Applicant	Novartis South Africa (Pty) Ltd.
Product Name	**MIGROBEN® 80, 160, 320 TABLETS**
Dosage form and strength	Each film-coated tablet contains: Valsartan 80 mg Valsartan 160 mg Valsartan 320 mg

1.3.1.1 Approved Professional Information

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

MIGROBEN® 80 TABLETS

(Film-coated tablet)

MIGROBEN® 160 TABLETS

(Film-coated tablet)

MIGROBEN® 320 TABLETS

(Film-coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 80 mg, 160 mg or 320 mg valsartan.

For the full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Film Coated tablets

MIGROBEN® 80 mg – Pale red, round film-coated tablet with bevelled edges, imprinted “D/V” on the one side and “NVR” on the other side

Length: approximately 8.2 mm

Width: approximately 5.9 mm

MIGROBEN® 160 mg – Grey orange, ovaloid film-coated tablet, imprinted with “DX” on the one side and “NVR” on the other side

Length: approximately 13.1 mm

Width: approximately 7.6 mm

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MIGROBEN® 320 mg – Dark grey-violet, ovaloid film-coated tablet with bevelled edges, imprinted "DXL" on the one side and "NVR" on the other side.

Length: approximately 16.1 mm

Width: approximately 9.5 mm

The score line on one side of MIGROBEN 80 mg, 160 mg or 320 mg tablet is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension:

Treatment of mild to moderate essential hypertension in adult patients (18 years and older).

4.2 Posology and method of administration

Posology:

Hypertension:

The recommended dose of MIGROBEN is 80 mg or 160 mg once daily.

The antihypertensive effect is substantially present within 2 weeks and maximal effects are seen after 4 weeks. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to 320 mg, or a diuretic may be added.

MIGROBEN may also be administered with other antihypertensive medicines.

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Special population

Renal impairment

NOTE: No dosage adjustment is required for patients with mild and moderate renal impairment (where the creatinine clearance is above 30 to less than 90 ml/min). (see **section 4.4**). A lower dose should be considered for patients with a history of hepatic impairment. (see **section 4.4**).

Paediatric population

The safety and efficacy of MIGROBEN have not been established in children.

Currently available data are described in **section 5.1** and **5.2** but no recommendation on a posology can be made.

4.3 Contraindications

- Hypersensitivity to valsartan and any of MIGROBEN excipients
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Heredity or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Severe renal function impairment (creatinine clearance less than 30 ml/min)
- Bilateral renal artery stenosis
- Renal artery stenosis in patients with a single kidney
- Aortic valve stenosis
- Mitral valve stenosis
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see **section 4.5**).

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- Porphyria
- Lithium therapy: Concomitant administration with MIGROBEN may lead to toxic serum concentrations of lithium (see **section 4.5**).
- Pregnancy and lactation (see **section 4.6**).

Concomitant use of MIGROBEN with aliskiren in patients with Type 2 diabetes mellitus.

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving **MIGROBEN**, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine. (see **section 4.3** and **section 4.6**)

Sodium- and/or volume-depleted patients:

In sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, and/or patients with moderate to severe renal impairment, symptomatic hypotension may occur after initiation of therapy with MIGROBEN. Sodium- and/or volume- depletion should be corrected before starting treatment with MIGROBEN for example, by reducing the diuretic dose.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has stabilised. Reduced doses must be considered in patients with hepatic impairment.

Renal artery stenosis:

Since other medicines that affect the renin-angiotensin-aldosterone system such as MIGROBEN may increase serum urea and serum creatinine in patients with bilateral or unilateral renal artery stenosis;

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MIGROBEN should not be used in patients with bilateral renal artery stenosis or unilateral renal artery stenosis, aortic valve stenosis, mitral valve stenosis or hyportrophic obstructive cardiomyopathy (see **section 4.3**)

Impaired renal function:

No dosage adjustment is required for patients with mild to moderate renal impairment. MIGROBEN is contraindicated in severe renal function impairment (creatinine clearance less than 30 ml/min (see **section 4.3**).

Since hyperkalaemia may occur, serum-potassium concentrations should be monitored especially in the elderly and patients with renal impairment and the concomitant use of potassium-sparing diuretics should be avoided (see **section 4.3** and **section 4.5**).

The use of MIGROBEN with aliskiren should be avoided in patients with severe renal impairment (GFR < 30 mL/min) (see **section 4.5**, subsection dual blockade of the RAAS).

Hepatic impairment:

MIGROBEN is mostly eliminated unchanged in the bile, and patients with biliary obstructive disorders showed lower MIGROBEN clearance (see **section 5.2***)*. Particular caution should be exercised when administering MIGROBEN to patients with biliary obstructive disorders. In patients with mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan.

Angioedema

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Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported in patients treated with valsartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. MIGROBEN should be immediately discontinued in patients who develop angioedema, and MIGROBEN should not be re-administered.

Patients with heart failure/post-myocardial infarction

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin receptor antagonists (e.g. valsartan as contained in TN) has been associated with oliguria and/or progressive uraemia, and with acute renal failure and/or death.

Evaluation of patients with heart failure or with history of recent myocardial infarction should always include assessment of renal function.

Dual Blockade of the Renin-Angiotensin - Aldosterone System (RAAS)

Caution is required while co-administering ARBs, including MIGROBEN, with other medicines blocking the RAAS such as ACEIs or aliskiren (see **section 4.3** and **4.5**, subsection dual blockade of the RAAS).

4.5 Interaction with other medicines and other forms of interaction

Dual blockade of the Renin-Angiotensin-Aldosterone-System (RAAS) with ARBs, ACEIs, or aliskiren

The concomitant use of MIGROBEN, with other medicines acting on the RAAS is associated with an increased incidence of hypotension, hyperkalemia, and changes in renal function compared to

monotherapy. It is recommended to monitor blood pressure, renal function and electrolytes in patients on MIGROBEN and other medicines that affect the RAAS (see **section 4.4**).

The concomitant use of ARBs - including MIGROBEN - or of ACEIs with aliskiren, should be avoided in patients with severe renal impairment (GFR < 30 ml/min) (see **section 4.4**).

The concomitant use of ARBs - including MIGROBEN - or ACEIs with aliskiren is contraindicated in patients with Type 2 diabetes (see **section 4.3**).

Potassium:

Concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium, and in patients with heart failure to increase in serum creatinine (see **section 4.3**).

Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors):

When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur.

Furthermore, in elderly patients, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying the treatment in patients on valsartan who are taking NSAIDs concomitantly.

Lithium

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Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists, including MIGROBEN. Therefore, careful monitoring of serum lithium levels is recommended during concomitant use. If a diuretic is also used, the risk of lithium toxicity may presumably be increased further with MIGROBEN.

Transporters

The results from an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (e.g., rifampin, ciclosporin) or efflux transporter (e.g., ritonavir) may increase the systemic exposure to valsartan.

No interactions of clinical significance have been found. Compounds studied in clinical trials include: cimetidine, warfarin, furosemide, digoxin, atenolol, hydrochlorothiazide, amlodipine and glibenclamide.

As MIGROBEN is not metabolised to a significant extent, clinically relevant interactions in the form of metabolic induction or inhibition of the cytochrome P450 system are not expected with valsartan. Although valsartan is highly bound to plasma proteins, *in vitro* studies have not shown any interaction at this level with a range of molecules which are also highly protein-bound, such as diclofenac, furosemide and warfarin.

Concurrent use with sympathomimetics may reduce the antihypertensive effect of MIGROBEN.

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4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

MIGROBEN acts directly on the RAAS and therefore should not be used in women planning to become pregnant. Healthcare professionals prescribing MIGROBEN should counsel women of childbearing potential about the potential risk during pregnancy.

Women of childbearing age should ensure effective contraception.

Pregnancy

When pregnancy is planned or confirmed MIGROBEN should be discontinued as soon as possible. Not to be used in pregnancy as teratogenicity has been shown in experimental animals.

Medicines affecting the renin-angiotensin-aldosterone system, such as MIGROBEN, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.

Safety in pregnancy and lactation has not been established (see **section 4.3**).

In case of accidental exposure to MIGROBEN, appropriate foetal monitoring should be considered.

Infants whose mothers have taken MIGROBEN should be closely observed for hypotension.

There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction when pregnant women have inadvertently taken valsartan**.**

Breastfeeding

It is not known whether valsartan is excreted in human milk. Since valsartan was excreted in the milk of lactating rats, mothers taking MIGROBEN should not breastfeed their infants

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Fertility

There is no information on the effects of MIGROBEN on human fertility. Studies in rats did not show any effects of valsartan on fertility.

4.7 Effects on ability to drive and use machines

Patients treated with MIGROBEN should be advised to take into account that somnolence, headache, dizziness or fatigue can occur. Therefore, their ability to drive and use machinery maybe impaired.

4.8 Undesirable effects

Frequencies are defined as: very common (≥ 1/10); Common (≥ 1/100, <1/10); uncommon (≥ 1/100, < 1/1 000); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000)

Table 1: Adverse drug reactions in Hypertension from clinical trials

Ear and labyrinth system disorders	
Uncommon	Vertigo
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Abdominal pain
General disorders and administration site conditions	
Uncommon	Fatigue

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Table 2: Adverse drug reactions from Post Marketing Surveillance Frequency: Unknown

Blood and lymphatic system disorders Haemoglobin decreased, haematocrit decreased, neutropenia, thrombocytopenia
Immune system disorders Hypersensitivity including serum sickness
Metabolism and nutrition disorders Serum potassium increased
Vascular disorders Vasculitis
Hepato-biliary disorders Liver function test abnormal including serum bilirubin increase
Skin and subcutaneous tissue disorders Angioedema, dermatitis bullous, rash, pruritus
Musculoskeletal and connective tissue disorders Myalgia
Renal and urinary disorders Renal failure and impairment, serum creatinine increased

The following events have also been observed during clinical trials in hypertensive patients irrespective of their causal association with the study drug: Arthralgia, asthenia, back pain, diarrhoea, dizziness, headache, insomnia, libido decrease, nausea, oedema, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral infections.

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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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Overdose with MIGROBEN may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. If the ingestion is recent, vomiting should be induced if the patient is conscious. Otherwise, the usual treatment would be intravenous infusion of normal saline solution.

MIGROBEN is unlikely to be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification

A 7.1.3 Vascular medicines – other hypotensives

Valsartan is an orally active, specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the angiotensin 1 (AT_1) receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor, which appears to counterbalance the effect of the AT_1 receptor. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has much greater affinity (about 20 000 fold) for the AT_1 receptor than for the AT_2 receptor.

The angiotensin 2 (AT_2) receptor subtype is unrelated to cardiovascular effect.

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Paediatric population (Hypertension)

The antihypertensive effect of valsartan have been evaluated in four randomised, double-blind clinical studies in 561 paediatric patients from 6 to 18 years of age and 165 paediatric patients 1 to 6 years of age. Renal and urinary disorders, and obesity were the most common underlying medical conditions potentially contributing to hypertension in the children enrolled in these studies.

Clinical experience in children at or above 6 years of age

In a clinical study involving 261 hypertensive paediatric patients 6 to 16 years of age, patients who weighed <35 kg received 10, 40 or 80 mg of valsartan tablets daily (low, medium and high doses), and patients who weighed ≥35 kg received 20, 80, and 160 mg of valsartan tablets daily (low, medium and high doses). At the end of 2 weeks, valsartan reduced both systolic and diastolic blood pressure in a dose-dependent manner. Overall, the three dose levels of valsartan (low, medium and high) significantly reduced the systolic blood pressure by 8, 10, 12 mm Hg from the systolic blood pressure recorded at baseline, respectively. Patients were re-randomised to either continue receiving the same dose of valsartan or were switched to placebo treatment. In patients who continued to receive the medium and high doses of valsartan, the systolic blood pressure at trough was -4 and -7 mm Hg lower than the systolic blood pressure recorded in patients who received the placebo treatment. In patients receiving the low dose of valsartan, the systolic blood pressure at trough was similar to that observed in patients who received the placebo treatment. Overall, the dose-dependent antihypertensive effect of valsartan was consistent across all the demographic subgroups. In another clinical study involving 300 hypertensive paediatric patients 6 to 18 years of age, eligible patients were randomised to receive valsartan or enalapril tablets for 12 weeks. Children weighing between ≥18 kg and <35 kg received valsartan 80 mg or enalapril 10 mg; those between ≥35 kg and <80 kg received valsartan 160 mg or enalapril 20 mg; those ≥80 kg received valsartan 320 mg or enalapril 40 mg. Reductions in systolic blood pressure were comparable in patients receiving valsartan (15 mmHg) and enalapril (14 mm Hg) (non-

inferiority p-value <0.0001). Consistent results were observed for diastolic blood pressure with reductions of 9.1 mmHg and 8.5 mmHg with valsartan and enalapril, respectively.

Clinical experience in children less than 6 years of age

Two clinical studies were conducted in patients aged 1 to 6 years with 90 and 75 patients, respectively. No children below the age of 1 year were enrolled in these studies. In the first study, the efficacy of valsartan was confirmed compared to placebo but a dose-response could not be demonstrated. In the second study, higher doses of valsartan were associated with greater BP reductions, but the dose response trend did not achieve statistical significance and the treatment difference compared to placebo was not significant. Because of these inconsistencies, valsartan is not recommended in this age group (see section 4.8).

5.2 Pharmacokinetic properties

Absorption

Valsartan is absorbed after oral administration, although the amount absorbed varies widely. Mean absolute bioavailability for valsartan is 23 %. When valsartan is given with food, the area under the plasma concentration curve (AUC) of valsartan is reduced by 48 %, although from about 8 hours post dosing plasma valsartan concentrations are similar for the fed and fasted group. This reduction in AUC, however, is not accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution

Valsartan is highly bound to serum protein (94 to 97 %), mainly serum albumin. Steady-state volume of distribution is low (about 17 L) indicating that valsartan is not distributed into tissues extensively.

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Biotransformation

Valsartan is not biotransformed to a high extent as only about 20 % of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10 % of the valsartan AUC). This metabolite is pharmacologically inactive.

Elimination

Valsartan shows multi exponential decay kinetics (t½ α < 1 h and t½ β about 9 h). Plasma clearance is relatively slow (about 2 L/h) when compared with hepatic blood flow (about 30 L/h). Of the absorbed dose of valsartan 70 % is excreted in the faeces and after iv administration, 30 % in the urine, mainly as unchanged compound. The half-life of valsartan is 6 hours.

The pharmacokinetics of valsartan is linear in the dose range tested. There is no change in the kinetics of valsartan on repeated administration and little accumulation when dosed once daily. Plasma concentrations are similar in males and females.

Elderly:

A significantly higher systemic exposure to valsartan was observed in elderly patients.

Impaired Renal Function:

Renal clearance accounts for only 30 % of total plasma clearance and no correlation is seen between renal function and systemic exposure to valsartan. Dose adjustment is therefore not required in patients with mild renal impairment. No studies have been performed in patients undergoing dialysis. However, valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis.

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Hepatic impairment:

About 70 % of the absorbed dose is excreted in the bile mainly as unchanged compound. Valsartan does not undergo extensive biotransformation and systemic exposure to valsartan is not correlated with the degree of liver dysfunction. The AUC with valsartan has been observed to be approximately double in patients with biliary cirrhosis or biliary obstruction (see section *Special warnings and precautions for use*).

Paediatric population

In a study of 26 paediatric hypertensive patients (aged 1 to 16 years) given a single dose of a suspension of valsartan (mean: 0.9 to 2 mg/kg, with a maximum dose of 80 mg), the clearance (litres/h/kg) of valsartan was comparable across the age range of 1 to 16 years and similar to that of adults receiving the same formulation (see section 4.4).

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential and effects on fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, crospovidone, colloidal anhydrous silica, magnesium stearate, hypromellose, titanium dioxide (E171), Macrogol 8000, red iron oxide (E172), yellow iron oxide (E172), black iron oxide (E172; 160 mg and 320 mg only).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30 °C. Protect from moisture.

KEEP OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

28 tablets in (PVC/PE/PVDC) aluminium foil blisters (Triplex) or (PA/Al/PVC) aluminium foil blisters (alu-alu or double-sided aluminium blisters), (PVC/PVDC) with aluminium foil (Duplex) blisters. The aluminium foil is silver and the PVC/PVDC is clear, colourless and transparent.

The outer container is a printed cardboard box.

6.6 Special precautions for disposal and other handling

No specific requirements for disposal

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7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd.

Magwa Crescent West,

Waterfall City,

Jukskei view,

Johannesburg,

2090

8. REGISTRATION NUMBERS

MIGROGEN® 80 Tablet: 43/7.1.3/0032

MIGROBEN® 160 Tablet: 43/7.1.3/0033

MIGROBEN® 320 Tablet: 43/7.1.3/0523

9. DATE OF FIRST AUTHORISATION

21 April 2016

10. DATE OF REVISION OF THE TEXT

07 February 2022