1.3.1. Shot product characteristic (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Ranolazine Extended-Release Tablets 500 mg

Cartinex-500

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated extended-release tablet contains: Ranolazine 500 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Extended-release Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ranolazine is indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies (such as beta-blockers and/or calcium antagonists).

4.2 Posology and method of administration

Patients should be given the Ranolazine package leaflet and the Patient Alert Card and instructed to present their Patient Alert Card and medication list to their health care professional at each visit.

Posology

Ranolazine is available as 375 mg, 500 mg, and 750 mg prolonged-release tablets.

Adults: The recommended initial dose of Ranolazine is 375 mg twice daily. After 2–4 weeks, the dose should be titrated to 500 mg twice daily and, according to the patient's response, further titrated to a recommended maximum dose of 750 mg twice daily

If a patient experiences treatment-related adverse events (e.g. dizziness, nausea, or vomiting), down-titration of Ranolazine to 500 mg or 375 mg twice daily may be required. If symptoms do not resolve after dose reduction, treatment should be discontinued.

Concomitant treatment with CYP3A4 and P-glycoprotein (P-gp) inhibitors: Careful dose titration is recommended in patients treated with moderate CYP3A4 inhibitors (e.g. diltiazem, fluconazole, erythromycin) or P-gp inhibitors (e.g. verapamil, ciclosporin).

Concomitant administration of potent CYP3A4 inhibitors is contraindicated.

Renal impairment: Careful dose titration is recommended in patients with mild to moderate renal impairment (creatinine clearance 30–80 ml/min). Ranolazine is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min).

Hepatic impairment: Careful dose titration is recommended in patients with mild hepatic impairment. Ranolazine is contraindicated in patients with moderate or severe hepatic impairment.

Elderly: Dose titration in elderly patients should be exercised with caution.

Elderly may have increased ranolazine exposure due to age-related decrease in renal function. The incidence of adverse events was higher in the elderly

Low weight: The incidence of adverse events was higher in patients with low weight (≤ 60 kg). Dose titration in patients with low weight should be exercised with caution.

Congestive heart failure (CHF): Dose titration in patients with moderate to severe CHF (NYHA Class III–IV) should be exercised with caution.

Paediatric population

The safety and efficacy of Ranolazine in children below the age of 18 years have not been established.

No data are available

Method of administration

Ranolazine tablets should be swallowed whole and not crushed, broken, or chewed. They may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients

Severe renal impairment (creatinine clearance < 30 ml/min)

Moderate or severe hepatic impairment

Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, voriconazole, posaconazole, HIV protease inhibitors, clarithromycin, telithromycin, nefazodone)

Concomitant administration of Class Ia (e.g. quinidine) or Class III (e.g. dofetilide, sotalol) antiarrhythmics other than amiodarone.

4.4 Special warnings and precautions for use

Caution should be exercised when prescribing or up titrating ranolazine to patients in whom an increased exposure is expected:

- Concomitant administration of moderate CYP3A4 inhibitors
- Concomitant administration of P-gp inhibitors
- Mild hepatic impairment
- Mild to moderate renal impairment (creatinine clearance 30–80 ml/min)
- Elderly
- Patients with low weight (≤ 60 kg)
- Patients with moderate to severe CHF (NYHA Class III–IV)

In patients with a combination of these factors, additional exposure increases are expected. Dose-dependent side effects are likely to occur. If Ranolazine is used in patients with a combination of several of these factors, monitoring of adverse events should be frequent, the dose reduced, and treatment discontinued, if needed.

The risk for increased exposure leading to adverse events in these different subgroups is higher in patients lacking CYP2D6 activity (poor metabolisers, PM) than subjects with CYP2D6 metabolising capacity (extensive metabolisers, EM. The above precautions are based on the risk in a CYP2D6 PM patient, and are needed when the CYP2D6 status is unknown. There is a lower need for precautions in patients with CYP2D6 EM status. If the CYP2D6 status of the patient has been determined (e.g. by genotyping) or is previously known to be EM, Ranolazine can be used with caution in these patients when they have a combination of several of the above risk factors.

QT prolongation: A population-based analysis of combined data from patients and healthy volunteers demonstrated that the slope of the plasma concentration-QTc relationship was estimated to be 2.4 msec per 1000 ng/ml, which is approximately equal to a 2- to 7-msec increase over the plasma concentration range for ranolazine 500 to 1000 mg twice daily. Therefore, caution should be observed when treating patients with a history of congenital or a family history of long QT syndrome, in patients with known acquired QT interval prolongation, and in patients treated with drugs affecting the QTc interval

Drug-drug interactions: Co-administration with CYP3A4 inducers is expected to lead to lack of efficacy. Ranolazine should not be used in patients treated with CYP3A4 inducers (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, St. John's Wort)

Renal impairment: Renal function decreases with age and it is therefore important to check renal function at regular intervals during treatment with ranolazine <750 mg tablet>

Lactose: This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on Ranolazine

CYP3A4 or P-gp inhibitors: Ranolazine is a substrate of cytochrome CYP3A4. Inhibitors of CYP3A4 increase plasma concentrations of Ranolazine. The potential for dose-related adverse events (e.g. nausea, dizziness) may also increase with increased plasma concentrations. Concomitant treatment with ketoconazole 200 mg twice daily increased the AUC of Ranolazine by 3.0- to 3.9-fold during Ranolazine treatment. Combining Ranolazine with potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, voriconazole, posaconazole, HIV protease inhibitors, clarithromycin, telithromycin, and nefazodone) is contraindicated. Grapefruit juice is also a potent CYP3A4 inhibitor.

Diltiazem (180 to 360 mg once daily), a moderately potent CYP3A4 inhibitor, causes dose-dependent increases in average Ranolazine steady-state concentrations of 1.5- to 2.4-fold. Careful dose titration of Ranolazine is recommended in patients treated with Diltiazem and other

moderately potent CYP3A4 inhibitors (e.g. erythromycin, fluconazole). Down-titration of Ranolazine may be required.

Ranolazine is a substrate for P-gp. Inhibitors of P-gp (e.g. ciclosporin, verapamil) increase plasma levels of Ranolazine. Verapamil (120 mg three times daily) increases Ranolazine steady-state concentrations 2.2-fold. Careful dose titration of Ranolazine is recommended in patients treated with P-gp inhibitors. Down-titration of Ranolazine may be required.

CYP3A4 inducers: Rifampicin (600 mg once daily) decreases Ranolazine steady-state concentrations by approximately 95%. Initiation of treatment with Ranolazine should be avoided during administration of inducers of CYP3A4 (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, St. John's Wort).

CYP2D6 inhibitors: Ranolazine is partially metabolised by CYP2D6; therefore, inhibitors of this enzyme may increase plasma concentrations of Ranolazine. The potent CYP2D6 inhibitor paroxetine, at a dose of 20 mg once daily, increased steady-state plasma concentrations of Ranolazine 1000 mg twice daily by an average of 1.2-fold. No dose adjustment is required. At the dose level 500 mg twice daily, co-administration of a potent inhibitor of CYP2D6 could result in an increase in Ranolazine AUC of about 62%.

Effects of Ranolazine on other medicinal products

Ranolazine is a moderate to potent inhibitor of P-gp and a mild inhibitor of CYP3A4, and may increase plasma concentrations of P-gp or CYP3A4 substrates. Tissue distribution of drugs which are transported by P-gp may be increased.

Dose adjustment of sensitive CYP3A4 substrates (e.g., simvastatin, lovastatin) and CYP3A4 substrates with a narrow therapeutic range (e.g., ciclosporin, tacrolimus, sirolimus, everolimus) may be required as RANOLAZINE may increase plasma concentrations of these drugs.

Available data suggest that Ranolazine is a mild inhibitor of CYP2D6. Ranolazine 750 mg twice daily increased plasma concentrations of metoprolol by 1.8-fold. Therefore the exposure to metoprolol or other CYP2D6 substrates (e.g. propafenone and flecainide or, to a lesser extent, tricyclic antidepressants and antipsychotics) may be increased during co-administration with Ranolazine, and lower doses of these medicinal products may be required.

The potential for inhibition of CYP2B6 has not been evaluated. Caution is advised during co-administration with CYP2B6 substrates (e.g. bupropion, efavirenz, and cyclophosphamide).

Digoxin: An increase in plasma digoxin concentrations by an average of 1.5-fold has been reported when Ranolazine and digoxin are co-administered. Therefore, digoxin levels should be monitored following initiation and termination of Ranolazine therapy.

Simvastatin: Simvastatin metabolism and clearance are highly dependent on CYP3A4. Ranolazine 1000 mg twice daily increased plasma concentrations of simvastatin lactone, simvastatin acid by about 2 fold. Rhabdomyolysis has been associated with high doses of simvastatin and cases of rhabdomyolysis have been observed in patients receiving Ranolazine and simvastatin, in post marketing experience. Limit the dose of simvastatin to 20 mg once daily in patients taking any dose of Ranolazine.

Atorvastatin: Ranolazine 1000 mg twice daily increased Cmax and AUC of atorvastatin 80 mg once daily by 1.4- and 1.3 -fold, respectively and changed the Cmax and AUC of atorvastatin metabolites less than 35%. Dose limitation of atorvastatin and appropriate clinical monitoring may be considered when taking Ranolazine.

Dose limitation of other statins, metabolised by CYP3A4 (e.g. lovastatin), may be considered when taking Ranolazine.

Tacrolimus, ciclosporin, sirolimus, everolimus:

Increased plasma concentrations of tacrolimus, a CYP3A4 substrate, have been observed in patients after Ranolazine administration. It is recommended that tacrolimus blood levels are monitored when co-administering Ranolazine and tacrolimus and that tacrolimus dosage is adjusted accordingly. This is also recommended for other CYP3A4 substrates with a narrow therapeutic range (e.g., ciclosporin, sirolimus, and everolimus).

Drugs transported by the Organic Cation Transporter-2 (OCT2):

Plasma exposure of metformin (1000 mg twice daily) increased 1.4- and 1.8-fold in subjects with type 2 diabetes mellitus when co-administered with RANOLAZINE 500 mg and 1000 mg twice daily respectively. The exposure of other OCT2 substrates, including but not limited to pindolol and varenicline may be affected to a similar degree.

There is a theoretical risk that concomitant treatment of Ranolazine with other drugs known to prolong the QTc interval may give rise to a Pharmacodynamic interaction and increase the possible risk of ventricular arrhythmias. Examples of such drugs include certain antihistamines (e.g.

terfenadine, astemizole, and mizolastin), certain antiarrhythmic (e.g. quinidine, disopyramide, and procainamide), erythromycin, and tricyclic antidepressants.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of Ranolazine in pregnant women. Animal studies are insufficient with respect to effects on pregnancy and embryo foetal development. The potential risk for humans is unknown. It should not be used during pregnancy unless clearly necessary.

Lactation

It is unknown whether Ranolazine is excreted in human breast milk. The excretion of Ranolazine in milk has not been studied in animals. Ranolazine should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects of Ranolazine on the ability to drive and use machines have been performed. Ranolazine may cause dizziness, blurred vision, diplopia, confusional state, coordination abnormal, hallucination, which may affect the ability to drive and use machines

4.8 Undesirable effects

Undesirable effects in patients receiving Ranolazine are generally mild to moderate in severity and often develop within the first 2 weeks of treatment. These were reported during the Phase 3 clinical development programme, which included a total of 1,030 chronic angina patients treated with Ranolazine.

The adverse events, considered to be at least possibly related to treatment, are listed below by body system, organ class, and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), and very rare (< 1/10,000).

Metabolism and nutrition disorders

Uncommon: anorexia, decreased appetite, dehydration.

Psychiatric disorders

Uncommon: anxiety, insomnia, confusional state, hallucination.

Rare: disorientation.

Nervous system disorders

Common: dizziness, headache.

Uncommon: lethargy, syncope, hypoaesthesia, somnolence, tremor, postural dizziness, paresthesia.

Rare: amnesia, depressed level of consciousness, loss of consciousness, coordination abnormal, gait disturbance, parosmia.

Eye disorders

Uncommon: blurred vision, visual disturbance, diplopia.

Ear and labyrinth disorders

Uncommon: vertigo, tinnitus.

Rare: impaired hearing.

Vascular disorders

Uncommon: hot flush, hypotension.

Rare: peripheral coldness, orthostatic hypotension.

Respiratory, thoracic, and mediastinal disorders

Uncommon: dyspnoea, cough, epistaxis.

Rare: throat tightness.

Gastrointestinal disorders

Common: constipation, vomiting, nausea.

Uncommon: abdominal pain, dry mouth, dyspepsia, flatulence, stomach discomfort.

Rare: pancreatitis, erosive duodenitis, oral hypoaesthesia.

Skin and subcutaneous tissue disorders

Uncommon: pruritus, hyperhidrosis.

Rare: angioedema, allergic dermatitis, urticaria, cold sweat, rash.

Musculoskeletal and connective tissue disorders

Uncommon: pain in extremity, muscle cramp, joint swelling, muscular weakness.

Renal and urinary disorders

Uncommon: dysuria, haematuria, crematoria.

Rare: acute renal failure, urinary retention.

Reproductive system and breast disorders

Rare: erectile dysfunction.

General disorders and administration site conditions

Common: asthenia.

Uncommon: fatigue, peripheral oedema.

Investigations

Uncommon: increased blood creatinine, increased blood urea, prolonged QT corrected interval, increased platelet or white blood cell count, and decreased weight.

Rare: elevated levels of hepatic enzyme.

The adverse event profile was generally similar in the MERLIN-TIMI 36 study. In this long term study, acute renal failure was also reported with an incidence less than 1% in placebo and Ranolazine patients. Evaluations in patients who may be considered at higher risk of adverse events when treated with other antianginals medicinal products, e.g. patients with diabetes, Class I and II heart failure, or obstructive airway disease, confirmed that these conditions were not associated with clinically meaningful increases in the incidence of adverse events.

Elderly, renal impairment and low weight:

In general, adverse events occurred more frequently among elderly patients and patients with renal impairment; however, the types of events in these subgroups were similar to those observed in the general population. Of the most commonly reported, the following events occurred more often with Ranolazine (placebo-corrected frequencies) in elderly (≥ 75 years of age) than younger patients (< 75 years of age): constipation (8% versus 5%), nausea (6% versus 3%), hypotension (5% versus 1%), and vomiting (4% versus 1%).

In patients with mild or moderate renal impairment (creatinine clearance ≥ 30–80 ml/min) compared to those with normal renal function (creatinine clearance > 80 ml/min), the most commonly reported events and their placebo-corrected frequencies included: constipation (8% versus 4%), dizziness (7% versus 5%), and nausea (4% versus 2%).

In general, the type and frequency of adverse events reported in patients with low body weight (≤ 60 kg) were similar to those of patients with higher weight (> 60 kg); however, the placebo-corrected frequencies of the following common adverse events were higher in low body weight than heavier patients: nausea (14% versus 2%), vomiting (6% versus 1%), and hypotension (4% versus 2%).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Hemodynamic Effects

Patients with chronic angina treated with Ranolazine in controlled clinical studies had minimal changes in mean heart rate (< 2 bpm) and systolic blood pressure (< 3 mm Hg). Similar results were observed in subgroups of patients with CHF NYHA Class I or II, diabetes, or reactive airway disease, and in elderly patients.

Electrocardiographic Effects

Dose and plasma concentration-related increases in the QTc interval, reductions in T wave amplitude, and, in some cases, notched T waves have been observed in patients treated with Ranolazine. These effects are believed to be caused by Ranolazine and not by its metabolites. The relationship between the change in QTc and Ranolazine plasma concentrations is linear, with a slope of about 2.6 msec/1000 ng/mL, through exposures corresponding to doses several-fold higher than the maximum recommended dose of 1000 mg twice daily. The variable blood levels attained after a given dose of Ranolazine give a wide range of effects on QTc. At Tmax following repeat dosing at 1000 mg twice daily, the mean change in QTc is about 6 msec, but in the 5% of the population with the highest plasma concentrations, the prolongation of QTc is at least 15 msec. In subjects with mild or moderate hepatic impairment, the relationship between plasma level of Ranolazine and QTc is much steeper.

Age, weight, gender, race, heart rate, congestive heart failure, diabetes, and renal impairment did not alter the slope of the QTc-concentration relationship of Ranolazine.

No proarrhythmic effects were observed on 7-day Holter recordings in 3,162 acute coronary syndrome patients treated with Ranolazine. There was a significantly lower incidence of arrhythmias (ventricular tachycardia, bradycardia, supraventricular tachycardia, and new atrial fibrillation) in patients treated with Ranolazine (80%) versus placebo (87%), including ventricular tachycardia ≥ 3 beats (52% versus 61%). However, this difference in arrhythmias did not lead to a reduction in mortality, a reduction in arrhythmia hospitalization, or a reduction in arrhythmia symptoms.

5.2 Pharmacokinetic properties

Absorption

The mean absolute bioavailability of Ranolazine after oral administration of immediate-release Ranolazine tablets ranged from 35−50%, with large inter-individual variability. Ranolazine exposure increases more than in proportion to dose. There was a 2.5- to 3-fold increase in steady-state AUC as the dose was increased from 500 mg to 1000 mg twice daily. In a pharmacokinetic study in healthy volunteers, steady-state Cmax was, on average, approximately 1770 (SD 1040) ng/ml, and steady-state AUC0-12 was, on average, 13,700 (SD 8290) ng x h/ml following a dose of 500 mg twice daily. Food does not affect the rate and extent of absorption of Ranolazine.

Distribution and Plasma Protein Binding

Approximately 62% of Ranolazine is bound to plasma proteins, mainly alpha-1 acid glycoprotein and weakly to albumin. The mean steady-state volume of distribution (Vss) is about 180 l.

Metabolism

Ranolazine undergoes rapid and extensive metabolism. In healthy young adults, Ranolazine accounts for approximately 13% of the radioactivity in plasma following a single oral 500 mg dose of [14C]-Ranolazine. A large number of metabolites has been identified in human plasma (47 metabolites), urine (> 100 metabolites), and faeces (25 metabolites). Fourteen primary pathways have been identified of which O-demethylation and N-dealkylation are the most important. In vitro studies using human liver microsomes indicate that Ranolazine is metabolised primarily by CYP3A4, but also by CYP2D6. At 500 mg twice daily, subjects lacking CYP2D6 activity (poor metabolizers, PM) had 62% higher AUC than subjects with CYP2D6 metabolizing capacity (extensive metabolizers, EM). The corresponding difference at the 1000 mg twice-daily dose was 25%.

Elimination

Ranolazine is eliminated primarily by metabolism. Less than 5% of the dose is excreted unchanged in the urine and faeces. Following oral administration of a single 500 mg dose of [14C]-Ranolazine to healthy subjects, 73% of the radioactivity was recovered in urine and 25% in faeces.

Clearance of Ranolazine is dose-dependent, decreasing with increased dose. The elimination half-life is about 2−3 hours after intravenous administration. The terminal half-life at steady state after oral administration of Ranolazine is about 7 hours, due to the absorption rate-limited elimination.

Special Population

The influence of various factors on the pharmacokinetics of Ranolazine was assessed in a population pharmacokinetic evaluation in 928 angina patients and healthy subjects.

Gender effects:

Gender had no clinically relevant effect on pharmacokinetic parameters.

Elderly patients:

Age alone had no clinically relevant effect on pharmacokinetic parameters. However, the elderly may have increased Ranolazine exposure due to age-related decrease in renal function.

Body weight:

Compared to subjects weighing 70 kg, exposure was estimated to be about 1.4-fold higher in subjects weighing 40 kg.

CHF:

CHF NYHA Class III and IV were estimated to have about 1.3-fold higher plasma concentrations.

Renal impairment:

In a study evaluating the influence of renal function on Ranolazine pharmacokinetics, Ranolazine AUC was on average 1.7- to 2-fold higher in subjects with mild, moderate, and severe renal impairment compared with subjects with normal renal function. There was a large inter-individual variability in AUC in subjects with renal impairment. The AUC of metabolites increased with decreased renal function. The AUC of one pharmacologically active Ranolazine metabolite was 5-fold increased in patients with severe renal impairment.

In the population pharmacokinetic analysis, a 1.2-fold increase in Ranolazine exposure was estimated in subjects with moderate impairment (creatinine clearance 40 ml/min). In subjects with severe renal impairment (creatinine clearance 10–30 ml/min), a 1.3- to 1.8-fold increase in Ranolazine exposure was estimated.

The influence of dialysis on the pharmacokinetics of Ranolazine has not been evaluated.

Hepatic impairment:
The pharmacokinetics of Ranolazine have been evaluated in patients with mild or moderate hepatic impairment. There are no data in patients with severe hepatic impairment. Ranolazine AUC was unaffected in patients with mild hepatic impairment but increased 1.8-fold in patients with moderate impairment. QT prolongation was more pronounced in these patients.

Paediatric population:
The pharmacokinetic parameters of Ranolazine have not been studied in the paediatric population (< 18 years).

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals at levels similar to clinical exposure, were as follows: Ranolazine was associated with convulsions and increased mortality in rats and dogs at plasma concentrations approximately 3-fold higher than at the proposed maximum clinical dose.

Chronic toxicity studies in rats indicated that treatment was associated with adrenal changes at exposures slightly greater than those seen in clinical patients. This effect is associated with increased plasma cholesterol concentrations. No similar changes have been identified in humans. No effect on the adreno-cortical axis was noted in humans.
In long-term carcinogenicity studies at doses of ranolazine up to 50 mg/kg/day (150 mg/m2/day) in mice and 150 mg/kg/day (900 mg/m2/day) in rats, no relevant increases in the incidence of any tumour types were seen. These doses are equivalent to 0.1 and 0.8 times, respectively, the maximum recommended human dose of 2 grams on a mg/m2 basis, and represent the maximum tolerated doses in these species.

Signs of embryonal and maternal toxicity, but not teratogenicity, were seen at doses of ranolazine up to 400 mg/kg/day (2400 mg/m2/day) in rats and 150 mg/kg/day (1800 mg/m2/day) in rabbits. These doses represent 2.7 and 2 times, respectively, the maximum recommended human dose.

Animal studies do not indicate direct or indirect harmful effects of ranolazine with respect to male or female fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose BP, Lactose (Manohydrate) BP, Povidone (K-30) BP, Purified water BP, Lactose (Pharmatose DCL-15) BP, Hypermellose (Methocel K4M) BP, Magnesium Stearate BP.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

The Shelf life is 36 months from the date of manufacture

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture

6.5 Nature and contents of container

Alu/Alu blister pack of 3x10's Tablets, such a three strips are packed in outer carton along with pack insert.

6.6 Special precautions for disposal and other handling

No Special requirement

7. Marketing Authorization Holder

MICRO LABS LIMITED
92, Sipcot Industrial Complex,
Hosur - 635 126 (T.N.)
INDIA

8. Number from the register of medicinal product.

Not applicable

9. Date of authorization or of the last renewal of the authorization

Not applicable

10. Date of revision of the text

July 2019

1.3.5. SPC is already approved in member state

Not Applicable,

1.4. Information about experts

1.4.1. Information about quality expert

DR. SHIVANAND SHIVRAJ DHANURE

- VICE PRESIDENT - CLINICAL AFFAIRS AT MICRO LABS LTD, BANGALORE, INDIA - (2010 - TILL DATE)
- GENERAL MANAGER - CLINICAL AFFAIRS AT MICRO LABS LTD, BANGALORE, INDIA - (2006 - 2010)

Working as Head of Clinical Affairs Department, located at Corporate Office in Bangalore, to provide an integrated service platform ranging from services in Clinical Research, BA/BE Studies, Clinical End Point studies, Medical Writing,

Pharmacovigilance, Clinical Data Management and Clinical Pharmacology. Objective of the current profile is to receive Marketing Authorization for Generic products in Regulated Markets by ensuring scientific delivery that is complementing to strong interdisciplinary project management across relevant units of the organization viz. R&D and Regulatory Affairs.

1.4.2. Information about non-clinical expert

DR. SHIVANAND SHIVRAJ DHANURE

- VICE PRESIDENT - CLINICAL AFFAIRS AT MICRO LABS LTD, BANGALORE, INDIA - (2010 - TILL DATE)
- GENERAL MANAGER - CLINICAL AFFAIRS AT MICRO LABS LTD, BANGALORE, INDIA - (2006 - 2010)

Working as Head of Clinical Affairs Department, located at Corporate Office in Bangalore, to provide an integrated service platform ranging from services in Clinical Research, BA/BE Studies, Clinical End Point studies, Medical Writing,

Pharmacovigilance, Clinical Data Management and Clinical Pharmacology. Objective of the current profile is to receive Marketing Authorization for Generic products in Regulated Markets by ensuring scientific delivery that is complementing to strong interdisciplinary project management across relevant units of the organization viz. R&D and Regulatory Affairs.

1.4.3. Information about clinical expert

DR. SHIVANAND SHIVRAJ DHANURE

ACADEMIC QUALIFICATIONS (Most Current Academic Position First)

Degree	Institution/University/year
MD [Pharmacology]	Topiwala National Medical College & BYL Nair Hospital, Mumbai. University: Mumbai, India [2004]
MBBS	Rajiv Gandhi Medical College, CSM Hospital. University: Mumbai, India [1998]
Marketing management	Wellingkar's Institute of Management University: Mumbai, India [2003]

EXPERTISE:

Clinical Research, Medical Writing, Pharmacovigilance, Clinical Data Management and Clinical Pharmacology.

Expertise in design and conduct of Bioavailability/Bioequivalence studies for various global regulatory bodies (including USFDA, EU, CANADA and WHO) and execution of clinical trial from protocol preparation to data management & final report submission. Experience in design and conduct of Bioequivalence studies include Fasted / Fed BE studies/Multiple Dose studies for Immediate / Modified release Preparations. Comparative Bioavailability studies for NDDS in Population involving Healthy Volunteers / Patients/ Special Population.

Design and conduct of Clinical End Point Studies Monitoring all study activities to ensure compliance to Protocol, SOPs, GCP, GLP and other regulations.

STUDY RESPONSIBILITIES:

- Ensuring regulatory compliance of study design
- Auditing CROs for compliance to GCP and GLP requirements
- Conducting study specific monitoring
- Review of report to ensure accurate reflection of the raw & source data.
- Coordinating all regulatory inspections and applicable pre and post study audits.
- Handling and resolution of regulatory queries to ensure timely processing of MAs.

MEDICAL WRITING AND DOSSIER PREPARATION RESPONSIBILITIES:

Writing Clinical Expert Reports, Clinical & Non-Clinical Overviews as well as Product Prescribing Information (SmPC and PILs) in applicable Regulatory formats.

Preparation of Module 2 and Module 5 of the Dossiers in compliance with ICH E3 guidelines/applicable regulatory formats including electronic versions (eCTD) in EU, US, Canada and WHO.

GLOBAL PHARMACOVIGILANCE RESPONSIBILITIES:

Implementation of Global Pharmacovigilance system in accordance with regulations in support of Marketing Authorization Applications as well as maintenance of Authorized Applications in EU and US. Ensuring compliance to Regulatory obligations and undergoing Regulatory Inspections.

Writing Pharmacovigilance SOPs, Product Risk Management Plans, Drug Safety Database Management, Adverse Event/ Serious Adverse Event Processing, ICSR Handling, Literature search, PSUR generation, Signal detection and evaluation

HISTORICAL ACCOMPLISHMENTS:

- While heading the Clinical Department, have audited more than 20 CRO's within and outside the country and conducted over 125 Bioequivalence Studies for Regulated Markets.
- Submission studies were part of Successful Marketing Authorization Applications in US, EU, CANADA and WHO.
- Successfully undergone study specific inspection by EU Agency.
- Successfully undergone study specific inspection by WHO.
- Implemented Pharmacovigilance System in compliance with the EU/US Guidelines. Successfully undergone Pharmacovigilance inspection by UK MHRA.
- Attended various International Conferences on Bioavailability, Bioequivalence, Dissolution testing and IVIVC.
- Was invited as a Speaker in Bioavailibity and Bioequivalence Conference 2009 in Hungary, 2009 organized by IRR, UK.

- Attended and actively participated in scientific conferences held in Germany, Czech Republic and London.

Curriculum Vitae of the expert

Name:	DR. Shivanand Shivraj Dhanure
Work address:	Micro Labs Limited, No. 27, Race Course Road, Bangalore -560001-INDIA
Phone:	00 91 80 22370464
Fax:	+918025744565
Email:	shivanandd@microlabs.in
Education:	MD [Pharmacology]
Professional Experience:	Vice President - Clinical affairs at Micro Labs Ltd, Bangalore, INDIA - (2010 - Till date) General Manager - Clinical affairs at Micro Labs Ltd, BANGALORE, INDIA - (2006 - 2010) Worked in the Capacity of Manager - Medical Services At Emcure Pharmaceutical Ltd April 2004 - June 2006