DATA SHEET

1 IKOREL

Ikorel 10 mg and 20 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mg tablet contains 10 mg nicorandil.

Each 20 mg tablet contains 20 mg nicorandil

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

10 mg tablets: Off-white round tablets, scored, plain on one side, and IK10 on the other.

20 mg tablets: Off-white round tablets, scored, plain on one side, and IK20 on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Nicorandil is indicated for the symptomatic treatment of stable angina pectoris that is inadequately controlled or have a contraindication or intolerance to first-line anti-anginal therapies.

4.2 DOSE AND METHOD OF ADMINISTRATION

The usual therapeutic range is 10 to 20 mg twice daily.

The usual starting dose is 10 mg twice daily, in the morning and in the evening preferably, and should be titrated upwards in accordance with patients' needs, response and tolerance up to 40mg twice daily, if necessary. An even lower starting dose of 5 mg twice daily may be used in patients particularly prone to headache.

Elderly

There are no special dosage requirements for elderly patients, but as with all medicines the lowest effective dose should be used. Nicorandil should be administered with care, using low starting dosages, in the elderly.

Paediatric Population

Nicorandil is not recommended in paediatric patients since its safety and effectiveness have not been established in this age group.

Diabetes, Renal or Hepatic Dysfunction

Nicorandil should be used with caution in patients with serious hepatic dysfunction.

4.3 CONTRAINDICATIONS

- in patients with known or idiosyncratic hypersensitivity to nicorandil, nicotinamide, nicotinic acid or any of the excipients listed in Section 6.1
- in patients with severe hypotension or with a risk of developing severe hypotension including shock (including cardiogenic shock) or left ventricular failure with low filling pressure and hypovolaemia.
- hypotension
- in patients receiving any soluble guanylate cyclase stimulators (see section 4.5).
- 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).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypotension

Nicorandil should be used with caution in patients who present with low systolic blood pressure (eg. below 100 mm Hg).

The hypotensive effect of other vasodilators, tricyclic antidepressants or alcohol can be increased by administration in combination with nicorandil.

Hypertension

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

Ulcerations

Gastrointestinal, skin, mucosal, corneal and conjunctival ulcerations have been reported with nicorandil (see section 4.8). Ulceration may occur at different locations in the same patient. Gastrointestinal haemorrhage secondary to gastrointestinal ulceration has also been reported with nicorandil. Weight loss has been reported in association with gastrointestinal ulcerations. Occurrence of persisting ulcers should lead to drug discontinuation because the ulcers may be refractory to treatment while taking nicorandil. (see section 4.8).

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

Based on available information, the time between starting nicorandil use and the onset of ulceration ranges from shortly after initiating nicorandil treatment to several years after starting nicorandil.

Diverticular Disease

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

Corticosteroids

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

NSAIDS

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.

Glaucoma

Caution is advised for the use of nicorandil in patients with glaucoma.

Hyperkalaemia

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).

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 t1/2 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.

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.

Paediatric Use

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

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.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

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 Cmax, tmax 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 of t1/2β. 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.

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). 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).

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.

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 human studies when nicorandil is administered concomitantly with beta-blockers, calcium antagonists, digoxin, a combination of digoxin/furosemide, acenocoumarol, rifampicin, and cimetidine. However, the possibility that nicorandil may potentiate the effect of tricyclic antidepressants, antihypertensive drugs or other vasodilators, particularly alcohol, can not be excluded.

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.

Smoking

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

4.6 FERTILITY, PREGNANCY AND LACTATION

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 is unknown. Nicorandil should not be used during pregnancy unless it is considered essential by the physician.

Breastfeeding

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 UNDESIRABLE EFFECTS

The following CIOMS frequency rating is used:

very common	≥1/10 (10%)
common	≥ 1/100 (1%) and < 1/10 (10%)
uncommon	≥ 1/1000 (0.1%) and < 1/100 (1%)
rare	≥ 1/10000 (0.01%) and < 1/1000 (0.1%)
very rare	< 1/10000 (< 0.01%)

Body as a Whole

common: abdominal pain, lethargy, back pain, chest pain, infection, feeling of weakness

uncommon: malaise, face oedema, fever, leg pain, neck pain, pain, pain in the arm

Cardiovascular System

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

Gastrointestinal Disorders

common: dyspepsia, nausea, vomiting

uncommon: anorexia, diarrhoea, constipation, gastrointestinal disorder

rare: gastrointestinal ulcerations, such as stomatitis/mouth ulceration, tongue ulcers, small intestine ulcer, large intestine ulcer and anal ulcer. These ulcers, if advanced, may develop into perforation, fistulating disease, or abscess formation or may lead to gastrointestinal haemorrhage or weight loss (see section 4.4).

Musculoskeletal and Connective Tissue Disorders

common: myalgia

Nervous System

very common: headache, usually transient in nature, especially when treatment is initiated.

common: dizziness, vertigo

uncommon: insomnia, sleep disorder, nervousness, paraesthesia, somnolence, depression

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.

Respiratory System

common: bronchitis, dyspnoea, respiratory disorder

uncommon: epistaxis, increased cough

Metabolic Disorder

uncommon: peripheral oedema, oedema

rare: hepatic function abnormalities

very rare: liver disorders such as hepatitis, cholestasis, or jaundice

Skin and Subcutaneous Tissue Disorders

uncommon: pruritus, different types of rash, sweating

very rare: angioedema

Eye Disorder

very rare: conjunctivitis, conjunctival ulcer and corneal ulcer

Special Senses

uncommon: vestibular disorder

rare: tinnitus

Post-Marketing Adverse Events

The following additional adverse reactions have been reported during postmarketing experience; they are derived from spontaneous reports and therefore, the frequency of these adverse reactions is not known:

Skin and Subcutaneous Tissue Disorders

Skin and mucosal ulcerations (mainly peri-anal ulcerations, genital ulcerations and para-stomal ulcerations)

Eye Disorders

Diplopia

Blood and Lymphatic System Disorders

Thrombocytopenia has been rarely reported in association with nicorandil treatment

Metabolism and Nutrition Disorders

Hyperkalaemia (see section 4.4)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

No data are available concerning overdosage of nicorandil in humans. However, in the 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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

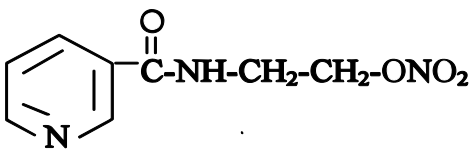
5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other vasodilators used in cardiac diseases, ATC code: C01DX16

Chemical Name

Nicorandil

Chemical Structure



CAS Registry Number

65141-46-0

Description

Nicorandil is N-(2-hydroxyethyl)-nicotinamide nitrate (ester). It 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.

Mechanism of action

The coronary vasodilating activity of nicorandil is considered to be the consequence of the increasing cyclic GMP production by stimulating guanylyl cyclase in the coronary vascular smooth muscle, similar to other nitrates/nitrites (*in vitro*). In addition, other mechanisms such as hyperpolarization of the cell membrane were investigated concerning its coronary blood flow-increasing and coronary vasospasmolytic effects.

The vasorelaxant effect of nicorandil in isolated blood vessels is suppressed by an ATP-sensitive K channel blocker or a guanylate cyclase inhibitor. Moreover, in a canine model of acute heart failure, the cardiac haemodynamics-improving effect of the drug (e.g. effect of increasing the aortic blood flow) was suppressed by an ATP-sensitive K channel blocker. Furthermore, the drug caused an increase in the cGMP content in isolated blood vessels. These facts suggest that the vasodilating effect of the drug is related to the effect of opening the ATP-sensitive K channel, as well as to the effect of increasing production of cGMP.

Pharmacodynamic effects

Potassium channel opening effects a titratable and sustained dilating action on both arterial and coronary vasculature, including both coronary artery conductance and resistance vessels, to reduce cardiac afterload. The nitrate moiety effect dilates venous capacitance vessels to decrease cardiac preload.

Nicorandil has a marked coronary spasmolytic action, exerting a direct effect on both normal and stenotic segments of coronary arteries without significant effects on myocardial contractility or conductivity, or the development of the so-called "steal phenomenon". Furthermore, the reduction of end-diastolic pressure and wall tension decreases the extravascular component of vascular resistance. This results in an improved oxygen balance in the myocardium and improved blood flow in the post-stenotic areas of the myocardium.

Clinical Efficacy and Safety

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 ß-blocker or calcium channel blocker, but this was not statistically significant. Efficacy testings at 2-hour and 12-hour 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 completely from the gastrointestinal tract. The absolute bioavailability is about 75%. There is no significant hepatic first-pass effect.

Maximum plasma concentrations are reached after about 30-60 minutes. The plasma concentration (and the area under the curve) show a linear proportionality to the dose. The drug disposition processes (distribution volume, mean residence time, total body clearance and apparent elimination half-life) remain stable whatever the dose in the therapeutic range.

The pharmacokinetic parameters of nicorandil were observed in 6 healthy adult volunteers after a single oral dose of 10 mg of nicorandil. The plasma concentration was 112.6 ± 35.5 (mean ± S.E.) ng/mL, 133.5 ± 26.3 ng/mL, 104.9 ± 14.3 ng/mL, 63.2 ± 12.0 ng/mL, 9.9 ± 2.5 ng/mL, at 0.25 hours, 0.5 hours, 1.0 hour, 2.0 hours, and 4.0 hours after administration, respectively. The area under the curve (AUC) in steady-state was 262.5 ± 43.1 hr·ng/mL. The maximum concentration (Cmax) was 152.3 ± 29.2 ng/mL at 0.55 ± 0.12 hours (Tmax).

Distribution

Nicorandil is only slightly bound to human plasma proteins (free fraction estimated at about 75%). The decrease in plasma concentration reveals two different processes:

1. a rapid elimination phase with a half-life of about 1 hour, which covers about 96% of the plasma concentration
2. a slow elimination phase occurring between the 8th and the 24th hour following the oral dose

According to an *in vitro* study using human serum, the serum protein binding rate of the compound was 34.2 to 41.5% (as tested at nicorandil concentrations of 1 to 100 μg/mL).

Metabolism

Metabolism takes place mainly via denitration of the molecule with the denitrated product then merging into the nicotinamide pathway. Nicorandil and its metabolites are mainly excreted by the kidney. About 21% of the administered dose is eliminated through the urine with about 1% as the unchanged compound and the remainder as mainly the denitrated metabolite (about 7%) and derivatives following denitration (eg. nicotinuric acid, nicotinamide, N-methylnicotinamide and nicotinic acid).

Steady state is rapidly achieved during twice daily administration.

A metabolism/excretion study performed in 4 healthy adult volunteers administered a single oral dose of 20 mg of [D]-nicorandil revealed that the compound was mostly metabolised via denitration to N-(2-hydroxyethyl) nicotinamide. The metabolite was found in the plasma as early as 0.5 hour after the administration, reached a peak plasma concentration at 2 hours, and was almost completely eliminated from the plasma by 8 hours. The cumulative urinary excretion rate in 24 hours after dosing was 0.7 to 1.2% of the dose given as nicorandil and 6.8 to 17.3% as its metabolite N-(2-hydroxyethyl) nicotinamide.

Pharmacokinetic/ pharmacodynamic relationship

No clinically relevant modifications of the nicorandil pharmacokinetic profile is evidenced in populations at risk such as elderly people, or patients with liver disease or chronic renal failure. Moreover, the metabolism of nicorandil does not appear to significantly interact with that of cimetidine, rifampicin, anticoagulants, digoxin or other antianginal treatments.

5.3 PRECLINICAL SAFETY DATA

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

Carcinogenicity

Carcinogenicity studies found no indication of carcinogenic activity in rats administered nicorandil for 2 years.

Mutagenicity

Mutagenicity and genotoxicity studies, with and without metabolic activation where appropriate, have shown that nicorandil has no mutagenic activity *in vitro* in either bacterial (Ames test) or mammalian cells (Chinese hamster lung DON). Nicorandil does not induce chromosomal damage *in vivo* in the mouse micronucleus assay.

Impairment of Fertility

Fertility studies showed no effects on mating ability in either male or female rats, but decreases of alive foetuses and implantation sites were noted at 50 mg/kg/day and over. Additional investigative studies for testicular toxicity revealed histopathological changes in spermatogenic cells, as well as decreases of blood flow in the testis and testosterone level in the blood. These results suggest that testicular toxicity by nicorandil is related to sustained decrease of blood flow caused by reduction of cardiac output. Upon cessation of treatment, recovery from nicorandil-induced testicular toxicity was observed after 4 weeks, that indicates reversible changes.

Teratogenicity

Teratogenic studies in rats and rabbits indicate that, following exposure to nicorandil at doses that were maternally toxic, there was embryotoxicity observed. There was no evidence of teratogenicity (rats and rabbits), or abnormal pre- or postnatal physical or behavioral development (rats). Embryotoxic/teratogenic effects were not observed in rats at 25 mg/kg/day or rabbits at 12.5 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

maize starch

croscarmellose sodium

stearic acid

mannitol

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

18 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Store in a dry place.

6.5 NATURE AND CONTENTS OF CONTAINER

10 mg tablets: Off-white round, scored, plain on one side, and IK10 on the other. 60s

20 mg tablets: Off-white round, scored, plain on one side, and IK20 on the other. 60s

1 silica gel desiccant capsule positioned at one end of the strip. Each cavity containing an Ikorel tablet is connected with the desiccant capsule by a channel.

The desiccant capsule must not be swallowed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

sanofi-aventis new zealand limited

Level 8, 56 Cawley Street

Ellerslie

Auckland

Toll Free Number (medical information): 0800 283 684

Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

28 October 1993

10 DATE OF REVISION OF THE TEXT

18 September 2018

Section	Change
All	Format changes to align with new data sheet format
4.2	Addition of paediatric warning
4.3	Revised contraindications
4.4	Editorial changes
4.8	Editorial changes
5.1	New mechanism of action information; editorial changes
5.2	New information
5.3	New information
6.3	New information
6.5	New information
8	Expanded contact details