SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cardene 30mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains nicardipine hydrochloride 30 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule with an opaque blue cap and opaque pale blue body, marked in red ink with the strength and company logo.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cardene is indicated in adults for the prophylaxis of patients with chronic stable angina. For the treatment of hypertension considered to be mild to moderate in severity.

4.2 Posology and method of administration

Posology

Prophylaxis of chronic stable angina:
Starting dose: 20 mg every 8 hours titrating upwards as required.

Usual effective dose: 30 mg every 8 hours (range of total dose 60 mg – 120 mg per day).

Allow at least 3 days before increasing the dose of Cardene to ensure steady state plasma levels have been achieved.

Hypertension:
Starting dose: 20 mg every 8 hours titrating upwards as required.

Usual effective dose: 30 mg every 8 hours (range of total dose 60 mg – 120 mg per day).

Use in elderly

Starting dose is 20 mg 3 times a day. Titrate upwards with care as nicardipine may lower systolic pressure more than diastolic pressure in these patients.

Paediatric population

The safety and efficacy in low birth weight infants, newborns, nursing infants, infants, and children has not been established. Cardene is not recommended in patients under the age of 18.

Method of administration

Cardene capsules are for oral administration.

The capsules should be taken with a little water and swallowed whole.

4.3 Contraindications

Pregnancy and lactation.

Hypersensitivity to the active substance or other dihydropyridines because of the theoretical risk of cross reactivity, or to any of the excipients listed in section 6.1.

Because part of the effect of nicardipine is secondary to reduced afterload, the drug should not be given to patients with severe aortic stenosis. Reduction of diastolic pressure in these patients may worsen rather than improve myocardial infarction.

Cardene should not be used in cardiogenic shock, clinically significant aortic stenosis, unstable angina, and during or within one month of a myocardial infarction.

Cardene should not be used for acute attacks of angina.

Cardene should not be used for secondary prevention of myocardial infarction.

4.4 Special warnings and precautions for use

When Cardene is used as monotherapy, caution is advised to avoid an excessive decrease in blood pressure. If used in combination with diuretics or beta-blockers, careful titration of Cardene is advised.

Caution should be exercised when using nicardipine in combination with a beta-blocker in patients with decreased cardiac function.

If switching from beta-blockers to Cardene, gradually reduce the beta-blocker dose (preferably over 8 – 10 days) since nicardipine gives no protection against the dangers of abrupt beta-blocker withdrawal.

Stop Cardene in patients experiencing ischaemic pain within 30 minutes of starting therapy or after increasing the dose.

Ischemic heart disease:
Short-acting dihydropyridines are associated with an increased risk of ischemic
cardiovascular events.

Use in patients with congestive heart failure or poor cardiac reserve:
Haemodynamic studies in patients with heart failure have shown that nicardipine reduces afterload and improves overall haemodynamics. In one study, intravenous nicardipine reduced myocardial contractility in patients with severe heart failure despite increases in cardiac index and ejection fraction noted in the same patients.

Since nicardipine has not been extensively studied in patients with severe left ventricular dysfunction and cardiac failure one must consider that worsening of cardiac failure may occur.

Use in patients with impaired hepatic or renal function:
Since Cardene is subject to first-pass metabolism, use with caution in patients with impaired liver function or reduced hepatic blood flow. Patients with severe liver disease showed elevated blood levels and the half-life of nicardipine was prolonged. Cardene blood levels may also be elevated in some renally impaired patients. Therefore the lowest starting dose and extending the dosing interval should be individually considered in these patients.

Use in patients following a stroke (infarction or haemorrhage):
Avoid inducing systemic hypotension when administering Cardene to these patients.

Laboratory tests:
Transient elevations of alkaline phosphatase, serum bilirubin, SGPT, SGOT and glucose, have been observed. BUN and creatinine may also become elevated. While out-of-range values were seen in T_3, T_4 and TSH, the lack of consistent alterations suggest that any changes were not drug-related.

Treatment with short acting nicardipine may induce an exaggerated fall in blood pressure and reflex tachycardia which can cause cardiovascular complications such as myocardial and cerebrovascular ischaemia.

There has been some concern about increased mortality and morbidity in the treatment of ischaemic heart disease using higher than recommended doses of some other short-acting dihydropyridines.

4.5 Interaction with other medicinal products and other forms of interaction

Inhibitors and inducers of cytochrome P450 3A4
Nicardipine is metabolized by cytochrome P450 3A4. Concomitant administration of nicardipine with inducers (e.g. carbamazepine and rifampicin) or inhibitors (e.g cimetidine and grapefruit juice) of cytochrome P450 3A4 may alter the plasma levels of nicardipine.
Clinical monitoring during treatment with an enzyme inducing or inhibiting agent, and after its discontinuation, is required.

Cyclosporine, tacrolimus and sirolimus:
Concomitant administration of nicardipine and cyclosporine, tacrolimus or sirolimus results in elevated plasma cyclosporine, tacrolimus or sirolimus levels. Cyclosporine, tacrolimus or sirolimus level should be monitored and dosage of immunosuppressant and/or nicardipine should be reduced, if required.

Digoxin
Careful monitoring of serum digoxin levels is advised in patients also receiving Cardene as levels may be increased.

Beta-blockers and other anti-hypertensive drugs
Cardene may be used in combination with beta-blocking and other anti-hypertensive drugs but the possibility of an additive effect resulting in postural hypotension should be considered.

Propranolol, Dipyridamole, Warfarin, Quinidine, Naproxen:

Therapeutic concentrations of these drugs does not change the *in vitro* plasma protein binding of nicardipine.

Fentanyl Anaesthesia:
Severe hypotension has been reported during fentanyl anaesthesia with concomitant use of a beta-blocker and calcium blockade. Even though such interactions have not been seen in clinical trials, such hypotensive episodes should be vigorously treated with conventional therapy such as intravenous fluids.

4.6 Fertility, Pregnancy and lactation

Pregnancy
See contra-indications (section 4.3)

Acute pulmonary oedema has been observed when nicardipine has been used as tocolytic during pregnancy (see section 4.8), especially in cases of multiple pregnancy (twins or more), with the intravenous route and/or concomitant use of beta-2 agonists.

Breast-feeding

Because nicardipine was found in maternal milk, breast-feeding must be discontinued during nicardipine treatment (see section 5.3).

4.7 Effects on ability to drive and use machines

Caution should be exercised because the hypotensive effects of this drug may cause dizziness.

4.8 Undesirable effects

Majority are not serious and are expected consequences of the vasodilator effects of Cardene.

The most frequent side-effects reported are headache, oedema peripheral, heat sensation and/or flushing, palpitations, nausea and dizziness.

Other side-effects noted in clinical trials include the following:

Cardiac disorders
Tachycardia

As with the use of other short-acting dihydropyridines in patients with ischaemic heart disease, exacerbation of angina pectoris may occur frequently at the start of treatment with nicardipine capsules. The occurrence of myocardial infarction has been reported although it is not possible to distinguish such an event from the natural course of ischaemic heart disease.

Gastro-intestinal disorders
Gastro-intestinal upset
Gingival hyperplasia
Vomiting

General disorders and administration site conditions
Asthenia

Hepatobiliary disorders
Hepatic function abnormal

Renal and urinary disorders
Renal function abnormal
Frequency of micturition

Nervous system disorders
Drowsiness
Insomnia
Tinnitus
Paraesthesia
Functional disorders

Respiratory, thoracic and mediastinal disorders
Dyspnoea
Frequency: unknown
Pulmonary oedema*
*cases have been also reported when used as tocolytic during pregnancy (see section 4.6)

Skin and subcutaneous tissue disorders
Erythema
Pruritis
Rash

Vascular disorders
Hypotension
Orthostatic hypotension

Immune system disorders
Anaphylactic reaction
Frequency: Unknown

Investigations
Hepatic enzyme increased

Frequency: Unknown

Rarely, depression, impotence and thrombocytopenia have been reported.

The above mentioned listed adverse reactions have been observed during clinical studies and/or during marketed use.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms may include marked hypotension, bradycardia, palpitations, flushing, drowsiness, confusion and slurred speech. In laboratory animals, overdosage also resulted in reversible hepatic function abnormalities, sporadic focal hepatic necrosis and progressive atrioventricular conduction block.

For treatment of overdose, standard measures including monitoring of cardiac and respiratory functions should be implemented. The patient should be positioned so as to avoid cerebral anoxia. Frequent blood pressure determinations are essential. Vasopressors are clinically indicated for patients exhibiting profound hypotension. Intravenous calcium gluconate may help reverse the effects of calcium entry blockade.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective calcium channel blocker (dihydropyridine derivative) with mainly vascular effects, ATC code: C08CA04.

Mechanism of action

Cardene is a potent calcium antagonist. Pharmacological studies demonstrate its preferential high selectivity for the peripheral vasculature over the myocardium which accounts for its minimal negative inotropic effects. Cardene produces smooth muscle relaxation and marked peripheral vasodilatation.

Pharmacodynamic effects

In man Cardene produces a significant decrease in systemic vascular resistance, the degree of vasodilatation being more predominant in hypertensive patients than in normotensive subjects.

Clinical efficacy and safety

Haemodynamic studies in patients with coronary artery disease and normal left ventricular function have shown significant increases in cardiac index and coronary blood flow, with little if any increase in left ventricular end-diastolic pressure.

Electrophysiologic effects: Electrophysiological studies in man show that Cardene does not depress sinus node function or atrial or ventricular conduction in patients with either normal or decreased electrical conduction systems. Refractory periods of the His-Purkinje system were actually shortened slightly by nicardipine and SA conduction time was improved.

5.2 Pharmacokinetic properties

Absorption

Nicardipine is rapidly and completely absorbed with plasma levels detectable 20 minutes following an oral dose. Maximal plasma levels are observed within 30 minutes to two hours (mean T_{max} = 1 hour). When given with a high fat meal peak plasma levels are reduced by 30%. Nicardipine is subject to saturable first-pass metabolism and the bioavailability is about 35% following a 30 mg oral dose at steady state.

Steady state plasma levels are achieved after about 3 days of dosing at 20 and 30 mg tds and remain relatively constant over 28 days of dosing at 30 mg tds. Considerable intersubject variability in plasma levels is observed. Following dosing to steady state using doses of 30 and 40 mg (tds), the terminal plasma half-life of nicardipine averaged 8.6 hours.

Distribution

Nicardipine is highly protein-bound (>99%) in human plasma over a wide concentration range.

Biotransformation

Nicardipine is metabolized by cytochrome P450 3A4. Studies involving either a single dose, or administration 3 times daily for 3 days, have shown that less than 0.03% of unchanged nicardipine is recovered in the urine in humans after oral or intravenous administration. The most abundant metabolite in human

urine is the glucuronide of the hydroxy form, which is formed by the oxidative cleaving of the N-methylbenzyl moiety and the oxidation of the pyridine. Nicardipine does not induce its own metabolism and does not induce hepatic microsomal enzymes.

Elimination

Following a radioactive oral solution dose, 60% of the radioactivity was recovered in the urine and 35% in faeces. Most of the dose (> 90%) was recovered within 48 hours of dosing.

Renal impairment
The pharmacokinetics of orally administered nicardipine SR capsule 45 mg were studied in subjects with severe renal dysfunction requiring hemodialysis (creatinine clearance < 10 ml/min), mild/moderate renal dysfunction (creatinine clearance 10 - 50 mi/min) and normal renal dysfunction (creatinine clearance >50 ml/min). At steady state, Cmax and AUC were significantly higher and clearance significantly lower in subjects with mild/moderate renal dysfunction compared with in subjects with normal renal function. There were no significant differences in the principal pharmacokinetic parameters between severe renal dysfunction and normal renal dysfunction. These results are similar to those seen with other oral formulations (see section 4.4).

Linearity/non-linearity

The pharmacokinetics of Cardene are non-linear due to saturable hepatic first pass metabolism.

5.3 Preclinical safety data

Please refer to section 4.6 Fertility, pregnancy and lactation.

Nicardipine has been shown to pass into the milk of lactating animals. It has been reported in animal experiments that the drug is excreted into breast milk.

In animal experiments where this drug was administered at a high dose during the terminal stage of pregnancy, an increase in fetal deaths, delivery disturbances, decrease in the body weight of offsprings, and suppression of post-natal body weight gain were reported.

However, the toxicity to reproduction has not been reported.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Starch, Pregelatinised
Magnesium Stearate

Capsule shell body
Indigotine E132
Titanium Dioxide E171
Gelatin

Capsule shell cap
Indigotine E132
Titanium Dioxide E171
Gelatin

6.2 Incompatibilities

None known

6.3 Shelf life

Securitainer: 5 years.
Blister packs of 21, 56, 60, 84, 100 and 200 capsules: 3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Securitainer packs of 50 and 100.
PVC/aluminium foil blister strips of 21, 56, 60, 84, 100 and 200 capsules.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Laboratoire X.O
170 Bureaux de la Colline
92213 Saint-Cloud Cedex
France

8 MARKETING AUTHORISATION NUMBER(S)

PL 50164/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/05/1998 / 15/07/2002

10 DATE OF REVISION OF THE TEXT

07/12/2021