fluent
- Right gaze preference
- Left hemispatial neglect
- NIHSS=12

---

Not an actual patient. Patient symptoms may vary; individual clinical evaluation should be done to determine the best course of therapy.
Patient Profile 3: Hypertension in AIS

Patient history and presentation
- 39-year-old male
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- History of hypertension and hypercholesterolemia
- Noncompliant with dietary measures and medication (lisinopril 10 mg)

Arrival/ABCD exam/BP assessment
Exams/Blood work
CT started
CT interpreted
Decision time

- CT started at 5 minutes
- CT scans use x-rays to take clear, detailed images of the brain
  – Primary method of determining whether a stroke is ischemic or hemorrhagic

Not an actual patient. Patient symptoms may vary; individual clinical evaluation should be done to determine the best course of therapy.
Patient Profile 3: Hypertension in AIS

Patient history and presentation
- 39-year-old male
- Sudden onset of left-sided weakness and slurred speech witnessed by wife (2.5 hours prior to ED)
- History of hypertension and hypercholesterolemia
- Noncompliant with dietary measures and medication (lisinopril 10 mg)

POCT/imaging results
- Glucose=143 mg/dL
- INR=1.1
- Noncontrast CT shows hyperdense right MCA

Abbreviations: INR, international normalized ratio; MCA, middle cerebral artery.

Not an actual patient. Patient symptoms may vary; individual clinical evaluation should be done to determine the best course of therapy.
Patient Profile 3: Hypertension in AIS

Patient history and presentation

- 39-year-old male
- Sudden onset of left-sided weakness and slurred speech witnessed by wife (2.5 hours prior to ED)
- History of hypertension and hypercholesterolemia
- Noncompliant with dietary measures and medication (lisinopril 10 mg)

How would you treat this patient’s acute hypertension?

ASA/AHA Guidelines recommend:

“Because time is critical, fibrinolytic therapy should not be delayed while awaiting the results of the PT, aPTT, or platelet count unless a bleeding abnormality or thrombocytopenia is suspected, the patient has been taking warfarin and heparin, or anticoagulation use is uncertain.”

“Specific blood pressure management recommendations include a gentle approach to bringing the pressure below 185/110 mm Hg to qualify for fibrinolytic therapy with intravenous rtPA.”

“Once intravenous rtPA is given, the blood pressure must be maintained below 180/105 mm Hg to limit the risk of ICH. Higher blood pressures during the initial 24 hours were associated with greater risk of sICH in a linear fashion.”

Abbreviations: aPTT, activated partial thromboplastin time; ICH, intracerebral hemorrhage; PT, prothrombin time; rtPA, recombinant tissue plasminogen activator; sICH, spontaneous intracerebral hemorrhage.

Not an actual patient. Patient symptoms may vary; individual clinical evaluation should be done to determine the best course of therapy.
Patient Profile 3: Hypertension in AIS

Patient history and presentation

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- History of hypertension and hypercholesterolemia
- Noncompliant with dietary measures and medication (lisinopril 10 mg)

BP management is a key component for patients with AIS being considered for tPA therapy

- Door-to-tPA treatment in ≤60 minutes is the standard of care
  - Gently bring BP to ≤185/110 mm Hg to qualify for tPA therapy
  - Maintain BP at ≤180/105 mm Hg after tPA is administered
- “Controlled blood pressure lowering during acute stroke can best be achieved with intravenous antihypertensive therapies. A single optimal medication to lower the blood pressure in all patients with acute stroke has not been determined, and an individualized approach is best”
- Treating emergent elevated BP is a major consideration for improving rapid triage and management of patients

“The Stroke Expert Panel...emphasized the importance of timely management of BP prior to tPA administration…”

—Shulkin et al, 2011

Effective BP intervention may be critical to achieving Golden Hour goals

See next pages for goals

Abbreviation: tPA, tissue plasminogen activator.

Not an actual patient. Patient symptoms may vary; individual clinical evaluation should be done to determine the best course of therapy.
Controlling BP during the Golden Hour may be critical for patients with AIS

Key milestones during the Golden Hour

≤10 minutes
Door-to-medical department
Emergency physician to examine patient within 10 minutes
Controlling BP during the Golden Hour may be critical for patients with AIS

Key milestones during the Golden Hour

≤15 minutes
Door-to-neurologic expertise
Notify/consult the stroke team within 15 minutes"
Controlling BP during the Golden Hour may be critical for patients with AIS

Key milestones during the Golden Hour

≤25 minutes
Door-to-CT scan
Perform CT scan of the head within 25 minutes

1
Controlling BP during the Golden Hour may be critical for patients with AIS

Key milestones during the Golden Hour

≤45 minutes
Door-to-CT interpretation

CT scan to be interpreted by radiology or neurology specialist within 45 minutes in order to determine if the patient has had a stroke, and whether it is categorized as ischemic or hemorrhagic."
Controlling BP during the Golden Hour may be critical for patients with AIS

Key milestones during the Golden Hour

≤60 minutes
Door-to-drug (tPA)

Eligibility for tPA may require BP treatment when deemed appropriate¹
Patient Profile 3: Hypertension in AIS

Patient history and presentation
- 39-year-old male
- Sudden onset of left-sided weakness and slurred speech witnessed by wife (2.5 hours prior to ED)
- History of hypertension and hypercholesterolemia
- Noncompliant with dietary measures and medication (lisinopril 10 mg)

Treatment discussion

1. Which antihypertensive agent do you currently use to treat a patient with a similar presentation?

See next page to compare agents

Not an actual patient. Patient symptoms may vary; individual clinical evaluation should be done to determine the best course of therapy.
<table>
<thead>
<tr>
<th>Medication</th>
<th>Administration</th>
<th>Onset of action</th>
<th>Half-life</th>
<th>Offset of action</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clevidipine³</td>
<td>Initial infusion of 1–2 mg/hr, double dose at short (90 sec) intervals initially; max of 1000 mL or an average of 21 mg/hr recommended over 24 hr</td>
<td>2–4 min</td>
<td>Initial phase half-life: &lt;1 min</td>
<td>5–15 min</td>
<td>3rd generation dihydropyridine calcium channel blocker; arterolar vasodilator</td>
</tr>
<tr>
<td>Esmolol⁴</td>
<td>Immediate Control: 1 mg/kg bolus over 30 sec followed by an infusion of 150 mcg/kg/min if necessary. Adjust rate as required up to 300 mcg/kg/min</td>
<td>Within 2 min</td>
<td>Distribution half-life: 2 min</td>
<td>10–20 min</td>
<td>Cardioslective beta 1-adrenergic antagonist</td>
</tr>
<tr>
<td></td>
<td>Gradual Control: 500 mcg/kg bolus over 1 min followed by maintenance infusion of 50 mcg/kg/min for 4 min</td>
<td></td>
<td>Elimination half-life: &gt;9 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine⁵</td>
<td>20–40 mg IV bolus injection directly into vein; some patients such as those with advanced renal damage may require a lower dose</td>
<td>10–20 min</td>
<td>Not included in package insert</td>
<td>1–4 hr</td>
<td>Vascular smooth muscle vasodilator</td>
</tr>
<tr>
<td>Labetalol⁶</td>
<td>Repeated IV Injection: Initial 20-mg dose by slow IV injection over 2 min</td>
<td>Within 5 min</td>
<td>5.5 hr</td>
<td>3–6 hr</td>
<td>Alpha 1- and nonselective, competitive beta-adrenergic antagonist; alpha to beta blocking ratio is 1:7</td>
</tr>
<tr>
<td></td>
<td>• Additional injections of 40 or 80 mg can be given at 10-min intervals until a desired supine BP is achieved or a total of 300 mg has been injected</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Slow Continuous Infusion:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 1 mg/mL of labetalol infusion solution delivered at a rate of 2 mL/min to deliver 2 mg/min, OR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 2 mg/3 mL labetalol infusion solution at 3 mL/min to deliver 2 mg/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicardipine hydrochloride⁷</td>
<td>Initiate therapy at 5 mg/hr. If desired BP reduction is not achieved at this dose, infusion may be increased by 2.5 mg/hr every 5 min (for rapid titration) to 15 min (for gradual titration) up to max of 15 mg/hr, until desired BP reduction is achieved</td>
<td>Within minutes</td>
<td>α-half-life: 2.7 min</td>
<td>50% offset of action in about 30 min</td>
<td>2nd generation dihydropyridine calcium channel blocker; arterolar vasodilator</td>
</tr>
<tr>
<td>Nitroglycerin⁸</td>
<td>5 mcg/min; may increase by 5 mcg/min every 3–5 min until response noted. If 20 mcg/min is inadequate, increase to 10 and later 20 mcg/min every 3–5 min (max dose: 480 mcg/mL)</td>
<td>2–5 min</td>
<td>β-half-life: 44.8 min</td>
<td>5–10 min</td>
<td>Vascular smooth muscle vasodilator</td>
</tr>
<tr>
<td>Sodium nitroprusside⁹</td>
<td>Initial dose of 0.3 mcg/kg/min; upward titration every few minutes until desired effect achieved or max infusion rate (10 mcg/kg/min) reached</td>
<td>Within seconds</td>
<td>2 min</td>
<td>1–2 min</td>
<td>Vascular smooth muscle vasodilator</td>
</tr>
</tbody>
</table>
Patient Profile 3: Hypertension in AIS

Patient history and presentation
- 39-year-old male
- Sudden onset of left-sided weakness and slurred speech witnessed by wife (2.5 hours prior to ED)
- History of hypertension and hypercholesterolemia
- Noncompliant with dietary measures and medication (lisinopril 10 mg)

Treatment discussion

1. Which antihypertensive agent do you currently use to treat a patient with a similar presentation?

2. What are the 3 most important characteristics of an antihypertensive agent in this clinical setting?

See next page to review characteristics

Not an actual patient. Patient symptoms may vary; individual clinical evaluation should be done to determine the best course of therapy.
Patient Profile 3: Hypertension in AIS

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Treatment discussion

1. Which antihypertensive agent do you currently use to treat a patient with a similar presentation?

2. What are the 3 most important characteristics of an antihypertensive agent in this clinical setting?

   A. Onset of action
   B. Offset of action
   C. Immediately available at point of care
   D. Safety
   E. Efficacy
   F. Cost
   G. Titratability
   H. Predictable BP response

Not an actual patient. Patient symptoms may vary; individual clinical evaluation should be done to determine the best course of therapy.
Patient Profile 3: Hypertension in AIS

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1. Which antihypertensive agent do you currently use to treat a patient with a similar presentation?

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   A. Onset of action
   B. Offset of action
   C. Immediately available at point of care
   D. Safety
   E. Efficacy
   F. Cost
   G. Titratability
   H. Predictable BP response

3. When treating acute hypertension in a patient with this profile, do you consider drug MOA?

Review BP equation on the next page

Not an actual patient. Patient symptoms may vary; individual clinical evaluation should be done to determine the best course of therapy.
The blood pressure equation

Acute hypertensive emergencies may result from an abrupt increase in SVR\(^{10,11}\)

\[
BP = CO \times SVR
\]

- blood pressure
- cardiac output
  - stroke volume \(SV\)
  - heart rate \(HR\)
- systemic vascular resistance

Selected Medications and the Blood Pressure Equation\(^{10,12}\)

- Esmolol\(^{4,13-15}\)
- Nicardipine hydrochloride\(^{7}\)
- Clevidipine\(^{3,16}\)
- Nitroprusside\(^{9,17,18}\)
- Hydralazine\(^{5}\)
- Labetalol\(^{6,21,22}\)
- Nitroglycerin\(^{6,19,20}\)
Would you consider treating this patient’s hypertension with CARDENE® I.V. (nicardipine hydrochloride)?

CARDENE I.V. is not indicated for the treatment or prevention of AIS, ICH, or aSAH

**Indication**
CARDENE® I.V. (nicardipine hydrochloride) Premixed Injection is indicated for the short-term treatment of hypertension when oral therapy is not feasible or not desirable. For prolonged control of blood pressure, transfer patients to oral medication as soon as their clinical condition permits.

**Safety Information**
CARDENE I.V. is contraindicated in patients with advanced aortic stenosis.

Please see Important Safety Information. For more information, visit [www.cardeneiv.com](http://www.cardeneiv.com).
Delivers smooth, predictable BP control

Rapid BP reduction in patients with AIS, ICH, and aSAH—control maintained over 24 hours

- 89% of patients achieved SBP goals within 60 minutes
- ≤1 dose adjustment* needed to reach BP goal
- No rescue therapy required during 24 hours

**CARDENE I.V. (nicardipine hydrochloride) is not indicated for the treatment of AIS, ICH, or aSAH**

A prospective study of patients who presented to the ED with primary AIS (n=9), ICH (n=16), or aSAH (n=1) and received CARDENE I.V. for 24 hours. CARDENE I.V. was administered at 5 mg/hr and increased every 15 minutes by 2.5 mg/hr until target SBP range was reached or a maximum of 15 mg/hr was achieved. Blood pressure goals were defined using current consensus recommendations. Vital signs (BP and HR) were taken every 15 minutes until goal BP was achieved. Initial SBP was 215 mm Hg.**

*Median.

Safety Information

Slow titration of CARDENE I.V. is recommended in patients with heart failure or significant left ventricular dysfunction, particularly in combination with a beta-blocker.

Please see Important Safety Information.
**Dosing**

<table>
<thead>
<tr>
<th>For Rapid Titration</th>
<th>For Gradual Titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiate at 5 mg/hr*</td>
<td>Initiate at 5 mg/hr*</td>
</tr>
<tr>
<td>If necessary, may increase by 2.5 mg/hr to a maximum dose of 15 mg/hr</td>
<td>If necessary, may increase by 2.5 mg/hr to a maximum dose of 15 mg/hr</td>
</tr>
<tr>
<td>Titrate q 5 min†</td>
<td>Titrate q 15 min</td>
</tr>
<tr>
<td>Adjust infusion rate as needed to maintain desired response</td>
<td>Adjust infusion rate as needed to maintain desired response</td>
</tr>
</tbody>
</table>

*Dosage for initiation of therapy in a patient not receiving oral nicardipine.
†Following achievement of BP goal, decrease infusion rate to 3 mg/hr.

**Safety Information**

Close monitoring of response to CARDENE I.V. is advised in patients with angina, heart failure, impaired hepatic function, or renal impairment.

Please see Important Safety Information. For more information, visit www.cardeneiv.com.
Ready-to-use CARDENE® I.V. (nicardipine hydrochloride) benefits

The *only* available FDA-approved premixed formulation of nicardipine hydrochloride

- Rapid, precise BP control with onset of effect in minutes
- Arteriolar-specific vasodilation decreases SVR
- Increases cardiac output — Coronary steal has not been observed
- Not associated with bradycardia or rebound hypertension
- An alternative to sodium nitroprusside with fewer dose adjustments and low rates of hypotension
- No soy or egg allergens
- Lipid-free formulation

Safety Information
Close monitoring of response to CARDENE I.V. is advised in patients with angina, heart failure, impaired hepatic function, or renal impairment.

Please see Important Safety Information. For more information, visit [www.cardeneiv.com](http://www.cardeneiv.com).
Ready-to-use CARDENE® I.V. (nicardipine hydrochloride) benefits

The only available FDA-approved premixed formulation of nicardipine hydrochloride

- Immediately available for rapid intervention
  - Guaranteed stability for 24 months under appropriate storage conditions
  - Admixed generic nicardipine hydrochloride IV is guaranteed stable for only 24 hours under appropriate storage conditions
- Minimizes medication admixture errors
- Can be stored at point of care
- Supports The Joint Commission, American Society of Health-System Pharmacists, and Institute for Safe Medication Practices recommendations for the use of ready-to-use medications
- Ready-to-use bags save time and labor

Safety Information
Close monitoring of response to CARDENE I.V. is advised in patients with angina, heart failure, impaired hepatic function, or renal impairment.

Please see Important Safety Information. For more information, visit www.cardeneiv.com.
CARDENE® I.V. (nicardipine hydrochloride) Premixed Injection

Indication
CARDENE® I.V. (nicardipine hydrochloride) Premixed Injection is indicated for the short-term treatment of hypertension when oral therapy is not feasible or not desirable. For prolonged control of blood pressure, transfer patients to oral medication as soon as their clinical condition permits.

Important Safety Information
CARDENE I.V. is contraindicated in patients with advanced aortic stenosis.

Hypotension and reflex tachycardia may potentially occur during treatment with CARDENE I.V.; therefore, close monitoring of blood pressure and heart rate is required. If unacceptable hypotension or tachycardia occurs, the infusion should be discontinued.

Slow titration of CARDENE I.V. is recommended in patients with heart failure or significant left ventricular dysfunction, particularly in combination with a beta-blocker.

Close monitoring of response to CARDENE I.V. is advised in patients with angina, heart failure, impaired hepatic function, or renal impairment.

CARDENE I.V. may elevate serum concentrations of cyclosporine or tacrolimus. Serum concentrations of cyclosporine or tacrolimus should be monitored during coadministration with CARDENE I.V.

To reduce the possibility of venous thrombosis, phlebitis, local irritation, and extravasation, administer CARDENE I.V. through large peripheral veins or central veins rather than arteries or small peripheral veins. If CARDENE I.V. is administered in a peripheral vein, to minimize the risk of venous irritation, change the site of infusion every 12 hours.

The most common adverse reactions (>3%) are headache, nausea/vomiting, hypotension, and tachycardia.

Please see full prescribing information. For more information, visit www.cardeneiv.com.
**Indication**
CLEVIPREX® (clevidipine) injectable emulsion is a dihydropyridine calcium channel blocker indicated for the reduction of blood pressure when oral therapy is not feasible or not desirable.

**Important Safety Information**
CLEVIPREX is contraindicated in patients with:

- Allergies to soybeans, soy products, eggs, or egg products;
- Defective lipid metabolism seen in conditions such as pathologic hyperlipemia, lipoid nephrosis, or acute pancreatitis if it is accompanied by hyperlipidemia; and
- Severe aortic stenosis.

CLEVIPREX is intended for intravenous use. Use aseptic technique and discard any unused product within 12 hours of stopper puncture.

Hypotension and reflex tachycardia are potential consequences of rapid upward titration of CLEVIPREX. If either occurs, decrease the dose of CLEVIPREX. There is limited experience with short-duration therapy with beta-blockers as a treatment for CLEVIPREX-induced tachycardia. Beta-blocker use for this purpose is not recommended.

CLEVIPREX contains approximately 0.2 g of lipid per mL (2.0 kcal). Lipid intake restrictions may be necessary for patients with significant disorders of lipid metabolism.

Dihydropyridine calcium channel blockers can produce negative inotropic effects and exacerbate heart failure. Monitor heart failure patients carefully.

CLEVIPREX is not a beta-blocker, does not reduce heart rate, and gives no protection against the effects of abrupt beta-blocker withdrawal. Beta-blockers should be withdrawn only after a gradual reduction in dose.

Patients who receive prolonged CLEVIPREX infusions and are not transitioned to other antihypertensive therapies should be monitored for the possibility of rebound hypertension for at least 8 hours after the infusion is stopped.

There is no information to guide use of CLEVIPREX in treating hypertension associated with pheochromocytoma.

Most common adverse reactions for CLEVIPREX (>2%) are headache, nausea, and vomiting.

Please see full prescribing information. For more information, visit www.cleviprex.com.
References

CARDENE IV (nicardipine hydrochloride) premixed injection for intravenous use

Initial U.S. Approval: 1988

INDICATIONS AND USAGE

- Cardene I.V. Premixed Injection is a calcium channel blocker indicated for the short-term treatment of hypertension when oral therapy is not feasible.

DOSAGE AND ADMINISTRATION

- For Intravenous Use.
- No further dilution is required.
- When substituting for oral nicardipine therapy, use the intravenous infusion rate from the table below (2.1):

<table>
<thead>
<tr>
<th>Oral Cardene Dose</th>
<th>Equivalent I.V. Infusion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg q8h</td>
<td>0.5 mg/hr = 5 mL/hr</td>
</tr>
<tr>
<td>30 mg q8h</td>
<td>1.2 mg/hr = 12 mL/hr</td>
</tr>
<tr>
<td>40 mg q8h</td>
<td>2.2 mg/hr = 22 mL/hr</td>
</tr>
</tbody>
</table>

- In a patient not receiving oral nicardipine, initiate therapy at 50 mL/hr (5 mg/hr). Increase the infusion rate by 25 mL/hr every 5 minutes (for rapid titration) to 15 minutes (for gradual titration) up to a maximum of 150 mL/hr until desired blood pressure reduction is achieved. (2.1)
- If unacceptable hypotension or tachycardia occurs, discontinue the infusion. When blood pressure and heart rate stabilize, restart the infusion at low doses such as 30-50 mL/hr. (2.2)

DOSAGE FORMS AND STRENGTHS

Cardene I.V. Premixed Injection is supplied as a single-use, ready-to-use, iso-osmotic solution for intravenous administration in a 200 mL GALAXY container with 20 mg (0.1 mg/mL) nicardipine hydrochloride in either dextrose or sodium chloride.

CONTRAINDICATIONS

- Do not use in patients with advanced aortic stenosis (4.1).

WARNINGS AND PRECAUTIONS

- Closely monitor response in patients with angina (5.2), heart failure (5.3), impaired hepatic function (5.4), or renal impairment. (5.5)
- To reduce the possibility of venous thrombosis, phlebitis, and vascular impairment, do not use small veins, such as those on the dorsum of the hand or wrist. Exercise extreme care to avoid intra-arterial administration or extravasation. (5.6)
- To minimize the risk of peripheral venous irritation, change the site of infusion of Cardene I.V. Premixed Injection every 12 hours. (5.6)

ADVERSE REACTIONS

Most common adverse reactions are headache (15%), hypotension (6%), tachycardia (4%) and nausea/vomiting (5%). (6.1)

DRUG INTERACTIONS

- Cimetidine increases oral nicardipine plasma levels. (7.2)
- Oral or intravenous nicardipine may increase cyclosporine and tacrolimus plasma levels. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended when co-administering Cardene I.V. Premixed Injection. (7.3, 7.4)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data may cause fetal harm. (8.1)
- Nursing mothers: Minimally excreted into human milk. (8.3)
- Safety and efficacy in patients under the age of 18 have not been established. (8.4)

Revised: 08/2016

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3. DOSAGE FORMS AND STRENGTHS
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   - 16.1 How Supplied
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FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1 Hypertension

Cardene® I.V. (nicardipine hydrochloride) Premixed Injection is indicated for the short-term treatment of hypertension when oral therapy is not feasible or not desirable. For prolonged control of blood pressure, transfer patients to oral medication as soon as their clinical condition permits [see Dosage and Administration (2.1)].

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

Cardene I.V. is intended for intravenous use. Titrate dose to achieve the desired blood pressure reduction. Individualize dosage depending on the blood pressure to be obtained and the response of the patient.

Dosage as a Substitute for Oral Nicardipine Therapy

The intravenous infusion rate required to produce an average plasma concentration equivalent to a given oral dose at steady state is shown in the following table:

<table>
<thead>
<tr>
<th>Oral Cardene Dose</th>
<th>Equivalent I.V. Infusion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg q8h</td>
<td>0.5 mg/hr = 5 mL/hr</td>
</tr>
<tr>
<td>30 mg q8h</td>
<td>1.2 mg/hr = 12 mL/hr</td>
</tr>
<tr>
<td>40 mg q8h</td>
<td>2.2 mg/hr = 22 mL/hr</td>
</tr>
</tbody>
</table>

Dosage for Initiation of Therapy in a Patient Not Receiving Oral Nicardipine

Initiate therapy at 50 mL/hr (5 mg/hr). If desired blood pressure reduction is not achieved at this dose, the infusion rate may be increased by 25 mL/hr (2.5 mg/hr) every 5 minutes (for rapid titration) to 15 minutes (for gradual titration) up to a maximum of 150 mL/hr (15 mg/hr), until desired blood pressure reduction is achieved.

Following achievement of the blood pressure goal utilizing rapid titration, decrease the infusion rate to 30 mL/hr (3 mg/hr).

Drug Discontinuation and Transition to an Oral Antihypertensive Agent

Discontinuation of infusion is followed by a 50% offset of action in about 30 minutes. If treatment includes transfer to an oral antihypertensive agent other than oral nicardipine, initiate therapy upon discontinuation of Cardene I.V. Premixed Injection.

If oral nicardipine is to be used, administer the first dose 1 hour prior to discontinuation of the infusion.

Special Populations

Titrate Cardene I.V. Premixed Injection slowly in patients with heart failure or impaired hepatic or renal function [see Warnings and Precautions (5.3, 5.4 and 5.5)]

2.2 Monitoring

The time course of blood pressure decrease is dependent on the initial rate of infusion and the frequency of dosage adjustment. With constant infusion, blood pressure begins to fall within minutes. It reaches about 50% of its ultimate decrease in about 45 minutes.

Monitor blood pressure and heart rate continually during infusion and avoid too rapid or excessive blood pressure drop during treatment. If there is concern of impending hypotension or tachycardia, the infusion should be discontinued. Then, when blood pressure has stabilized, infusion of Cardene I.V. Premixed Injection may be restarted at low doses such as 30-50 mL/hr (3 - 5 mg/hr) and adjusted to maintain desired blood pressure.

2.3 Instructions for Administration

Administer Cardene I.V. by a central line or through a large peripheral vein. Change the infusion site every 12 hours if administered via peripheral vein [see Intravenous Infusion Site (5.6)].

Cardene I.V. Premixed Injection is available as a single-use, ready-to-use, iso-osmotic solution for intravenous administration. No further dilution is required.

Inspect Cardene I.V. Premixed Injection visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Check the container for minute leaks prior to use by squeezing the bag firmly; ensure that the seal is intact. If leaks are found, discard solution as sterility may be impaired. Cardene I.V. Premixed Injection is normally a clear, colorless to yellow solution.

Do not combine Cardene I.V. Premixed Injection with any product in the same intravenous line or premixed container. Do not add supplementary medication to the bag. Protect from light until ready to use.

Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before the administration of the fluid from the secondary container is complete.

Preparation for administration

1. Suspend container from eyelet support.
2. Remove protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

3. DOSAGE FORMS AND STRENGTHS

Cardene I.V. Premixed Injection is supplied as a single-use, ready-to-use, iso-osmotic solution for intravenous administration in a 200 mL GALAXY container with 20 mg (0.1 mg/mL) nicardipine hydrochloride in either dextrose or sodium chloride.

4. CONTRAINDICATIONS

4.1 Advanced Aortic Stenosis

Cardene I.V. Premixed Injection is contraindicated in patients with advanced aortic stenosis because part of the effect of Cardene I.V. Premixed Injection is secondary to reduced afterload. Reduction of diastolic pressure in these patients may worsen rather than improve myocardial oxygen balance.

5. WARNINGS AND PRECAUTIONS

5.1 Excessive Pharmacodynamic Effects

In administering nicardipine, close monitoring of blood pressure and heart rate is required. Nicardipine may occasionally produce symptomatic hypotension or tachycardia. Avoid systemic hypotension when administering the drug to patients who have sustained an acute cerebral infarction or hemorrhage.

5.2 Use in Patients with Angina

Increases in frequency, duration, or severity of angina have been seen in chronic therapy with oral nicardipine. Induction or exacerbation of angina has been seen in less than 1% of coronary artery disease patients treated with Cardene I.V. The mechanism of this effect has not been established.

5.3 Use in Patients with Heart Failure

Titrates slowly when using Cardene I.V. Premixed Injection, particularly in combination with a beta-blocker, in patients with heart failure or significant left ventricular dysfunction because of possible negative inotropic effects.

5.4 Use in Patients with Impaired Hepatic Function

Since nicardipine is metabolized in the liver, consider lower doses and closely monitor responses in patients with impaired liver function or reduced hepatic blood flow.

5.5 Use in Patients with Impaired Renal Function

When Cardene I.V. was given to mild to moderate hypertensive patients with moderate renal impairment, a significantly lower systemic clearance and higher area under the curve (AUC) was observed. These results are consistent with those seen after oral administration of nicardipine. Titrate gradually in patients with renal impairment.

5.6 Intravenous Infusion Site

To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, extravasation, and the occurrence of vascular impairment, administer drug through large peripheral veins or central veins rather than arteries or small peripheral veins, such as those on the dorsum of the hand or wrist. To minimize the risk of peripheral venous irritation, change the site of the drug infusion every 12 hours.

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Two hundred forty-four patients participated in two multicenter, double-blind, placebo-controlled trials of Cardene I.V. Adverse experiences were generally not serious and most were expected consequences of vasodilation. Adverse experiences occasionally include...
required dosage adjustment. Therapy was discontinued in approximately 12% of patients, mainly due to hypotension, headache, and tachycardia. The table below shows percentage of patients with adverse events where the rate is >3% more common on Cardene I.V. than placebo.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Cardene I.V. (N=144)</th>
<th>Placebo (N=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache, n (%)</td>
<td>21 (15)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension, n (%)</td>
<td>8 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Tachycardia, n (%)</td>
<td>5 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Digestive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea/Vomiting, n (%)</td>
<td>7 (5)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Other adverse events have been reported in clinical trials or in the literature in association with the use of intravenously administered nicardipine:

- **Body as a Whole**: fever, neck pain
- **Cardiovascular**: angina pectoris, atrioventricular block, ST segment depression, inverted T wave, deep-vein thrombophlebitis
- **Digestive**: dyspepsia
- **Hemic and Lymphatic**: thrombocytopenia
- **Metabolic and Nutritional**: hypophosphatemia, peripheral edema
- **Nervous**: confusion, hypotension
- **Respiratory**: respiratory disorder
- **Special Senses**: conjunctivitis, ear disorder, tinnitus
- **Urogenital**: urinary frequency

*Sinus node dysfunction and myocardial infarction, which may be due to disease progression, have been seen in patients on chronic therapy with orally administered nicardipine.*

### 6.2 Post-Marketing and Other Clinical Experience

Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or to establish a causal relationship to drug exposure. The following adverse reaction has been identified during post-approval use of Cardene I.V.: decreased oxygen saturation (possible pulmonary shunting).

### 7. DRUG INTERACTIONS

#### 7.1 Beta-Blockers

In most patients, Cardene I.V. Premixed Injection can safely be used concomitantly with beta blockers. However, titrate slowly when using Cardene I.V. Premixed Injection in combination with a beta-blocker in heart failure patients (see Warnings and Precautions (5.3)).

#### 7.2 Cimetidine

Cimetidine has been shown to increase nicardipine plasma concentrations with oral nicardipine administration. Frequently monitor response in patients receiving both drugs. Data with other histamine-2 antagonists are not available.

#### 7.3 Cyclosporine

Concomitant administration of oral or intravenous nicardipine and cyclosporine results in elevated plasma cyclosporine levels through nicardipine inhibition of hepatic microsomal enzymes, including CYP3A4. Closely monitor plasma concentrations of cyclosporine during Cardene I.V. Premixed Injection administration, and reduce the dose of cyclosporine accordingly.

#### 7.4 Tacrolimus

Concomitant administration of intravenous nicardipine and tacrolimus may result in elevated plasma tacrolimus levels through nicardipine inhibition of hepatic microsomal enzymes, including CYP3A4. Closely monitor plasma concentrations of tacrolimus during Cardene I.V. Premixed Injection administration, and adjust the dose of tacrolimus accordingly.

### 7.5 In Vitro Interaction

The plasma protein binding of nicardipine was not altered when therapeutic concentrations of furosemide, propranolol, dipyridamole, warfarin, quinidine, or naproxen were added to human plasma in vitro.

### 8. USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of nicardipine use in pregnant women. However, limited human data in pregnant women with preeclampsia or pre-term labor are available. In animal studies, no embryotoxicity occurred in rats at oral doses of 8 times the maximum recommended human dose (MRHD) based on body surface area (mg/m²), but did occur in rabbits with oral doses at 24 times the maximum recommended human dose (MRHD) based on body surface area (mg/m²). Cardene I.V. should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Hypotension, reflex tachycardia, postpartum hemorrhage, tocolysis, headache, nausea, dizziness, and flushing have been reported in pregnant women who were treated with intravenous nicardipine for hypertension during pregnancy. Fetal safety results ranged from transient fetal heart rate decelerations to no adverse events. Neonatal safety data ranged from hypotension to no adverse events. Adverse events in women treated with intravenous nicardipine during pre-term labor include pulmonary edema, dyspnea, hypoxia, hypotension, tachycardia, headache, and phlebitis at site of injection. Neonatal adverse events include acidosis (pH<7.25).

In embryofetal toxicity studies, nicardipine was administered intravenously to pregnant rats and rabbits during organogenesis at doses up to 0.14 times the MRHD based on body surface area (mg/m²) (5 mg/kg/day) (rats) and 0.03 times the MRHD based on body surface area (mg/m²) (0.5 mg/kg/day) (rabbits). No embryotoxicity or teratogenicity was seen at these doses. Embryotoxicity, but no teratogenicity was seen at 0.27 times the MRHD based on body surface area (mg/m²) (10 mg/kg/day) in rats and at 0.05 times the MRHD based on body surface area are (mg/m²) (1 mg/kg/day) in rabbits.

In other animal studies, pregnant Japanese White rabbits received oral nicardipine during organogenesis, at doses 8 and 24 times the MRHD based on body surface area (mg/m²) (50 and 150 mg/kg/day). Embryotoxicity occurred at the high dose along with signs of maternal toxicity (marked maternal weight gain suppression). New Zealand albino rabbits received oral nicardipine during organogenesis, at doses up to 16 times the MRHD based on body surface area (mg/m²) (100 mg nicardipine/kg/day). While significant maternal mortality occurred, no adverse effects on the fetus were observed. Pregnant rats received oral nicardipine from day 6 through day 15 of gestation at doses up to 8 times the MRHD based on body surface area (mg/m²) (100 mg/kg/day). There was no evidence of embryotoxicity or teratogenicity; however, dystocia, reduced birth weights, reduced neonatal survival, and reduced neonatal weight gain were noted.

#### 8.3 Nursing Mothers

Nicardipine is minimally excreted into human milk. Among 18 infants exposed to nicardipine through breast milk in the postpartum period, calculated daily infant dose was less than 0.3 mcg and there were no adverse events observed. Consider the possibility of infant exposure when using nicardipine in nursing mothers.

In a study of 11 women who received oral nicardipine 4 to 14 days postpartum, 4 women received immediate-release nicardipine 40 to 80 mg daily, 6 received sustained-release nicardipine 100 to 150 mg daily, and one received intravenous nicardipine 120 mg daily. The peak milk concentration was 7.3 mcg/L (range 1.9-18.8), and the mean milk concentration was 4.4 mcg/L (range 1.3-13.8). Infants received an average of 0.073% of the weight-adjusted maternal oral dose and 0.14% of the weight-adjusted maternal intravenous dose.

In another study of seven women who received intravenous nicardipine for an average of 1.9 days in the immediate postpartum period as therapy for pre-eclampsia, 34 milk samples were obtained at unspecified times and nicardipine was undetectable (<5 mcg/L) in 82% of the samples. Four women who received 1 to 6.5 mg/hour of nicardipine had 6 milk samples with detectable nicardipine levels (range 5.1 to 18.5 mcg/L). The highest concentration of 18.5 mcg/L was found in a woman who received 5.5 mg/hour of nicardipine. The estimated maximum dose in a breastfed infant was <0.3 mcg daily or between 0.015 to 0.004% of the therapeutic dose in a 1 kg infant.

### 8.4 Pediatric Use

Safety and efficacy in patients under the age of 18 have not been established.
8.5 Geriatric Use

The steady-state pharmacokinetics of nicardipine are similar in elderly hypertensive patients (>65 years) and young healthy adults.

Clinical studies of nicardipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, use low initial doses in elderly patients, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

10. OVERDOSE

Several overdosages with orally administered nicardipine have been reported. One adult patient allegedly ingested 600 mg of immediate-release oral nicardipine, and another patient, 2160 mg of the sustained-release formulation of nicardipine. Symptoms included marked hypotension, bradycardia, palpitations, flushing, drowsiness, confusion and slurred speech. All symptoms resolved without sequelae. An overdose occurred in a one year old child who ingested half of the powder in a 30 mg nicardipine standard capsule. The child remained asymptomatic.

Based on results obtained in laboratory animals, lethal overdose may cause systemic hypotension, bradycardia (following initial tachycardia) and progressive atioventricular conduction block. Reversible hepatic function abnormalities and sporadic focal hepatic necrosis were noted in some animal species receiving very large doses of nicardipine.

For treatment of overdose, implement standard measures including monitoring of cardiac and respiratory functions. Position the patient so as to avoid cerebral anoxia. Use vasopressors for patients exhibiting profound hypotension.

11. DESCRIPTION

Cardene (nicardipine hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium channel blocker). Cardene I.V. Premixed Injection for intravenous administration contains 20 mg of nicardipine hydrochloride per 200 mL (0.1 mg/mL) in either dextrose or sodium chloride. Nicardipine hydrochloride is a dihydropyridine derivative with IUPAC (International Union of Pure and Applied Chemistry) chemical name (1S)-2-(benzyl-methyl amino) ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(m-nitrophenyl)-3,5-pyridinedicarboxylate monohydrochloride and has the following structure:

![Nicardipine Hydrochloride Structure](image)

Nicardipine hydrochloride is a greenish-yellow, odorless, crystalline powder that melts at about 169ºC. It is freely soluble in chloroform, methanol, and glacial acetic acid, sparingly soluble in anhydrous ethanol, slightly soluble in n-butanol, water, 0.01 M potassium dihydrogen phosphate, acetone, and dioxane, very slightly soluble in ethyl acetate, and practically insoluble in benzene, ether, and hexane. It has a molecular weight of 515.99.

Cardene I.V. Premixed Injection is available as a ready-to-use sterile, non-pyrogenic, clear, colorless to yellow, iso-osmotic solution for intravenous administration in a 200 mL GALAXY container with 20 mg (0.1 mg/mL) nicardipine hydrochloride in either dextrose or sodium chloride.

**Cardene I.V. Premixed Injection in 4.8% Dextrose**

20 mg in 200 mL (0.1 mg/mL)

Each mL contains 0.1 mg nicardipine hydrochloride, 48 mg dextrose hydrous, USP, 0.0192 mg citric acid, anhydrous, USP, and 1.92 mg sorbitol, NF. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH to 3.7 to 4.7.

**Cardene I.V. Premixed Injection in 0.86% Sodium Chloride**

20 mg in 200 mL (0.1 mg/mL)

Each mL contains 0.1 mg nicardipine hydrochloride, 8.6 mg sodium chloride, USP, 0.0192 mg citric acid, anhydrous, USP, and 1.92 mg sorbitol, NF. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH to 3.7 to 4.7.

The GALAXY container is fabricated from multilayered plastic (PL 2501). Solutions are in contact with the polyethylene layer of the container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. The suitability and safety of the plastic have been confirmed in tests in animals according to the USP biological tests for plastic containers, as well as by tissue culture toxicity studies.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nicardipine inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle without changing serum calcium concentrations. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. The effects of nicardipine are more selective to vascular smooth muscle than cardiac muscle. In animal models, nicardipine produced relaxation of coronary vascular smooth muscle at drug levels which cause little or no negative inotropic effect.

12.2 Pharmacodynamics

Hemodynamics

Cardene I.V. produces significant decreases in systemic vascular resistance. In a study of intra-arterially administered Cardene I.V., the degree of vasodilation and the resultant decrease in blood pressure were more prominent in hypertensive patients than in normotensive volunteers. Administration of Cardene I.V. to normotensive volunteers at dosages of 0.25 to 3 mg/hr for eight hours produced changes of <5 mmHg in systolic blood pressure and <3 mmHg in diastolic blood pressure.

An increase in heart rate is a normal response to vasodilation and decrease in blood pressure; in some patients these increases in heart rate may be pronounced. In placebo-controlled trials, the mean increases in heart rate were 7 ± 1 bpm in postoperative patients and 8 ± 1 bpm in patients with severe hypertension at the end of the maintenance period.

Hemodynamic studies following intravenous dosing in patients with coronary artery disease and normal or moderately abnormal left ventricular function have shown significant increases in ejection fraction and cardiac output with no significant change, or a small decrease, in left ventricular end-diastolic pressure (LVEDP). There is evidence that Cardene increases blood flow. Coronary dilatation induced by Cardene I.V. improves perfusion and aerobic metabolism in areas with chronic ischemia, resulting in reduced lactate production and augmented oxygen consumption.

In patients with coronary artery disease, Cardene I.V., administered after beta-blockade, significantly improved systolic and diastolic left ventricular function.

In congestive heart failure patients with impaired left ventricular function, Cardene I.V. increased cardiac output both at rest and during exercise. Decreases in left ventricular end-diastolic pressure were also observed. However, in some patients with severe left ventricular dysfunction, it may have a negative inotropic effect and could lead to worsened failure.

“Coronary steal” has not been observed during treatment with Cardene I.V. (Coronary steal is the detrimental redistribution of coronary blood flow in patients with coronary artery disease from underperfused areas toward better perfused areas.) Cardene I.V. has been shown to improve systolic shortening in both normal and hypokinetic segments of myocardial muscle. Radionuclide angiography has confirmed that wall motion remained improved during increased oxygen demand. (Occasional patients have developed increased angina upon receiving oral nicardipine. Whether this represents coronary steal in these patients, or is the result of increased heart rate and decreased diastolic pressure, is not clear.)

In patients with coronary artery disease, Cardene I.V. improves left ventricular diastolic distensibility during the early filling phase, probably due to a faster rate of myocardial relaxation in previously underperfused areas. There is little or no effect on normal myocardium, suggesting the improvement is mainly by indirect mechanisms such as afterload reduction and reduced ischemia. Cardene I.V. has no negative effect on myocardial relaxation at therapeutic doses. The clinical benefits of these properties have not yet been demonstrated.

Electrophysiologic Effects

In general, no detrimental effects on the cardiac conduction system have been seen with Cardene I.V. During acute electrophysiologic studies, it increased heart rate and prolonged the corrected QT interval to a minor degree. It did not affect sinus node recovery or SA conduction times. The PA, AH, and HV intervals* or the functional and effective refractory periods of the atrium were not prolonged. The relative and effective refractory periods of the His-Purkinje system were slightly shortened.

*PA = conduction time from high to low right atrium; AH = conduction time from low right atrium to His bundle deflection, or AV nodal conduction time; HV = conduction time through the His bundle and the bundle branch-Purkinje system.
Hepatic Function
Because the liver extensively metabolizes nicardipine, plasma concentrations are influenced by changes in hepatic function. In clinical studies with oral nicardipine in patients with severe liver disease, plasma concentrations were elevated and the halflife was prolonged [see Warnings and Precautions (5.4)]. Similar results were obtained in patients with hepatic disease when Cardene I.V. (nicardipine hydrochloride) was administered for 24 hours at 0.6 mg/hr.

Renal Function
When Cardene I.V. was given to mild to moderate hypertensive patients with moderate degrees of renal impairment, significant reduction in glomerular filtration rate (GFR) and effective renal plasma flow (RPF) was observed. No significant differences in liver blood flow were observed in these patients. A significantly lower systemic clearance and higher area under the curve (AUC) were observed.

When oral nicardipine (20 mg or 30 mg TID) was given to hypertensive patients with impaired renal function, mean plasma concentrations, AUC, and Cmax were approximately two-fold higher than in healthy controls. There is a transient increase in electrolyte excretion, including sodium [see Warnings and Precautions (5.5)].

Acute bolus administration of Cardene I.V. (2.5 mg) in healthy volunteers decreased mean arterial pressure and renal vascular resistance; glomerular filtration rate (GFR), renal plasma flow (RPF), and the filtration fraction were unchanged. In healthy patients undergoing abdominal surgery, Cardene I.V. (10 mg over 20 minutes) increased GFR with no change in RPF when compared with placebo. In hypertensive type II diabetic patients with nephropathy, oral nicardipine (20 mg TID) did not change RPF and GFR, but reduced renal vascular resistance.

Pulmonary Function
In two well-controlled studies of patients with obstructive airway disease treated with oral nicardipine, no evidence of increased bronchospasm was seen. In one of the studies, oral nicardipine improved forced expiratory volume 1 second (FEV1) and forced vital capacity (FVC) in comparison with metoprolol. Adverse experiences reported in a limited number of patients with asthma, reactive airway disease, or obstructive airway disease are similar to all patients treated with oral nicardipine.

12.3 Pharmacokinetics

Distribution
Rapid dose-related increases in nicardipine plasma concentrations are seen during the first two hours after the start of an infusion of Cardene I.V. Plasma concentrations increase at a much slower rate after the first few hours, and approach steady state at about 16 mg/kg/day or about 8 times the maximum recommended human oral dose). Nicardipine is highly protein bound (>95%) in human plasma over a wide concentration range.

Following infusion, nicardipine plasma concentrations decline tri-exponentially, with a rapid early distribution phase (a-half-life of 2.7 minutes), an intermediate phase (b-half-life of 44.8 minutes), and a slow terminal phase (c-half-life of 14.4 hours) that can only be detected after long-term infusions. Total plasma clearance (CL) is 0.4 L/hr/kg, and the apparent volume of distribution (Vd) using a non-compartment model is 8.3 L/kg. The pharmacokinetics of Cardene I.V. are linear over the dosage range of 0.5 to 40 mg/hr.

Metabolism and Excretion
Cardene I.V. has been shown to be rapidly and extensively metabolized by the hepatic cytochrome P450 enzymes, CYP2C8, 2D6, and 3A4. Nicardipine does not induce or inhibit its own metabolism, however, nicardipine has been shown to inhibit certain cytochrome P450 enzymes (including CYP3A4, CYP2D6, CYP2C8, and CYP2C19). Inhibition of these enzymes may result in increased plasma levels of certain drugs, including cyclosporine and tacrolimus (7.3, 7.4). The altered pharmacokinetics may necessitate dosage adjustment of the affected drug or discontinuation of treatment.

After coadministration of a radioactive intravenous dose of Cardene I.V. with an oral 30 mg dose given every 8 hours, 49% of the radioactivity was recovered in the urine and 43% in the feces within 96 hours. None of the dose was recovered as unchanged nicardipine.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Rats treated with nicardipine in the diet (at concentrations calculated to provide daily dosages levels of 5, 15, or 45 mg/kg/day) for two years showed a dose-dependent increase in thyroid hyperplasia and neoplasia (follicular adenoma/carcinoma). One- and three-month studies in the rat have suggested that these results are linked to a nicardipine-induced reduction in plasma thyroxine (T4) levels with a consequent increase in plasma levels of thyroid stimulating hormone (TSH). Chronic elevation of TSH is known to cause hyperstimulation of the thyroid.

In rats on an iodine deficient diet, nicardipine administration for one month was associated with thyroid hyperplasia that was prevented by T4 supplementation. Mice treated with nicardipine in the diet (at concentrations calculated to provide daily dosage levels of up to 100 mg/kg/day) for up to 18 months showed no evidence of neoplasia of any tissue and no evidence of thyroid changes.

There was no evidence of thyroid pathology in dogs treated with up to 25 mg nicardipine/kg/day for one year and no evidence of effects of nicardipine on thyroid function (plasma T4 and TSH) in man.

There was no evidence of a mutagenic potential of nicardipine in a battery of genotoxicity tests conducted on microbial indicator organisms, in micronucleus tests in mice and hamsters, or in a sister chromatid exchange study in hamsters.

No impairment of fertility was seen in male or female rats administered nicardipine at oral doses as high as 100 mg/kg/day (human equivalent dose about 16 mg/kg/day, 8 times the maximum recommended oral dose).

13.2 Reproductive and Developmental Toxicology

Embryotoxicity, but no teratogenicity, was seen at intravenous doses of 10 mg nicardipine/kg/day in rats and 1 mg/kg/day in rabbits. These doses in the rat and rabbit are equivalent to human IV doses of about 1.6 mg/kg/day and 0.32 mg/kg/day respectively. (The total daily human dose delivered by a continuous IV infusion ranges from 1.2 to 6 mg/kg/day, depending on duration at different infusion rates ranging from 3 to 15 mg/hr as individual patients are titrated for optimal results.) Nicardipine was also embryotoxic when administered orally to pregnant Japanese White rabbits, during organogenesis, at 150 mg/kg/day (a dose associated with marked body weight gain suppression in the treated doe), but not at 50 mg/kg/day (human equivalent dose about 16 mg/kg/day or about 8 times the maximum recommended human oral dose).

No adverse effects on the fetus were observed when New Zealand albino rabbits were treated orally, during organogenesis, with up to 100 mg nicardipine/kg/day (a dose associated with significant mortality in the treated doe). In pregnant rats administered nicardipine orally at doses of up to 100 mg/kg/day (human equivalent dose about 16 mg/kg/day) there was no evidence of embryotoxicity or teratogenicity. However, dystocia, reduced birth weight, reduced neonatal survival and reduced neonatal weight gain were noted.

14. CLINICAL STUDIES

Effects In Hypertension
In patients with mild to moderate chronic stable essential hypertension, Cardene I.V. (0.5 to 4 mg/hr) produced dose-dependent decreases in blood pressure. At the end of a 48-hour infusion at 4 mg/hr, the decreases were 26 mmHg (17%) in systolic blood pressure and 20.7 mmHg (20%) in diastolic blood pressure. In other settings (e.g., patients with severe or postoperative hypertension), Cardene I.V. (5 to 15 mg/hr) produced dose-dependent decreases in blood pressure. Higher infusion rates produced therapeutic responses more rapidly. The mean time to therapeutic response for severe hypertension, defined as diastolic blood pressure ≤55 mmHg or ≥25 mmHg decrease and systolic blood pressure ≤160 mmHg, was 77 ± 5.2 minutes. The average maintenance dose was 8 mg/hr. The mean time to therapeutic response for postoperative hypertension, defined as ≥15% reduction in diastolic or systolic blood pressure, was 11.5 ± 0.8 minutes. The average maintenance dose was 3 mg/hr.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
Cardene I.V. Premixed Injection is supplied as a single-use, ready-to-use, iso-osmotic solution for intravenous administration in a 200 mL GALAXY container with 20 mg (0.1 mg/mL) nicardipine hydrochloride in either dextrose or sodium chloride.

Pack Size Diluent NDC Number
10 bags, each containing 20 mg in 4.8% Dextrose NDC 10122-314-10 200 mL (0.1 mg/mL)
10 bags, each containing 20 mg in 0.86% Sodium Chloride NDC 10122-313-10 200 mL (0.1 mg/mL)

16.2 Storage and Handling
Store at controlled room temperature 20° to 25°C (68° to 77°F), refer to USP Controlled Room Temperature. Protect from freezing. Avoid excessive heat. Protect from light, store in carton until ready to use.
CARDENE IV (nicardipine hydrochloride) premixed injection for intravenous use
Initial U.S. Approval: 1988

INDICATIONS AND USAGE

• Cardene I.V. Premixed Injection is a calcium channel blocker indicated for the short-term treatment of hypertension when oral therapy is not feasible.

Dosage and Administration

• For Intravenous Use.

• No further dilution is required.

• When substituting for oral nicardipine therapy, use the intravenous infusion rate from the table below (2.1):

<table>
<thead>
<tr>
<th>Oral Cardene Dose</th>
<th>Equivalent I.V. Infusion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg q8h</td>
<td>0.5 mg/hr = 2.5 mL/hr</td>
</tr>
<tr>
<td>30 mg q8h</td>
<td>1.2 mg/hr = 6 mL/hr</td>
</tr>
<tr>
<td>40 mg q8h</td>
<td>2.2 mg/hr = 11 mL/hr</td>
</tr>
</tbody>
</table>

• In a patient not receiving oral nicardipine, initiate therapy at 25 mL/hr (5 mg/hr). Increase the infusion rate by 12.5 mL/hr every 5 minutes (for rapid titration) to 15 minutes (for gradual titration) up to a maximum of 75 mL/hr until desired blood pressure reduction is achieved. (2.1)

• If unacceptable hypotension or tachycardia occurs, discontinue the infusion. When blood pressure and heart rate stabilize, restart the infusion at low doses such as 15-25 mL/hr. (2.2)

ADVERSE REACTIONS

Most common adverse reactions are headache (15%), hypotension (6%), tachycardia (4%) and nausea/vomiting (5%). (6.1)

DRUG INTERACTIONS

• Cimetidine increases oral nicardipine plasma levels. (7.2)

• Oral or intravenous nicardipine may increase cyclosporine and tacrolimus plasma levels. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended when co-administering Cardene I.V. Premixed Injection. (7.3, 7.4)

USE IN SPECIFIC POPULATIONS

• Pregnancy: Based on animal data may cause fetal harm. (8.1)

• Nursing mothers: Minimally excreted into human milk. (8.3)

• Safety and efficacy in patients under the age of 18 have not been established. (8.4)

Revised: 08/2016
FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1 Hypertension
Cardene® I.V. (nicardipine hydrochloride) Premixed Injection is indicated for the short-term treatment of hypertension when oral therapy is not feasible or not desirable. For prolonged control of blood pressure, transfer patients to oral medication as soon as their clinical condition permits [see Dosage and Administration (2.1)].

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing
Cardene I.V. is intended for intravenous use. Titrate dose to achieve the desired blood pressure reduction. Individualize dosage depending on the blood pressure to be obtained and the response of the patient.

Dosage as a Substitute for Oral Nicardipine Therapy
The intravenous infusion rate required to produce an average plasma concentration equivalent to a given oral dose at steady state is shown in the following table:

<table>
<thead>
<tr>
<th>Oral Cardene Dose</th>
<th>Equivalent I.V. Infusion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg q8h</td>
<td>0.5 mg/hr = 2.5 mL/hr</td>
</tr>
<tr>
<td>30 mg q8h</td>
<td>1.2 mg/hr = 6 mL/hr</td>
</tr>
<tr>
<td>40 mg q8h</td>
<td>2.2 mg/hr = 11 mL/hr</td>
</tr>
</tbody>
</table>

Dosage for Initiation of Therapy in a Patient Not Receiving Oral Nicardipine
Initiate therapy at 25 mL/hr (5 mg/hr). If desired blood pressure reduction is not achieved at this dose, the infusion rate may be increased by 12.5 mL/hr (2.5 mg/hr) every 5 minutes (for rapid titration) to 15 minutes (for gradual titration) up to a maximum of 75 mL/hr (15 mg/hr), until desired blood pressure reduction is achieved.

Following achievement of the blood pressure goal utilizing rapid titration, decrease the infusion rate to 15 mL/hr (3 mg/hr).

Drug Discontinuation and Transition to an Oral Antihypertensive Agent
Discontinuation of infusion is followed by a 50% offset of action in about 30 minutes. If treatment includes transfer to an oral antihypertensive agent other than oral nicardipine, initiate therapy upon discontinuation of Cardene I.V. Premixed Injection.

If oral nicardipine is to be used, administer the first dose 1 hour prior to discontinuation of the infusion.

Special Populations
Titrate Cardene I.V. Premixed Injection slowly in patients with heart failure or impaired hepatic or renal function [see Warnings and Precautions (5.3, 5.4 and 5.5)]

2.2 Monitoring
The time course of blood pressure decrease is dependent on the initial rate of infusion and the frequency of dosage adjustment. With constant infusion, blood pressure begins to fall within minutes. It reaches about 50% of its ultimate decrease in about 45 minutes.

Monitor blood pressure and heart rate continually during infusion and avoid too rapid or excessive blood pressure drop during treatment. If there is concern of impending hypotension or tachycardia, the infusion should be discontinued. Then, when blood pressure has stabilized, infusion of Cardene I.V. Premixed Injection may be restarted at low doses such as 15-25 mL/hr (3 - 5 mg/hr) and adjusted to maintain desired blood pressure.

2.3 Instructions for Administration
Administer Cardene I.V. by a central line or through a large peripheral vein. Change the infusion site every 12 hours if administered via peripheral vein [see Intravenous Infusion Site (5.6)].

Cardene I.V. Premixed Injection is available as a single-use, ready-to-use, iso-osmotic solution for intravenous administration. No further dilution is required.

Inspect Cardene I.V. Premixed Injection visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Check the container for minute leaks prior to use by squeezing the bag firmly; ensure that the seal is intact. If leaks are found, discard solution as sterility may be impaired. Cardene I.V. Premixed Injection is normally a clear, colorless to yellow solution.

Do not combine Cardene I.V. Premixed Injection with any product in the same intravenous line or premixed container. Do not add supplementary medication to the bag. Protect from light until ready to use.

Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before the administration of the fluid from the secondary container is complete.

Preparation for administration:
1. Suspend container from eyelet support.
2. Remove protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

3. DOSAGE FORMS AND STRENGTHS
Cardene I.V. Premixed Injection is supplied as a single-use, ready-to-use, iso-osmotic solution for intravenous administration in a 200 mL GALAXY container with 40 mg (0.2 mg/mL) nicardipine hydrochloride in either dextrose or sodium chloride.

4. CONTRAINDICATIONS
4.1 Advanced Aortic Stenosis
Cardene I.V. Premixed Injection is contraindicated in patients with advanced aortic stenosis because part of the effect of Cardene I.V. Premixed Injection is secondary to reduced afterload. Reduction of diastolic pressure in these patients may worsen rather than improve myocardial oxygen balance.

5. WARNINGS AND PRECAUTIONS
5.1 Excessive Pharmacodynamic Effects
In administering nicardipine, close monitoring of blood pressure and heart rate is required. Nicardipine may occasionally produce symptomatic hypotension or tachycardia. Avoid systemic hypotension when administering the drug to patients who have sustained an acute cerebral infarction or hemorrhage.

5.2 Use in Patients with Angina
Increases in frequency, duration, or severity of angina have been seen in chronic therapy with oral nicardipine. Induction or exacerbation of angina has been seen in less than 1% of coronary artery disease patients treated with Cardene I.V. The mechanism of this effect has not been established.

5.3 Use in Patients with Heart Failure
Titrate slowly when using Cardene I.V. Premixed Injection, particularly in combination with a beta-blocker, in patients with heart failure or significant left ventricular dysfunction because of possible negative inotropic effects.

5.4 Use in Patients with Impaired Hepatic Function
Since nicardipine is metabolized in the liver, consider lower doses and closely monitor responses in patients with impaired liver function or reduced hepatic blood flow.

5.5 Use in Patients with Impaired Renal Function
When Cardene I.V. was given to mild to moderate hypertensive patients with moderate renal impairment, a significantly lower systemic clearance and higher area under the curve (AUC) was observed. These results are consistent with those seen after oral administration of nicardipine. Titrate gradually in patients with renal impairment.

5.6 Intravenous Infusion Site
To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, extravasation, and the occurrence of vascular impairment, administer drug through large peripheral veins or central veins rather than arteries or small peripheral veins, such as those on the dorsum of the hand or wrist. To minimize the risk of peripheral venous irritation, change the site of the drug infusion every 12 hours.

6. ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Two hundred forty-four patients participated in two multicenter, double-blind, placebo-controlled trials of Cardene I.V. Adverse experiences were generally not serious and most were expected consequences of vasodilation. Adverse experiences occasionally
required dosage adjustment. Therapy was discontinued in approximately 12% of
patients, mainly due to hypotension, headache, and tachycardia.

The table below shows percentage of patients with adverse events where the rate is
>3% more common on Cardene I.V. than placebo.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Cardene I.V. (N=144)</th>
<th>Placebo (N=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a Whole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache, n (%)</td>
<td>21 (15)</td>
<td>2 (2)</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension, n (%)</td>
<td>8 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Tachycardia, n (%)</td>
<td>5 (4)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Digestive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea/Vomiting, n (%)</td>
<td>7 (5)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Other adverse events have been reported in clinical trials or in the literature in
association with the use of intravenously administered nicardipine:

Body as a Whole: fever, neck pain
Cardiovascular: angina pectoris, atroventricular block, ST segment depression,
inverted T wave, deep-vein thrombophlebitis
Digestive: dyspepsia
Hemic and Lymphatic: thrombocytopenia
Metabolic and Nutritional: hypophosphatemia, peripheral edema
Nervous: confusion, hypotension
Respiratory: respiratory disorder
Special Senses: conjunctivitis, ear disorder, tinnitus
Urogenital: urinary frequency

Sinus node dysfunction and myocardial infarction, which may be due to disease
progression, have been seen in patients on chronic therapy with orally administered
nicardipine.

6.2 Post-Marketing and Other Clinical Experience

Because adverse reactions are reported voluntarily from a population of uncertain
size, it is not always possible to estimate reliably their frequency or to establish a
causal relationship to drug exposure. The following adverse reaction has been
identified during post-approval use of Cardene I.V.: decreased oxygen saturation
(possible pulmonary shunting).

7. DRUG INTERACTIONS

7.1 Beta-Blockers

In most patients, Cardene I.V. Premixed Injection can safely be used concomitantly
with beta blockers. However, titrate slowly when using Cardene I.V. Premixed
Injection in combination with a beta-blocker in heart failure patients [see Warnings and
Precautions (5.3)].

7.2 Cimetidine

Cimetidine has been shown to increase nicardipine plasma concentrations with oral
nicardipine administration. Frequently monitor response in patients receiving both
drugs. Data with other histamine-2 antagonists are not available.

7.3 Cyclosporine

Concomitant administration of oral or intravenous nicardipine and cyclosporine results
in elevated plasma cyclosporine levels through nicardipine inhibition of hepatic
microsomal enzymes, including CYP3A4. Closely monitor plasma concentrations of
cyclosporine during Cardene I.V. Premixed Injection administration, and reduce the
dose of cyclosporine accordingly.

7.4 Tacrolimus

Concomitant administration of intravenous nicardipine and tacrolimus may result in
elevated plasma tacrolimus levels through nicardipine inhibition of hepatic microsomal
enzymes, including CYP3A4. Closely monitor plasma concentrations of tacrolimus
during Cardene I.V. Premixed Injection administration, and adjust the dose of
tacrolimus accordingly.

7.5 In Vitro Interaction

The plasma protein binding of nicardipine was not altered when therapeutic
concentrations of furosemide, propranolol, dipyriramole, warfarin, quinine, or
naproxen were added to human plasma in vitro.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of nicardipine use in pregnant
women. However, limited human data in pregnant women with preeclampsia or pre-
term labor are available. In animal studies, no embryotoxicity occurred in rats with oral
doses 8 times the maximum recommended human dose (MRHD) based on body
surface area (mg/m²), but did occur in rabbits with oral doses at 24 times the maximum
recommended human dose (MRHD) based on body surface area (mg/m²). Cardene
I.V. should be used during pregnancy only if the potential benefit justifies the potential
risk to the fetus.

Hypotension, reflex tachycardia, postpartum hemorrhage, tocolysis, headache,
nausea, dizziness, and flushing have been reported in pregnant women who were
treated with intravenous nicardipine for hypertension during pregnancy. Fetal safety
results ranged from transient fetal heart rate decelerations to no adverse events.
Neonatal safety data ranged from hypotension to no adverse events.

Adverse events in women treated with intravenous nicardipine during pre-term labor
include pulmonary edema, dyspnea, hypoxia, hypotension, tachycardia, headache,
and phlebitis at site of injection. Neonatal adverse events include acidosis (pH<7.25).

In embryofetal toxicity studies, nicardipine was administered intravenously to pregant
rats and rabbits during organogenesis at doses up to 0.14 times the MRHD based on
body surface area (mg/m²) (5 mg/kg/day) (rats) and 0.03 times the MRHD based on
body surface area (mg/m²) (0.5 mg/kg/day) (rabbits). No embryotoxicity or
teratogenicity was seen at these doses. Embryotoxicity, but no teratogenicity was
seen at 0.27 times the MRHD based on body surface area (mg/m²) (10 mg/kg/day) in
rabbits and at 0.05 times the MRHD based on body surface area (mg/m²) (1 mg/kg/day) in
rats.

In other animal studies, pregnant Japanese White rabbits received oral nicardipine
during organogenesis, at doses 8 and 24 times the MRHD based on body surface
area (mg/m²) (50 and 150 mg/kg/day). Embryotoxicity occurred at the high dose along
with signs of maternal toxicity (marked maternal weight gain suppression). New
Zealand albino rabbits received oral nicardipine during organogenesis, at doses up to
16 times the MRHD based on body surface area (mg/m²) (100 mg/kg/day). While
significant maternal mortality occurred, no adverse effects on the fetus were
observed. Pregnant rabbits received oral nicardipine from day 6 through day 15 of
gestation at doses up to 8 times the MRHD based on body surface area (mg/m²) (100
mg/kg/day). There was no evidence of embryotoxicity or teratogenicity; however,
dystocia, reduced birth weights, reduced neonatal survival, and reduced neonatal
weight gain were noted.

8.3 Nursing Mothers

Nicardipine is minimally excreted into human milk. Among 18 infants exposed to
nicardipine through breast milk in the postpartum period, calculated daily infant dose
was less than 0.3 mcg and there were no adverse events observed. Consider the
possibility of infant exposure when using nicardipine in nursing mothers.

In a study of 11 women who received oral nicardipine 4 to 14 days postpartum, 4
women received immediate-release nicardipine 40 to 80 mg daily, 6 received
sustained-release nicardipine 100 to 150 mg daily, and one received intravenous
nicardipine 120 mg daily. The peak milk concentration was 7.3 mcg/L (range 1.9-18.8),
and the mean milk concentration was 4.4 mcg/L (range 1.3-13.8). Infants received an
average of 0.073% of the weight-adjusted maternal oral dose and 0.14% of the weight-
adjusted maternal intravenous dose.

In another study of seven women who received intravenous nicardipine for an average
of 1.9 days in the immediate postpartum period as therapy for pre-eclampsia, 34 milk
samples were obtained at unspecified times and nicardipine was undetectable (<5
mcg/L) in 82% of the samples. Four women who received 1 to 6.5 mg/hour of
nicardipine had 6 milk samples with detectable nicardipine levels (range 5.1 to 18.5
mcg/L). The highest concentration of 18.5 mcg/L was found in a woman who received
5.5 mg/hour of nicardipine. The estimated maximum dose in a breastfed infant was <
0.3 mcg daily or between 0.015 to 0.004% of the therapeutic dose in a 1 kg infant.

8.4 Pediatric Use

Safety and efficacy in patients under the age of 18 have not been established.
8.5 Geriatric Use

The steady-state pharmacokinetics of nicardipine are similar in elderly hypertensive patients (>65 years) and young healthy adults.

Clinical studies of nicardipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, use low initial doses in elderly patients, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

10. OVERDOSAGE

Several overdosages with orally administered nicardipine have been reported. One adult patient allegedly ingested 600 mg of immediate-release oral nicardipine, and another patient, 2160 mg of the sustained-release formulation of nicardipine. Symptoms included marked hypotension, bradycardia, palpitations, flushing, drowsiness, confusion and slurred speech. All symptoms resolved without sequelae.

An overdosage occurred in a one year old child who ingested half of the powder in a 30 mg nicardipine standard capsule. The child remained asymptomatic.

Based on results obtained in laboratory animals, lethal overdose may cause systemic hypotension, bradycardia (following initial tachycardia) and progressive atrioventricular conduction block. Reversible hepatic function abnormalities and sporadic focal hepatic necrosis were noted in some animal species receiving very large doses of nicardipine.

For treatment of overdosage, implement standard measures including monitoring of cardiac and respiratory functions. Position the patient so as to avoid cerebral anoxia. Use vasopressors for patients exhibiting profound hypotension.

11. DESCRIPTION

Cardene (nicardipine hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium channel blocker). Cardene I.V. Premixed Injection for intravenous administration contains 40 mg of nicardipine hydrochloride per 200 mL (0.2 mg/mL) in either dextrose or sodium chloride. Nicardipine hydrochloride is a dihydropyridine derivative with IUPAC (International Union of Pure and Applied Chemistry) chemical name (1S)-2-(benzyl-methyl amino) ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate monohydrate and has the following structure:

![Nicardipine Structure](image)

Nicardipine hydrochloride is a greenish-yellow, odorless, crystalline powder that melts at about 169°C. It is freely soluble in chloroform, methanol, and glacial acetic acid, sparingly soluble in anhydrous ethanol, slightly soluble in n-butanol, water, 0.01 M potassium dihydrogen phosphate, acetone, and dioxane, very slightly soluble in ethyl acetate, and practically insoluble in benzene, ether, and hexane. It has a molecular weight of 515.99.

Cardene I.V. Premixed Injection is available as a ready-to-use sterile, non-pyrogenic, clear, colorless to yellow, iso-osmotic solution for intravenous administration in a 200 mL GALAXY container with 40 mg (0.2 mg/mL) nicardipine hydrochloride in either dextrose or sodium chloride.

**Cardene I.V. Premixed Injection in 5.0% Dextrose**

40 mg in 200 mL (0.2 mg/mL)

Each mL contains 0.2 mg nicardipine hydrochloride, 50 mg dextrose hydrous, USP, 0.0334 mg citric acid, anhydrous, USP. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH to 3.7 to 4.7.

**Cardene I.V. Premixed Injection in 0.83% Sodium Chloride**

40 mg in 200 mL (0.2 mg/mL)

Each mL contains 0.2 mg nicardipine hydrochloride, 8.3 mg sodium chloride, USP, 0.0384 mg citric acid, anhydrous, USP, and 3.84 mg sorbitol, NF. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH to 3.7 to 4.7.

The GALAXY container is fabricated from multilayered plastic (PL 2501). Solutions are in contact with the polyethylene layer of the container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. The suitability and safety of the plastic have been confirmed in tests in animals according to the USP biological tests for plastic containers, as well as by tissue culture toxicity studies.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nicardipine inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle without changing serum calcium concentrations. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. The effects of nicardipine are more selective to vascular smooth muscle than cardiac muscle. In animal models, nicardipine produced relaxation of coronary vascular smooth muscle at drug levels which cause little or no negative inotropic effect.

12.2 Pharmacodynamics

**Hemodynamics**

Cardene I.V. produces significant decreases in systemic vascular resistance. In a study of intra-arterially administered Cardene I.V., the degree of vasodilation and the resultant decrease in blood pressure were more prominent in hypertensive patients than in normotensive volunteers. Administration of Cardene I.V. to normotensive volunteers at dosages of 0.25 to 3 mg/hr for eight hours produced changes of <5 mmHg in systolic blood pressure and <3 mmHg in diastolic blood pressure.

An increase in heart rate is a normal response to vasodilation and decrease in blood pressure; in some patients these increases in heart rate may be pronounced. In placebo-controlled trials, the mean increases in heart rate were 7 ± 1 bpm in postoperative patients and 8 ± 1 bpm in patients with severe hypertension at the end of the maintenance period.

Hemodynamic studies following intravenous dosing in patients with coronary artery disease and normal or moderately abnormal left ventricular function have shown significant increases in ejection fraction and cardiac output with no significant change, or a small decrease, in left ventricular end-diastolic pressure (LVEDP). There is evidence that Cardene increases blood flow. Coronary dilatation induced by Cardene I.V. improves perfusion and aerobic metabolism in areas with chronic ischemia, resulting in reduced lactate production and augmented oxygen consumption. In patients with coronary artery disease, Cardene I.V., administered after beta-blockade, significantly improved systolic and diastolic left ventricular function.

In congestive heart failure patients with impaired left ventricular function, Cardene I.V. increased cardiac output both at rest and during exercise. Decreases in left ventricular end-diastolic pressure were also observed. However, in some patients with severe left ventricular dysfunction, it may have a negative inotropic effect and could lead to worsened failure.

“Coronary steal” has not been observed during treatment with Cardene I.V. (Coronary steal is the detrimental redistribution of coronary blood flow in patients with coronary artery disease from underperfused areas toward better perfused areas.) Cardene I.V. has been shown to improve systolic shortening in both normal and hypokinetic segments of myocardial muscle. Radionuclide angiography has confirmed that wall motion remained improved during increased oxygen demand. (Occasional patients have developed increased angina upon receiving oral nicardipine. Whether this represents coronary steal in these patients, or is the result of increased heart rate and decreased diastolic pressure, is not clear.)

In patients with coronary artery disease, Cardene I.V. improves left ventricular diastolic distensibility during the early filling phase, probably due to a faster rate of myocardial relaxation in previously underperfused areas. There is little or no effect on normal myocardium, suggesting the improvement is mainly by indirect mechanisms such as afterload reduction and reduced ischemia. Cardene I.V. has no negative effect on myocardial relaxation at therapeutic doses. The clinical benefits of these properties have not yet been demonstrated.

**Electrophysiologic Effects**

In general, no detrimental effects on the cardiac conduction system have been seen with Cardene I.V. During acute electrophysiologic studies, it increased heart rate and prolonged the corrected QT interval to a minor degree. It did not affect sinus node recovery or SA conduction times. The PA, AH, and HV intervals* or the functional and effective refractory periods of the atrium were not prolonged. The relative and effective refractory periods of the His-Purkinje system were slightly shortened.

*PA = conduction time from high to low atrium; AH = conduction time from low right atrium to His bundle deflection, or AV nodal conduction time; HV = conduction time through the His bundle and the bundle branch-Purkinje system.
12. Pharmacokinetics

Rapid dose-related increases in nicardipine plasma concentrations are seen during the first two hours after the start of an infusion of Cardene I.V. Plasma concentrations increase at a much slower rate after the first few hours, and approach steady state at first two hours after the start of an infusion of Cardene I.V. Plasma concentrations were elevated and the half-life was prolonged [see Warnings and Precautions (5.4)]. Similar results were obtained in patients with hepatic disease when Cardene I.V. (nicardipine hydrochloride) was administered for 24 hours at 0.6 mg/hr.

Renal Function

When Cardene I.V. was given to mild to moderate hypertensive patients with moderate degrees of renal impairment, significant reduction in glomerular filtration rate (GFR) and effective renal plasma flow (RPF) was observed. No significant differences in liver blood flow were observed in these patients. A significantly lower systemic clearance and higher area under the curve (AUC) were observed.

When oral nicardipine (20 mg or 30 mg TID) was given to hypertensive patients with impaired renal function, mean plasma concentrations, AUC, and Cmax were approximately two-fold higher than in healthy controls. There is a transient increase in electrolyte excretion, including sodium [see Warnings and Precautions (5.5)].

Acute bolus administration of Cardene I.V. (2.5 mg) in healthy volunteers decreased mean arterial pressure and renal vascular resistance; glomerular filtration rate (GFR), renal plasma flow (RPF), and the filtration fraction were unchanged. In healthy patients undergoing abdominal surgery, Cardene I.V. (10 mg over 20 minutes) increased GFR with no change in RPF when compared with placebo. In hypertensive type II diabetic patients with nephropathy, oral nicardipine (20 mg TID) did not change RPF and GFR, but reduced renal vascular resistance.

Pulmonary Function

In two well-controlled studies of patients with obstructive airway disease treated with oral nicardipine, no evidence of increased bronchospasm was seen. In one of the studies, oral nicardipine improved forced expiratory volume 1 second (FEV1) and oral nicardipine, no evidence of increased bronchospasm was seen. In one of the studies, oral nicardipine improved forced expiratory volume 1 second (FEV1) and forced vital capacity (FVC) in comparison with metoprolol. Adverse experiences reported in a limited number of patients with asthma, reactive airway disease, or obstructive airway disease are similar to all patients treated with oral nicardipine.

12.3 Pharmacokinetics

Distribution

Rapid dose-related increases in nicardipine plasma concentrations are seen during the first two hours after the start of an infusion of Cardene I.V. Plasma concentrations increase at a much slower rate after the first few hours, and approach steady state at 24 to 48 hours. The steady-state pharmacokinetics of nicardipine are similar in elderly and young healthy adults. On termination of the infusion, nicardipine concentrations decrease rapidly, with at least a 50% decrease during the first two hours post-infusion. The effects of nicardipine on blood pressure significantly correlate with plasma concentrations. Nicardipine is highly protein bound (>95%) in human plasma over a wide concentration range.

Following infusion, nicardipine plasma concentrations decline tri-exponentially, with a rapid early distribution phase (α-half-life of 2.7 minutes), an intermediate phase (β-half-life of 44.8 minutes), and a slow terminal phase (γ-half-life of 14.4 hours) that can only be detected after long-term infusions. Total plasma clearance (Cl) is 0.4 L/hr/kg, and the apparent volume of distribution (Vd) using a non-compartment model is 8.3 L/kg. The pharmacokinetics of Cardene I.V. are linear over the dosage range of 0.5 to 40 mg/hr.

Metabolism and Excretion

Cardene I.V. has been shown to be rapidly and extensively metabolized by the hepatic cytochrome P450 enzymes, CYP2C8, 2D6, and 3A4. Nicardipine does not induce or inhibit its own metabolism, however, nicardipine has been shown to inhibit certain cytochrome P450 enzymes (including CYP3A4, CYP2D6, CYP2C8, and CYP2C19). Inhibition of these enzymes may result in increased plasma levels of certain drugs, including cyclosporine and tacrolimus (7.3, 7.4). The altered pharmacokinetics may necessitate dosage adjustment of the affected drug or discontinuation of treatment.

After coadministration of a radioactive intravenous dose of Cardene I.V. with an oral 30 mg dose given every 8 hours, 49% of the radioactivity was recovered in the urine and 43% in the feces within 96 hours. None of the dose was recovered as unchanged nicardipine.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Rats treated with nicardipine in the diet (at concentrations calculated to provide daily dosages levels of 5, 15, or 45 mg/kg/day) for two years showed a dose-dependent increase in thyroid hyperplasia and neoplasia (follicular adenoma/carcinoma). One- and three-month studies in the rat have suggested that these results are linked to a nicardipine-induced reduction in plasma thyroxine (T4) levels with a consequent increase in plasma levels of thyroid stimulating hormone (TSH). Chronic elevation of TSH is known to cause hyperstimulation of the thyroid.

In rats on an iodine deficient diet, nicardipine administration for one month was associated with thyroid hyperplasia that was prevented by T4 supplementation. Mice treated with nicardipine in the diet (at concentrations calculated to provide daily dosages levels of up to 100 mg/kg/day) for up to 18 months showed no evidence of neoplasia of any tissue and no evidence of thyroid changes.

There was no evidence of thyroid pathology in dogs treated with up to 25 mg nicardipine/kg/day for one year and no evidence of effects of nicardipine on thyroid function (plasma T4 and TSH) in man.

There was no evidence of a mutagenic potential of nicardipine in a battery of genotoxicity tests conducted on microbial indicator organisms, in micronucleus tests in mice and hamsters, or in a sister chromatid exchange study in hamsters.

No impairment of fertility was seen in male or female rats administered nicardipine at oral doses as high as 100 mg/kg/day (human equivalent dose about 16 mg/kg/day, 8 times the maximum recommended oral dose).

13.3 Reproductive and Developmental Toxicology

Embryotoxicity, but no teratogenicity, was seen at intravenous doses of 10 mg nicardipine/kg/day in rats and 1 mg/kg/day in rabbits. These doses in the rat and rabbit are equivalent to human IV doses of about 1.6 mg/kg/day and 0.32 mg/kg/day respectively. (The total daily human dose delivered by a continuous IV infusion ranges from 1.2 to 6 mg/kg/day, depending on duration at different infusion rates ranging from 3 to 15 mg/hr as individual patients are titrated for optimal results.) Nicardipine was also embryotoxic when administered orally to pregnant Japanese White rabbits, during organogenesis, at 150 mg/kg/day (a dose associated with marked body weight gain suppression in the treated doe), but not at 50 mg/kg/day (human equivalent dose about 16 mg/kg/day or about 8 times the maximum recommended human oral dose). No adverse effects on the fetus were observed when New Zealand albino rabbits were treated orally, during organogenesis, with up to 100 mg nicardipine/kg/day (a dose associated with significant mortality in the treated doe). In pregnant rats administered nicardipine orally at doses of up to 100 mg/kg/day (human equivalent dose about 16 mg/kg/day) there was no evidence of embryotoxicity or teratogenicity. However, dystocia, reduced birth weight, reduced neonatal survival and reduced neonatal weight gain were noted.

14. CLINICAL STUDIES

Effects In Hypertension

In patients with mild to moderate chronic stable essential hypertension, Cardene I.V. (0.5 to 4 mg/hr) produced dose-dependent decreases in blood pressure. At the end of a 48-hour infusion at 4 mg/hr, the decreases were 26 mmHg (17%) in systolic blood pressure and 20.7 mmHg (20%) in diastolic blood pressure. In other settings (e.g., patients with severe or postoperative hypertension), Cardene I.V. (5 to 15 mg/hr) produced dose-dependent decreases in blood pressure. Higher infusion rates produced therapeutic responses more rapidly. The mean time to therapeutic response for severe hypertension, defined as diastolic blood pressure ≤95 mmHg or ≥25 mmHg decrease and systolic blood pressure ≤160 mmHg was 77 ± 5.2 minutes. The average maintenance dose was 8 mg/hr. The mean time to therapeutic response for postoperative hypertension, defined as ≥15% reduction in diastolic or systolic blood pressure, was 11.5 ± 0.8 minutes. The average maintenance dose was 3 mg/hr.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Cardene I.V. Premixed Injection is supplied as a single-use, ready-to-use, iso-osmotic solution for intravenous administration in a 200 mL GALAXY container with 40 mg (0.2 mg/mL) nicardipine hydrochloride in either dextrose or sodium chloride.

Pack Size Diluent NDC Number
10 bags, each containing 40 mg in 200 mL (0.2mg/mL) 5% Dextrose NDC 10122-326-10
10 bags, each containing 40 mg in 200 mL (0.2mg/mL) 0.83% Sodium Chloride NDC 10122-325-10

16.2 Storage and Handling

Store at controlled room temperature 20º to 25ºC (68º to 77ºF), refer to USP Controlled Room Temperature.

Protect from freezing. Avoid excessive heat. Protect from light, store in carton until ready to use.
Cleviprex is contraindicated in patients with:
- Allergy to soy or eggs (4.1)
- Defective lipid metabolism (4.2)
- Severe aortic stenosis (4.3)

Most common adverse reactions (>2%) are headache, nausea, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact The Medicines Company at 1-888-977-MDCO (6326) or FDA at 1-800 FDA-1088 or www.fda.gov/medwatch.

At clinically relevant concentrations, clevidipine and its metabolites do not inhibit or induce any CYP450 enzymes. The potential of clevidipine to interact with other drugs is low. (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2013
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
Cleviprex is indicated for the reduction of blood pressure when oral therapy is not feasible or not desirable.

2 DOSAGE AND ADMINISTRATION
2.1 Monitoring
Monitor blood pressure and heart rate continually during infusion, and then until vital signs are stable. Patients who receive prolonged Cleviprex infusions and are not transitioned to other antihypertensive therapies should be monitored for the possibility of rebound hypertension for at least 8 hours after the infusion is stopped. These patients may need follow-up adjustments in blood pressure control.

2.2 Recommended Dosing
Cleviprex is intended for intravenous use. Titrate drug to achieve the desired blood pressure reduction. Individualize dosage depending on the blood pressure to be obtained and the response of the patient.

Initial dose: Initiate the intravenous infusion of Cleviprex at 1-2 mg/hour.

Dose titration: The dose may be doubled at short (90 second) intervals initially. As the blood pressure approaches goal, the increase in doses should be less than doubling and the time between dose adjustments should be lengthened to every 5-10 minutes. An approximately 1-2 mg/hour increase will generally produce an additional 2-4 mmHg decrease in systolic pressure.

Maintenance dose: The desired therapeutic response for most patients occurs at doses of 4-6 mg/hour. Patients with severe hypertension may require doses up to 32 mg/hour, but there is limited experience at this dose rate.

Maximum dose: Most patients were treated with maximum doses of 16 mg/hour or less. There is limited short-term experience with doses up to 32 mg/hour. Because of lipid load restrictions, no more than 1000 mL or an average of 21 mg/hour of Cleviprex infusion is recommended per 24 hour period. In clinical trials, 55 hypertensive patients were treated with >500mL of Cleviprex infusion per 24 hour period. There is little experience with infusion durations beyond 72 hours at any dose.

Transition to an oral antihypertensive agent: Discontinue Cleviprex or titrate downward while appropriate oral therapy is established. When an oral antihypertensive agent is being instituted, consider the lag time of onset of the oral agent’s effect. Continue blood pressure monitoring until desired effect is achieved.

Special populations: Special populations were not specifically studied. In clinical trials, 78 patients with abnormal hepatic function (one or more of the following: elevated serum bilirubin, AST/SGOT, ALT/SGPT) and 121 patients with moderate to severe renal
impairment were treated with Cleviprex. An initial Cleviprex infusion rate of 1-2 mg/hour is appropriate in these patients.

Table 1 is a guideline for dosing conversion from mg/hour to mL/hour.

Table 1. Dose conversion

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2.3 Instructions for Administration

*Maintain aseptic technique while handling Cleviprex.* Cleviprex is a single-use parenteral product. Do not use if contamination is suspected. Once the stopper is punctured, use within 12 hours and discard any unused portion.

Cleviprex is supplied in sterile, pre-mixed, ready-to-use 50 mL, or 100 mL, or 250 mL vials. Invert vial gently several times before use to ensure uniformity of the emulsion prior to administration. Inspect parenteral drug products for particulate matter and discoloration prior to administration whenever solution and container permit. Administer Cleviprex using an infusion device allowing calibrated infusion rates. Commercially available standard plastic cannulae may be used to administer the infusion. Administer Cleviprex by a central line or a peripheral line.
Cleviprex should not be administered in the same line as other medications.

Cleviprex should not be diluted, but it can be administered with the following:

- Water for Injection, USP
- Sodium Chloride (0.9%) Injection, USP
- Dextrose (5%) Injection, USP
- Dextrose (5%) in Sodium Chloride (0.9%) Injection, USP
- Dextrose (5%) in Ringers Lactate Injection, USP
- Lactated Ringers Injection, USP
- 10% amino acid

3 DOSAGE FORMS AND STRENGTHS
Cleviprex is a sterile, milky white injectable emulsion for intravenous use, available in the following configurations:

- 50 mL single use vial with 0.5 mg/mL clevidipine
- 100 mL single use vial with 0.5 mg/mL clevidipine
- 250 mL single use vial with 0.5 mg/mL clevidipine

4 CONTRAINDICATIONS
4.1 Known Allergy
Cleviprex is contraindicated in patients with allergies to soybeans, soy products, eggs, or egg products.

4.2 Defective Lipid Metabolism
Cleviprex is contraindicated in patients with defective lipid metabolism such as pathologic hyperlipemia, lipoid nephrosis, or acute pancreatitis if it is accompanied by hyperlipidemia.

4.3 Severe Aortic Stenosis
Cleviprex is contraindicated in patients with severe aortic stenosis because afterload reduction can be expected to reduce myocardial oxygen delivery.

5 WARNINGS AND PRECAUTIONS
5.1 Need for Aseptic Technique
Use aseptic technique and discard any unused product within 12 hours of stopper puncture [see Dosage and Administration (2.3)].

5.2 Hypotension and Reflex Tachycardia
Cleviprex may produce systemic hypotension and reflex tachycardia. If either occurs, decrease the dose of Cleviprex. There is limited experience with short-duration therapy with beta-blockers as a treatment for Cleviprex-induced tachycardia. Beta-blocker use for this purpose is not recommended.

5.3 Lipid Intake
Cleviprex contains approximately 0.2 g of lipid per mL (2.0 kcal). Lipid intake restrictions may be necessary for patients with significant disorders of lipid metabolism. For these patients, a reduction in the quantity of concurrently administered lipids may be necessary to compensate for the amount of lipid infused as part of the Cleviprex formulation.
5.4 **Negative Inotropy**
Dihydropyridine calcium channel blockers can produce negative inotropic effects and exacerbate heart failure. Monitor heart failure patients carefully.

5.5 **Beta-Blocker Withdrawal**
Cleviprex is not a beta-blocker, does not reduce heart rate, and gives no protection against the effects of abrupt beta-blocker withdrawal. Beta-blockers should be withdrawn only after a gradual reduction in dose.

5.6 **Rebound Hypertension**
Patients who receive prolonged Cleviprex infusions and are not transitioned to other antihypertensive therapies should be monitored for the possibility of rebound hypertension for at least 8 hours after the infusion is stopped.

5.7 **Pheochromocytoma**
There is no information to guide use of Cleviprex in treating hypertension associated with pheochromocytoma.

6 **ADVERSE REACTIONS**

The following risk is discussed elsewhere in the labeling:

- Hypotension and Reflex Tachycardia [see Warnings and Precautions (5.2)]

6.1 **Clinical Trials Experience**
Cleviprex clinical development included 19 studies, with 99 healthy subjects and 1307 hypertensive patients who received at least one dose of clevidipine (1406 total exposures). Clevidipine was evaluated in 15 studies in hypertensive patients: 1099 patients with perioperative hypertension, 126 with severe hypertension and 82 patients with essential hypertension.

The desired therapeutic response was achieved at doses of 4-6 mg/hour. Cleviprex was infused for <24 hours in the majority of patients (n=1199); it was infused as a continuous infusion in an additional 93 patients for durations between 24 and 72 hours.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

**Perioperative Hypertension**
The placebo-controlled experience with Cleviprex in the perioperative setting was both small and brief (about 30 minutes). Table 2 shows treatment-emergent adverse reactions and the category of “any common adverse event” in ESCAPE-1 and ESCAPE-2 where the rate on Cleviprex exceeded the rate on placebo by at least 5% (common adverse reactions).
Table 2. Common adverse reactions in placebo-controlled perioperative studies.

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<th>ESCAPE-1</th>
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<tr>
<td></td>
<td>CLV N=53(%)</td>
<td>PBO N=51(%)</td>
</tr>
<tr>
<td>Any common adverse event</td>
<td>27 (51%)</td>
<td>21 (41%)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>5 (9%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
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<td>--</td>
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<tr>
<td>Nausea</td>
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Three randomized, parallel, open-label studies called ECLIPSE, with longer exposure in cardiac surgery patients define the adverse reactions for patients with perioperative hypertension. Each ECLIPSE study compared Cleviprex (n=752) to an active comparator: nitroglycerin (NTG, n=278), sodium nitroprusside (SNP, n=283), or nicardipine (NIC, n=193). The pooled mean maximum dose in these studies was 10 mg/hour and the mean duration of treatment was 8 hours.

There were many adverse events associated with the operative procedure in the clinical studies of Cleviprex and relatively few plausibly related to the drugs used to lower blood pressure. Thus, the ability to differentiate the adverse event profile between treatments is limited. The adverse events observed within one hour of the end of the infusion were similar in patients who received Cleviprex and in those who received comparator agents. There was no adverse reaction that was more than 2% more common on Cleviprex than on the average of all comparators.

**Serious Adverse Events and Discontinuation – Perioperative Hypertension Studies**

The incidence of adverse events leading to study drug discontinuation in patients with perioperative hypertension receiving Cleviprex was 5.9% versus 3.2% for all active comparators. For patients receiving Cleviprex and all active comparators the incidence of serious adverse events within one hour of drug infusion discontinuation was similar.

**Severe Hypertension**

The adverse events for patients with severe hypertension are based on an uncontrolled study in patients with severe hypertension (VELOCITY, n=126).

The common adverse reactions for Cleviprex in severe hypertension included headache (6.3%), nausea (4.8%), and vomiting (3.2%). The incidence of adverse events leading to study drug discontinuation for Cleviprex in severe hypertension was 4.8%.

**Less Common Adverse Reactions in Patients with Severe or Essential Hypertension**

Adverse reactions that were reported in <1% of patients with severe or essential hypertension included:
Cardiac: myocardial infarction, cardiac arrest
Nervous system: syncope
Respiratory: dyspnea

6.2 Post-Marketing and Other Clinical Experience
Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or to establish a causal relationship to drug exposure. The following adverse reactions have been identified during post-approval use of Cleviprex: increased blood triglycerides, ileus, hypersensitivity, hypotension, nausea, decreased oxygen saturation (possible pulmonary shunting) and reflex tachycardia.

7 DRUG INTERACTIONS
No clinical drug interaction studies were conducted. Clevidipine and its major dihydropyridine metabolite do not have the potential for blocking or inducing any CYP enzyme.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C
There are no adequate and well-controlled studies of Cleviprex use in pregnant women. In animal studies, clevidipine caused increases in maternal and fetal mortality and length of gestation. Cleviprex should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There was decreased fetal survival when pregnant rats and rabbits were treated with clevidipine during organogenesis at doses 0.7 times (on a body surface area basis) the maximum recommended human dose (MRHD) in rats and 2 times the MRHD in rabbits.

In pregnant rats dosed with clevidipine during late gestation and lactation, there were dose-related increases in maternal mortality, length of gestation and prolonged parturition at doses greater than or equal to 1/6 of the MRHD based on body surface area. When offspring of these dams were mated, they had a conception rate lower than that of controls. Clevidipine has been shown to cross the placenta in rats [see Nonclinical Toxicology (13.3)].

8.2 Labor and Delivery
Cleviprex in the labor and delivery setting has not been established as safe and effective. Other calcium channel blockers suppress uterine contractions in humans. Pregnant rats treated with clevidipine during late gestation had an increased rate of prolonged parturition.

8.3 Nursing Mothers
It is not known whether clevidipine is excreted in human milk. Because many drugs are excreted in human milk, consider possible infant exposure when Cleviprex is administered to a nursing woman.
8.4 Pediatric Use
The safety and effectiveness of Cleviprex in children under 18 years of age have not been established.

8.5 Geriatric Use
Of the 1406 subjects (1307 with hypertension) treated with Cleviprex in clinical studies, 620 were ≥65 years of age and 232 were ≥75 years of age. No overall differences in safety or effectiveness were observed between these and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, for an elderly patient doses should be titrated cautiously, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE
There has been no experience of overdosage in human clinical trials. In clinical trials, doses of Cleviprex up to 106 mg/hour or 1153 mg maximum total dose were administered. The expected major effects of overdose would be hypotension and reflex tachycardia.

Discontinuation of Cleviprex leads to a reduction in antihypertensive effects within 5 to 15 minutes [see Clinical Pharmacology (12.2)]. In case of suspected overdosage, Cleviprex should be discontinued immediately and the patient’s blood pressure should be supported.

11 DESCRIPTION
Cleviprex is a sterile, milky-white emulsion containing 0.5 mg/mL of clevidipine suitable for intravenous administration. Clevidipine is a dihydropyridine calcium channel blocker. Chemically, the active substance, clevidipine, is butyroxymethyl methyl 4-(2´,3´-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate. It is a racemic mixture with a molecular weight of 456.3 g/mol. Each enantiomer has equipotent antihypertensive activity. The structure and formula are:

![Chemical Structure of Clevidipine]

C₂₁H₂₃Cl₂NO₆
Cleviprex® (clevidipine) injectable emulsion

Clevidipine is practically insoluble in water and is formulated in an oil-in-water emulsion. In addition to the active ingredient, clevidipine, Cleviprex contains soybean oil (200 mg/mL), glycerin (22.5 mg/mL), purified egg yolk phospholipids (12 mg/mL), oleic acid (0.3 mg/mL), disodium edetate (0.05 mg/mL), and sodium hydroxide to adjust pH. Cleviprex has a pH of 6.0 – 8.0 and is a ready-to-use emulsion.

12  CLINICAL PHARMACOLOGY
12.1  Mechanism of Action
Clevidipine is a dihydropyridine L-type calcium channel blocker. L-type calcium channels mediate the influx of calcium during depolarization in arterial smooth muscle. Experiments in anesthetized rats and dogs show that clevidipine reduces mean arterial blood pressure by decreasing systemic vascular resistance. Clevidipine does not reduce cardiac filling pressure (pre-load), confirming lack of effects on the venous capacitance vessels.

12.2  Pharmacodynamics
Cleviprex is titrated to the desired reduction in blood pressure. The effect of Cleviprex appears to plateau at approximately 25% of baseline systolic pressure. The infusion rate for which half the maximal effect is observed is approximately 10 mg/hour.

Onset of Effect: In the perioperative patient population, Cleviprex produces a 4-5% reduction in systolic blood pressure within 2-4 minutes after starting a 0.4 mcg/kg/min infusion (approximately 1-2 mg/hr).

Maintenance of Effect: In studies up to 72 hours of continuous infusion, there was no evidence of tolerance or hysteresis.

Offset of Effect: In most patients, full recovery of blood pressure is achieved in 5-15 minutes after the infusion is stopped.

In studies up to 72 hours of continuous infusion, in patients that were not transitioned to other antihypertensive therapies, there was some evidence of rebound hypertension following Cleviprex discontinuation.

Hemodynamics: Cleviprex causes a dose-dependent decrease in systemic vascular resistance.

Heart Rate: An increase in heart rate is a normal response to vasodilation and decrease in blood pressure; in some patients these increases in heart rate may be pronounced [see Warnings and Precautions (5.2)].

Electrophysiologic Effects: In healthy volunteers, clevidipine or its major carboxylic acid metabolite, at therapeutic and supratherapeutic concentrations (approximately 2.8 times steady-state), did not prolong cardiac repolarization.
12.3 Pharmacokinetics

Clevidipine is rapidly distributed and metabolized resulting in a very short half-life. The arterial blood concentration of clevidipine declines in a multi-phasic pattern following termination of the infusion. The initial phase half-life is approximately 1 minute, and accounts for 85-90% of clevidipine elimination. The terminal half-life is approximately 15 minutes.

Distribution: Clevidipine is >99.5% bound to proteins in plasma at 37°C. The steady-state volume of distribution was determined to be 0.17 L/kg in arterial blood.

Metabolism and Elimination: Clevidipine is rapidly metabolized by hydrolysis of the ester linkage, primarily by esterases in the blood and extravascular tissues, making its elimination unlikely to be affected by hepatic or renal dysfunction. The primary metabolites are the carboxylic acid metabolite and formaldehyde formed by hydrolysis of the ester group. The carboxylic acid metabolite is inactive as an antihypertensive. This metabolite is further metabolized by glucuronidation or oxidation to the corresponding pyridine derivative. The clearance of the primary dihydropyridine metabolite is 0.03 L/h/kg and the terminal half-life is approximately 9 hours.

In vitro studies show that clevidipine and its metabolite at the concentrations achieved in clinical practice will not inhibit or induce any CYP enzyme.

In a clinical study with radiolabeled clevidipine, 83% of the drug was excreted in urine and feces. The major fraction, 63-74% is excreted in the urine, 7-22% in the feces. More than 90% of the recovered radioactivity is excreted within the first 72 hours of collection.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Clevidipine displayed positive genotoxic potential in vitro in the Ames test, mouse lymphoma thymidine kinase locus assay, and chromosomal aberration assay, but not in vivo in the mouse micronucleus test. Formaldehyde, a metabolite of clevidipine, a known genotoxicant in vitro and a probable human carcinogen, appears to be at least partially responsible for the positive in vitro results. Long-term studies for evaluation of carcinogenic potential have not been performed with clevidipine due to the intended short-term duration of human use. There were no adverse effects on fertility or mating behavior of male rats at clevidipine doses of up to 55 mg/kg/day, approximately equivalent to the maximum recommended human dose (MRHD) of 504 mg/day (21 mg/hour x 24 hours) on a body surface area basis. Female rats demonstrated pseudopregnancy and changes in estrus cycle at doses as low as 13 mg/kg/day (about 1/4th the MRHD); however, doses of up to 55 mg/kg/day did not affect mating performance or fertility.

13.3 Developmental Toxicology

When pregnant rats were dosed with clevidipine during late gestation and lactation, there were dose-related increases in mortality, length of gestation and prolonged parturition at
dose levels as low as 13 mg/kg/day (about 1/4<sup>th</sup> the maximum recommended human dose of 504 mg/day (21 mg/hour x 24 hours) on a body surface area basis). When offspring of these dams were mated, they had a conception rate lower than that of controls. Clevidipine crosses the placental membrane in this species and doses of 35 or more mg/kg/day (about 0.7 times the MRHD) administered during organogenesis adversely affected fetal survival. Fetal survival was also adversely affected when pregnant rabbits were treated during organogenesis with 55 mg/kg/day (about twice the MRHD on a body surface area basis).

14 CLINICAL STUDIES
14.1 Perioperative Hypertension
Cleviprex was evaluated in two double-blind, randomized, parallel, placebo-controlled, multicenter trials of cardiac surgery patients—pre-operative use in ESCAPE-1 (n=105) and post-operative use in ESCAPE-2 (n=110). Patients were undergoing coronary artery bypass grafting, with or without valve replacement. Inclusion in ESCAPE-1 required a systolic pressure ≥160 mmHg. In ESCAPE-2, the entry criterion was systolic pressure of ≥140 mmHg within 4 hours of the completed surgery. The mean baseline blood pressure was 178/77 mmHg in ESCAPE-1 and 150/71 mmHg in ESCAPE-2. The population of both studies included 27% females and 47% patients older than age 65.

Cleviprex was infused in ESCAPE-1 preoperatively for 30 minutes, until treatment failure, or until induction of anesthesia, whichever came first. Cleviprex was infused in ESCAPE-2 postoperatively for a minimum of 30 minutes unless alternative therapy was required. The maximum infusion time allowed in the ESCAPE studies was 60 minutes.

In both studies infusion of Cleviprex was started at a dose of 1-2 mg/hour and was titrated upwards, as tolerated, in doubling increments every 90 seconds up to an infusion rate of 16 mg/hour in order to achieve the desired blood pressure-lowering effect. At doses above 16 mg/hour, increments were 7 mg/hour. The average Cleviprex infusion rate in ESCAPE-1 was 15.3 mg/hour and in ESCAPE-2 it was 5.1 mg/hour. The mean duration of exposure in the same ESCAPE studies was 30 minutes for the Cleviprex-treated patients.

Approximately 4% of Cleviprex-treated subjects in ESCAPE-1 and 41% in ESCAPE-2 were on concomitant vasodilators during the first 30 minutes of Cleviprex administration.

Cleviprex lowered blood pressure within 2-4 minutes. The change in systolic blood pressure over 30 minutes for ESCAPE-1 (preoperative) and ESCAPE-2 (postoperative) are shown in Figure 1 and 2.
Figure 1. Mean change in systolic blood pressure (mmHg) during 30-minute infusion, ESCAPE-1 (preoperative)

![Graph showing mean change in systolic blood pressure (mmHg) during 30-minute infusion, ESCAPE-1 (preoperative).]

Figure 2. Mean change in systolic blood pressure (mmHg) during 30-minute infusion, ESCAPE-2 (postoperative)

![Graph showing mean change in systolic blood pressure (mmHg) during 30-minute infusion, ESCAPE-2 (postoperative).]

# The decrease in placebo group systolic BP reflects the number of placebo patients (N=49 at baseline) who bailed out during the 30-minute infusion period (n=10 remaining at 30 min).
The change in heart rate over 30 minutes for ESCAPE-1 (preoperative) and ESCAPE-2 (postoperative) are shown in Figure 3 and 4.

Figure 3. Mean change in heart rate (bpm) during 30-minute infusion, ESCAPE-1 (preoperative)

Figure 4. Mean change in heart rate (bpm) during 30-minute infusion, ESCAPE-2 (postoperative)
In three Phase 3 open-label clinical trials (ECLIPSE), 1512 patients were randomized to receive Cleviprex, nitroglycerin (perioperative hypertension), sodium nitroprusside (perioperative hypertension), or nicardipine (postoperative hypertension), for the treatment of hypertension in cardiac surgery. The mean exposure in the ECLIPSE studies was 8 hours at 4.5 mg/hour for the 752 patients who were treated with Cleviprex. Blood pressure control was assessed by measuring the magnitude and duration of SBP excursions outside the predefined pre- and post-operative SBP target range of 75-145 mmHg and the predefined intra-operative SBP range of 65-135 mmHg. In general, blood pressure control was similar with the four treatments.

14.2 Severe Hypertension
Cleviprex was evaluated in an open-label, uncontrolled clinical trial (VELOCITY) in 126 patients with severe hypertension (SBP >180 mmHg or diastolic blood pressure [DBP] >115 mmHg). Cleviprex infusion was initiated at 2 mg/hour and up-titrated every 3 minutes, doubling up to a maximum dose of 32 mg/hour as required to achieve a prespecified target blood pressure range within 30 minutes (primary endpoint). The transition to oral antihypertensive therapy was assessed for up to 6 hours following cessation of Cleviprex infusion.

The blood pressure effect in this study is shown in Figure 5. The average infusion rate was 9.5 mg/hour. The mean duration of Cleviprex exposure was 21 hours.

Figure 5. Mean percent change in SBP (%) during the first 30 minutes of infusion, VELOCITY (severe hypertension)

Oral antihypertensive therapy was instituted 1 hour prior to the anticipated cessation of Cleviprex infusion. Transition to oral antihypertensive therapy within 6 hours after discontinuing Cleviprex infusion was successful in 91% (115/126) of patients. No patient had IV antihypertensive therapy reinstituted following transition to oral therapy.
14.3 Essential Hypertension
Cleviprex was evaluated in a randomized, placebo-controlled, single-blind, parallel 72-hour continuous infusion study in 61 mild to moderate essential hypertensives. The mean baseline blood pressure was 151/86 mmHg.

Subjects were randomized to placebo or to 2, 4, 8, or 16 mg/hour. Doses above 2 mg/hour were started at 2 mg/hour and force-titrated in 2-fold increments at 3-minute intervals. Blood pressure, heart rate, and blood levels of clevidipine were measured during the infusion period. Blood levels were monitored 1 hour after the infusion was discontinued. Blood pressure and heart rate were monitored for 8 hours and also at 96 hours after the termination of infusion. Systolic blood pressure effect was related to the concentration of clevidipine and plateaued at higher measured concentrations, with the maximal effect estimated at 25% of baseline systolic blood pressure. The estimated infusion rate necessary to achieve half of this maximal effect was approximately 10 mg/hour.

16 HOW SUPPLIED/STORAGE AND HANDLING
Cleviprex (clevidipine) injectable emulsion is supplied as a sterile, milky white liquid emulsion product in single-use glass vials at a concentration of 0.5 mg/mL of clevidipine.

NDC 65293-005-50: 50 mL vial
NDC 65293-005-00: 100 mL vial
NDC 65293-005-25: 250 mL vial

Storage
Leave vials in cartons until use. Clevidipine is photosensitive and storage in cartons protects against photodegradation. Protection from light during administration is not required.

Store vials refrigerated at 2-8°C (36-46°F). Do not freeze. Vials in cartons may be transferred to 25°C (77°F, USP controlled room temperature) for a period not to exceed 2 months. Upon transfer to room temperature, mark vials in cartons “This product was removed from the refrigerator on _/_/_ date. It must be used or discarded 2 months after this date or the labeled expiration date (whichever date comes first).” Do not return to refrigerated storage after beginning room temperature storage.

Handling
Maintain aseptic technique while handling Cleviprex. Cleviprex is a single-use parenteral product that contains 0.005% disodium edetate to inhibit the rate of growth of microorganisms, for up to 12 hours, in the event of accidental contamination. However, Cleviprex can still support the growth of microorganisms, as it is not an antimicrobially preserved product under USP standards. Do not use if contamination is suspected. Once the stopper is punctured, use within 12 hours and discard any unused portion.
Cleviprex inhibits microbial growth for up to 12 hours, as demonstrated by test data for representative USP microorganisms, staphylococcus epidermidis and serratiamarcescens.

17 PATIENT COUNSELING INFORMATION

- Advise patients with underlying hypertension that they require continued follow up for their medical condition, and, if applicable, encourage patients to continue taking their oral antihypertensive medication(s) as directed.
- Advise patients to contact a healthcare professional immediately for any of the following signs of a new hypertensive emergency: neurological symptoms, visual changes, or evidence of congestive heart failure.

Manufactured by:
Fresenius Kabi Austria GmbH, Graz, Austria
Marketed by:
The Medicines Company
Parsippany, New Jersey 07054

For information call: 888-977-MDCO (6326)

US Patent 5,856,346
US Patent 5,739,152

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