

### 1 NAME OF THE MEDICINE

Nicorandil

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each IKOTAB tablet contains either 10 mg or 20 mg nicorandil as the active ingredient.

For the full list of excipients, see section 6.1 List of Excipients.

### 3 PHARMACEUTICAL FORM

IKOTAB 10 mg tablets are round, white tablets, scored on one side and bearing the inscription “10” on the other side.

IKOTAB 20 mg tablets are round, white tablets, scored on one side and bearing the inscription “20” on the other side.

### 4 CLINICAL PARTICULARS

#### 4.1 THERAPEUTIC INDICATIONS

Nicorandil is indicated for the treatment of chronic stable angina pectoris.

#### 4.2 DOSE AND METHOD OF ADMINISTRATION

##### Adults

The recommended therapeutic dose for nicorandil is 10 to 20 mg twice daily. The usual starting dose is 10 mg twice daily (preferably in the morning and in the evening). A lower starting dose of 5 mg twice daily may be used in patients who are prone to headache or other adverse reactions. Dosage should be titrated to the minimum effective dose.

##### Elderly

There are no dosage adjustments required for the elderly patients. However, as with all other medications, the lowest effective dose should be used.

##### Children

Not recommended for use in children as safety and efficacy have not been established.

#### 4.3 CONTRAINDICATIONS

- known or idiosyncratic hypersensitivity to nicorandil, nicotinamide, nicotinic acid or any of the excipients in this product
- cardiogenic shock
- hypotension
- in patients with severe hypotension or with a risk of developing severe hypotension including acute myocardial infarction with acute left ventricular failure and low filling pressures and hypovolaemia
- in patients receiving any soluble guanylate cyclase stimulators (see section 4.5 Interactions with Other Medicines and Other Forms of Interactions)

Due to the risk of severe hypotension, the concomitant use of nicorandil and phosphodiesterase 5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) is contraindicated (see section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

#### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Nicorandil should be used with caution in patients who may have blood volume depletion or in those who present low systolic blood pressure (e.g. below 100 mmHg). The use of nicorandil in patients with cardiogenic shock, or acute myocardial infarction with acute left ventricular failure and low filling pressures should be avoided.

If mouth ulceration stomatitis or persistent or severe buccal ulcerations appear, this drug should be discontinued and appropriate measures taken.

Nicorandil may lower the blood pressure of hypertensive patients and therefore should be used with care when prescribed with antihypertensive drugs.

Gastrointestinal, skin, mucosal, corneal and conjunctival ulcerations have been reported with nicorandil (see section 4.8 Adverse Effects (Undesirable Effects)). Ulceration may occur at different locations in the same patient. Gastrointestinal haemorrhage secondary to gastrointestinal ulceration has also been reported with nicorandil. The onset of ulceration may vary from shortly after initiation of nicorandil treatment to several years after starting nicorandil. Weight loss has been reported in association with gastrointestinal ulcerations. Gastrointestinal ulcerations, if advanced, may develop into perforation, fistulating disease, or abscess formation or may lead to gastrointestinal haemorrhage or weight loss. Occurrence of persisting ulcers should lead to drug discontinuation because the ulcers may be refractory to treatment while taking nicorandil (see section 4.8 Adverse Effects (Undesirable Effects)).

Patients with diverticular disease may be at particular risk of fistula formation or bowel perforation during nicorandil treatment.

Gastrointestinal perforations in the context of concomitant use of nicorandil and corticosteroids have been reported. Caution is advised when concomitant use is considered.

Gastrointestinal ulcerations and haemorrhage in the context of concomitant use of acetylsalicylic acid or non-steroidal anti-inflammatory drugs (NSAIDs) with nicorandil have also been reported. Caution is advised when concomitant use is considered.

Nicorandil should be used with care in combination with other medical products that may increase potassium levels because hyperkalaemia has been reported with nicorandil (see section 4.8 Adverse Effects (Undesirable Effects)).

##### **Use in Hepatic Impairment**

The pharmacokinetics of nicorandil in cirrhotic patients (n = 8) was compared with age matched controls (n = 8) after a single 10 mg oral tablet and IV dose of 0.1 mg/kg. In cirrhotic patients, the AUC after oral dosing was less and  $t_{1/2}$  was longer (1.6 h versus 1.1 h) than those for the control groups. As the changes after oral dosing were minor, it is unlikely that dosage adjustment would be necessary in patients with stabilised liver impairment based solely on pharmacokinetic consideration. However, as nicorandil is primarily metabolised in the liver, the need to reduce the nicorandil dose in patients with severe liver disease cannot be excluded to prevent the potential accumulation following repeated dosing.

##### **Use in Renal Impairment**

The pharmacokinetics of nicorandil was investigated in 3 groups of subjects with varying degrees of renal function (GFR > 80 mL/min, n = 6; 20-80 mL/min, n = 8 and < 20 mL/min, n = 7) receiving 20 mg of nicorandil twice daily for 5 days. Renal impairment did not significantly modify the rate and extent of nicorandil absorption. No correlation exists between nicorandil clearance and creatinine clearance. Thus the decrease of glomerular filtration rate does not significantly alter the disposition profile of nicorandil; thus no dosage adjustment is necessary in patients with renal impairment.

##### **Use in the Elderly**

The pharmacokinetics of nicorandil in 12 elderly patients was compared with 12 young adults receiving 10 mg twice daily for 8 days. There were no clinically relevant differences in the nicorandil pharmacokinetic

parameters. Results from this study suggest that dosage adjustment for elderly patients may not be necessary. However, as with all medicines, use of the lowest effective dose is recommended.

### **Paediatric Use**

Nicorandil is not recommended for use in children as its safety and efficacy in children have not been established.

### **Effects on Laboratory Tests**

No data available.

## **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

### **Smoking**

The effect of smoking on the pharmacokinetics of nicorandil has not been studied.

### **Cimetidine**

The effects of cimetidine (400 mg twice daily for 7 days) on the pharmacokinetics of nicorandil (20 mg twice daily given for 7 days alone and then another 7 days with cimetidine) were assessed in 12 healthy volunteers. The co-administration of cimetidine with nicorandil did not significantly modify the rate of absorption of nicorandil or other pharmacokinetic parameters (such as  $C_{max}$ ,  $t_{max}$  and urinary excretion parameters). Thus, cimetidine does not significantly inhibit the liver enzymes involved in the metabolism of nicorandil. A dose adjustment of nicorandil in patients treated concomitantly with cimetidine, a drug known to be an inhibitor of liver drug metabolising enzymes, may not be necessary.

### **Rifampicin**

The influence of rifampicin (600 mg/day) on nicorandil (20 mg twice daily) pharmacokinetics was assessed in 16 male volunteers. Rifampicin did not modify significantly the pharmacokinetics of nicorandil, except for a slight decrease on  $t_{1/2\beta}$ . Therefore, rifampicin does not modify significantly the extent of nicorandil metabolism or its disposition pattern. As a consequence, a dose adjustment of nicorandil in patients treated concomitantly with rifampicin, a drug known to be a potent inducer of liver drug-metabolising enzymes, may not be necessary.

### **Combination with Nitrate**

Although clinical experience to-date suggests that long-acting nitrate administered concomitantly with nicorandil does not appear to alter nicorandil's clinical acceptability, however, as nicorandil contains a nitrate moiety, caution should be taken for the likelihood of additive hypotensive effects.

### **Other Medicines**

Co-administration of nicorandil does not affect the anticoagulation effect of warfarin. No pharmacological and/or pharmacokinetic interaction has been observed in animal and clinical studies when nicorandil is administered concomitantly with  $\beta$ -blockers, a calcium antagonist, digoxin, a combination of digoxin/furosemide (frusemide), acenocoumarol, rifampicin, and cimetidine. However, the possibility that nicorandil may potentiate the effect of tricyclic antidepressants, antihypertensive drugs or other vasodilators, particularly alcohol, cannot be excluded.

### **Phosphodiesterase 5 Inhibitors**

As hypotensive effects of nitrates or nitric oxide donors are potentiated by phosphodiesterase 5 inhibitors (e.g. sildenafil, tadalafil, vardenafil), the concomitant use of nicorandil and phosphodiesterase 5 inhibitors is contraindicated (see section 4.3 Contraindications). Combination use can lead to a serious fall in blood pressure.

## Soluble Guanylate Cyclase Stimulators

Nicorandil is contraindicated in the concomitant use of soluble guanylate cyclase stimulators such as riociguat, since it can lead to a serious fall in blood pressure (see section 4.3 Contraindications).

## Corticosteroids

Gastrointestinal perforations in the context of concomitant use of nicorandil and corticosteroids or acetylsalicylic acid have been reported. Caution is advised when concomitant use is considered.

## Interactions with Food

Although food has been shown to delay the absorption of nicorandil (16%) it does not affect the extent of absorption. Thus, nicorandil tablets can be taken with meals.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Effects on Fertility

Nicorandil did not affect the fertility of male and female rats at oral doses up to 100 mg/kg/day.

### Use in Pregnancy

Pregnancy Category: B3

Nicorandil has not been studied in pregnant women. Although animal studies have shown that nicorandil is not teratogenic, it has been shown to increase pre-implantation loss at oral doses of 40 mg/kg/day in rats and to increase fetal mortality at doses of 100 mg/kg/day. The significance of these findings in human use is unknown. Nicorandil should not be used during pregnancy unless it is considered essential by the physician.

### Use in Lactation

It is not known whether nicorandil is excreted in milk. Animal studies have shown that nicorandil increases perinatal mortality at 50 mg/kg/day. The significance of this finding to human use is unclear. Thus, nicorandil is not recommended for use during breast feeding.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Nicorandil, as with other vasodilators, may cause dizziness and patients should be advised not to drive or operate any machinery, should dizziness occur. This is especially the case in combination with alcohol.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The following CIOMS frequency rating is used:

- Very common:  $\geq 1/10$  (10%)
- Common:  $\geq 1/100$  (1%) and  $< 1/10$  (10%)
- Uncommon:  $\geq 1/1000$  (0.1%) and  $< 1/100$  (1%)
- Rare:  $\geq 1/10000$  (0.01%) and  $< 1/1000$  (0.1%)
- Very rare:  $< 1/10000$  ( $< 0.01\%$ )

<b>Infections and Infestations</b>	
Common:	abscess (skin abscess)*
Uncommon:	Abscess (anal, genital or other gastrointestinal locations)*
<b>Body as a Whole</b>	
Common:	lethargy, back pain, chest pain infection, feeling of weakness
Uncommon:	malaise, face oedema, fever, leg pain, neck pain, pain, pain in arm
<b>Cardiovascular System</b>	
Common:	increase in heart rate particularly following the administration of nicorandil in high doses, angina pectoris, hypertension, palpitations, vasodilation/flush

Uncommon:	decrease in blood pressure particularly following the administration of nicorandil in high doses, postural hypotension, hypotension, tachycardia, arrhythmia, myocardial infarction, syncope, peripheral vascular disorder
<b>Gastrointestinal Disorders</b>	
Common:	diverticulitis, gastrointestinal haemorrhage, gastrointestinal ulcerations (stomatitis, aphthosis, mouth ulcer, tongue ulcer, small, intestinal ulcer, large intestinal ulcer, anal ulcer)* (See Section 4.4 Special Warnings and Precautions for Use) dyspepsia, nausea, vomiting
Uncommon:	gastrointestinal perforation*, fistula (anal, genital, gastrointestinal and skin fistula)*, anorexia, diarrhoea, constipation, abdominal pain, gastrointestinal disorder
<b>Musculoskeletal and Connective Tissue Disorders</b>	
Common:	myalgia
<b>Nervous System</b>	
Very common:	headache, usually transient in nature, especially when treatment is initiated  Headache is the most commonly reported adverse event (up to 36.4%). It is dose-related, and usually occurs during the first week of treatment and tends to diminish with time. Occasionally, headache may be severe and prolonged. In clinical trials, 5.3% of patients discontinued nicorandil treatment due to headache. Careful dose titration, using low starting dose (5 mg twice daily) for even two days, has significantly reduced the incidence of headache and number of patients discontinuing treatment due to headache.
Common:	dizziness, vertigo
Uncommon:	insomnia, sleep disorder, nervousness, paraesthesia, somnolence, depression
Unknown:	IIIrd nerve paralysis, VIth nerve paralysis
<b>Respiratory System</b>	
Common:	bronchitis, dyspnoea, respiratory disorder
Uncommon:	epistaxis, increased cough
<b>Metabolic Disorders</b>	
Uncommon:	peripheral oedema, oedema
Rare:	hepatic function abnormalities
Very rare:	liver disorders such as hepatitis, cholestasis, or jaundice
Unknown:	hyperkalaemia (see Section 4.4 Special Warnings and Precautions for Use)
<b>Skin and Subcutaneous Tissue Disorders</b>	
Common:	skin and mucosal ulcerations (mainly peri-anal ulcerations, genital ulcerations and para-stomal ulcerations)* (See Section 4.4 Special Warnings and Precautions for Use)
Uncommon:	pruritus, different types of rash, sweating
Very rare:	angioedema
<b>Eye Disorders</b>	
Uncommon	conjunctivitis, conjunctival ulcer and corneal ulcer
Unknown	diplopia, ophthalmoplegia
<b>Special Senses</b>	
Uncommon:	vestibular disorder
Rare:	tinnitus
<b>Blood and Lymphatic System Disorders</b>	
Unknown:	thrombocytopenia has been rarely reported in association with nicorandil treatment

## Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## 4.9 OVERDOSE

No data are available concerning overdosage of nicorandil in humans. However, in case of overdosage, peripheral vasodilation with a fall in blood pressure and reflex tachycardia can be expected. In such an event, monitoring of cardiac function and general supportive measures should be used. If not successful, circulating

plasma volume should be increased by substitution of fluid. In life-threatening situations, administration of vasopressors should be considered.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

#### Mechanism of Action

Nicorandil, a potassium channel opener with nitrate moiety, is an antianginal agent with a dual mechanism of action:

- (i) It opens ATP-dependent potassium (KATP) channels in vascular smooth muscle and hence causes a hyperpolarisation of the smooth muscle cells. This leads to arterial dilation and afterload reduction.
- (ii) Due to its nitrate moiety, nicorandil also relaxes vascular smooth muscle, particularly in the venous vascular system, via an increase in intracellular cyclic GMP. This results in an increase pooling in capacitance vessels with a decrease in preload.

Nicorandil has been shown to exert a direct effect on the coronary arteries, both on normal and stenotic segments, without leading to a steal phenomenon. Furthermore, the reduction of end-diastolic pressure and wall tension decreases the extravascular component of vascular resistance. Ultimately, this results in an improved oxygen balance in the myocardium and improved blood flow in the post-stenotic areas of the myocardium and, thus, reducing infarct size. Nicorandil has no direct effect on myocardial contractility, cardiac conduction and rhythm. Furthermore, nicorandil has demonstrated a powerful spasmolytic activity in both in-vitro and in-vivo studies and reverses coronary spasm induced by methacholine or noradrenaline.

The activation of ATP-dependant K-channels by nicorandil or other potassium channel openers causes relaxation of all types of smooth muscle. In an asthma model, the three known K-channel openers (cromakalim, pinacidil and nicorandil) were compared. Nicorandil was weakest of the three in terms of bronchodilator activity. Results from clinical trials with nicorandil have not shown any deterioration of airways function during treatment.

Nicorandil has no effect on renal function and electrolytes. Following 1-year therapy of nicorandil, plasma levels of sodium, potassium, creatinine and blood urea nitrogen remained unchanged.

Nicorandil has specificity for the KATP channels in the blood vessels and not for the KATP channels present in the pancreas. At the doses used for its vasodilatory action, nicorandil does not produce hyperpolarisation on the  $\beta$ -cells in the pancreas and therefore does not affect insulin secretion and hence blood glucose. There was no change in plasma glucose levels in patients receiving nicorandil therapy for 1 year. Animal studies show that the vascular effects of potassium channel openers can be inhibited by glibenclamide, however, to inhibit the vascular effect of potassium channel openers the sulphonylureas have to be administered at doses 100 to 1000 times higher than the therapeutic dose. There was no change in plasma lipids in patients receiving nicorandil therapy.

The pharmacological data and clinical findings give no indication of a direct interaction between nicorandil and the sympathetic-adrenergic system or neurohumoural mechanism. Indirect activation of the adrenergic system and the renin-angiotensin system may occur as a result of excessive vasodilation or reduction in blood pressure, but only at doses higher than the therapeutic recommended dosage.

#### Clinical Trials

Clinical studies employing exercise tolerance test as major end point show that nicorandil at doses 10 to 20 mg twice daily is as efficacious as other anti-anginal agents (including diltiazem, nifedipine, isosorbide mononitrate, isosorbide dinitrate, propranolol, metoprolol and atenolol) in treating patients with chronic stable angina. Most of the controlled, comparative studies were of limited duration (= 3 months) and included

patients with anginal attacks usually less than five per week. Data on the influence of nicorandil on myocardial infarction and mortality was limited. There is a trend to increased anti-anginal efficacy when nicorandil is added to  $\beta$ -blocker or calcium channel blocker, but this was not statistically significant. Efficacy testings at 2-hours and 12-hours suggest a prolonged anti-anginal effect of nicorandil which is longer than nicorandil's half-life. Some studies did investigate three times daily dosing with nicorandil, but this did not appear to present any advantages over twice daily dosing, although no strictly comparative studies of different dosing frequencies were performed. Long-term uncontrolled studies show that nicorandil maintains its efficacy with no evidence of tolerance developing up to 2 years after commencement of therapy.

The efficacy of nicorandil in preventing coronary artery spasm in patients with vasospastic angina was compared to nifedipine in provocation test using methylergometrine. Nicorandil was shown to be at least as effective as nifedipine. The benefit of nicorandil in unstable angina has not yet been fully established.

### Laboratory Safety Monitoring

Abnormal laboratory test results were very infrequent with nicorandil. However, in the short- and medium-term studies, the testings were performed at the beginning of the study (as a baseline) and at its termination (up to 3 months later). Thus, transient laboratory abnormalities could have been missed.

### Haemodynamic Safety Monitoring

In hypertensive patients (n = 12), single doses of nicorandil (10, 20 and 30 mg) compared to placebo produced an acute and significant reduction in both systolic and diastolic, supine and upright blood pressure which peaked at 4 to 6 hours. After 24 hours, only the 30 mg dose continued to have a significant effect. Heart rate did not alter significantly. In patients with ischaemic heart disease undergoing routine cardiac catheterisation, a single dose of 40 mg nicorandil caused significant decreases in aortic systolic and diastolic pressure which occurred 30 minutes after dosing and reached maximum at 45 minutes. When nicorandil was administered in doses of 60 mg and, to a lesser extent 40 mg, dizziness and hypotension became relatively common side effects. In normotensive volunteers, a single 10 mg and 20 mg nicorandil dose did not affect blood pressure.

## **5.2 PHARMACOKINETIC PROPERTIES**

### **Absorption**

After oral administration, nicorandil is absorbed rapidly and maximum plasma concentrations are reached after about 30-60 minutes. The absolute bioavailability of nicorandil is about 75% indicating that nicorandil is well absorbed from the gastrointestinal tract without undergoing significant hepatic first-pass effect. The plasma concentrations (and the area under the curve) show linear proportionality to the dose (5 mg to 40 mg). The drug disposition parameters (distribution volume, mean residence time, total body clearance and apparent elimination half-life) remain unchanged within the therapeutic dose range. Following repeated dosing of 10 or 20 mg nicorandil twice daily, higher nicorandil concentrations were observed at Day 10 compared to Day 1. Accumulation ratios ( $AUC_{Day 10}/AUC_{Day 1}$ ) of 1.7 for 10 mg and 2.0 for 20 mg were observed. Steady-state plasma concentrations of nicorandil usually are reached within approximately 96-120 h after twice daily dosing.

### **Distribution**

The decrease in plasma concentration reveals two distinct phases:

- a rapid elimination phase with a half-life of about 1 hour responsible for approximately 96% of the decline in the plasma concentration;
- a slow elimination phase occurring between the 8<sup>th</sup> and 24<sup>th</sup> hour following oral dosing

Nicorandil is not extensively bound to human plasma proteins (free fraction estimated to be about 75%).

### **Metabolism**

Metabolism occurs mainly by denitration of the molecule. The denitration product is then further metabolised via the nicotinamide pathway.

## Excretion

Nicorandil and its metabolites are mainly excreted in the urine. Only 1% of the administered dose was excreted in the faeces, whereas more than 60% of the administered dose was eliminated in the urine 24 hours after dosing. Only approximately 1% of nicorandil is excreted unchanged in the urine, and the remaining being mainly the denitrated metabolite (9%) and its derivatives (e.g. nicotinuric acid 6 %, nicotinamide 1%, nicotinamide 1%, N-methylnicotinamide < 1% and nicotinic acid < 1%).

## 5.3 PRECLINICAL SAFETY DATA

### Genotoxicity

Mutagenicity and carcinogenicity studies did not reveal any adverse effect of nicorandil under the experimental conditions. Nicorandil has shown no genotoxic potential in a series of assays for gene mutations and chromosomal damage.

### Carcinogenicity

Nicorandil has shown no carcinogenic potential in two year old studies in mice (100 mg/kg/day) and rats (20 and 40 mg/kg/day for male and female rats respectively).

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

The tablets also contain the following inactive ingredients: pregelatinised maize starch, croscarmellose sodium, stearic acid and mannitol.

### 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

### 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Store in the original package. Discard 30 days after opening the blister strip.

### 6.5 NATURE AND CONTENTS OF CONTAINER

Container type: blister pack (Al/Al)

Pack sizes: 20, 60

Some strengths, pack sizes and/or pack types may not be marketed.

### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

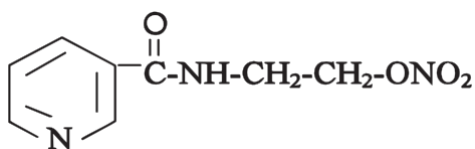
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

### 6.7 PHYSICOCHEMICAL PROPERTIES

#### Chemical Structure

Nicorandil is a white crystalline powder or white needles with a faint, characteristic odour. It is freely soluble in acetone, methanol, ethanol and acetonitrile; soluble in ethylacetate and chloroform; sparingly soluble in water; slightly soluble in ether.





Chemical name: N-(2-hydroxyethyl)-nicotinamide nitrate (ester)

Molecular formula: C<sub>8</sub>H<sub>9</sub>N<sub>3</sub>O<sub>4</sub>

Molecular weight: 211.2

### CAS Number

65141-46-0

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

## 8 SPONSOR

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## 9 DATE OF FIRST APPROVAL

14/11/2014

## 10 DATE OF REVISION

01/04/2021

### Summary Table of Changes

Section Changed	Summary of New Information
4.4	Additional information regarding gastrointestinal ulceration precaution
4.5	IHIN update – furosemide (frusemide). Addition of concomitant use of acetylsalicylic acid under heading Corticosteroids.
5.1	Added information regarding non statistically significant increased trend to anti-anginal efficacy when nicorandil is added to β-blocker or calcium channel blocker.
4.8, 5.3	Minor editorial changes
4.8	Update to infections and infestations, gastrointestinal disorders, nervous system, metabolic disorders, skin and subcutaneous issue disorders, eye disorders, blood and lymphatic system disorders

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