เอกสารกำกับยาภาษาอังกฤษ

(เหมือนกันทุกขนาดบรรจุ)

1. Name of the medicinal product

MANIDIP 20 mg Tablet

2. Qualitative and quantitative composition

Each tablet contains 20 mg Manidipine hydrochloride

3. Pharmaceutical Form

Tablet

MANIDIP 20 mg tablets are Light yellow, round and flat tablet with scored on both sides.

4. Clinical Particulars

4.1 Therapeutic indications

- Mild to moderate essential hypertension
- Hypertension with renal impairment
- Severe hypertension

4.2 Posology and method of administration

(1) Posology

Dosage in adult patients

The adult dose is 10 to 20 mg once daily in the morning after breakfast. The recommended starting dose is 10 mg daily. The dose may be increased to 20 mg daily if the antihypertensive effect is inadequate after 2 to 4 weeks. Avoid abrupt withdrawal of calcium channel blocker therapy if possible. Hypertensive crisis has been reported.

Dosage in geriatric patients

The data suggest that geriatric patients are at an increased risk of accumulation of manidipine, and that dose reductions to 10 mg daily should be considered in this population. Manidipine may cause hypotension which may result in cerebral infraction. Should start treatment with low dose.

Dosage in patients with impaired renal function

No dosage adjustment is required in patients with mild to moderate renal dysfunction, however caution is advised when increasing the dose from 10 to 20 mg daily.

Dosage in patients with impaired hepatic function

The data suggest that patients with hepatic insufficiency are at an increased risk of accumulation of manidipine, and that dose reductions should be considered in this population. The dose in patients with mild hepatic dysfunction should not exceed 10 mg daily.

(2) Method of administration

Orally administered, once a day, after breakfast.

4.3 Contraindication

- Known hypersensitivity to the active substance, other dihydropyridines or to any of the excipients of the product.
- Pregnant women or women suspected of being pregnant or plan to become pregnant.
- Women who are breast-feeding

4.4 Special warning and precautions for use

General cautions

- It has been reported that sudden withdrawal of a calcium antagonist causes aggravation of symptoms. Therefore, if discontinuation of manidipine tablet is necessary, the dosage should be gradually decreased under close observation. The patient should be cautioned against discontinuing the drug without the physician's instruction.
- Manidipine tablet may rarely cause an excessive drop of blood pressure. In such a case, appropriate measures, such as dosage reduction and cessation, should be taken.
- Since symptoms, such as dizziness or the like, may occur because of the drop in blood pressure, the patient should be admonished against working at a height or operating hazardous machinery, e.g., driving a car.

Careful administration

Caretiously administered to patients with severe hepatic impairment.

4.5 Interactions with other medicinal products and other forms of interactions

- Since manidipine tablet may intensify the action of other antihypertensive drugs, any combination with other drugs should be made with caution.
- Other calcium antagonists (nifedipine) reportedly increase the blood digoxin concentration.
- The action of other calcium antagonists (nifedipine, etc.) is reported to be intensified in combination with cimetidine.

4.6 Pregnancy and lactation

Pregnancy

It has been reported that manidipine tablet prolongs the gestation period and delivery time in animal experiments. Therefore, administration to pregnant women or women suspected of being pregnant should be avoided.

Labor and delivery

Not applicable

Nursing mothers

Transfer of this drug to the mother's milk has been reported in an experimental animal. Administration of manidipine tablet to nursing mothers is not recommended, if inevitable, the patient should be instructed to stop nursing.

Fertility

Not applicable

4.7 Effects on ability to drive and use machine

Since dizziness may be experienced due to reduced blood pressure, patients should be advised to take care while driving and operating machinery.

4.8 Undesirable effects

Manidipine was generally well tolerated in adults and elderly (aged > 60 years) patients in clinical trials of up to 3 years' duration. The most common adverse events associated with manidipine 10 or 20 mg once daily in patients with mild-to-moderate essential hypertension were ankle edema (6%), headache (4%), palpitations (3%), flushing (2%) and dizziness (2%). The incidence of adverse events was dose related and appeared similar with manidipine 10 or 20 mg once daily and placebo (15%, 23% and 15% respectively).

Liver function: Since elevation of GOT, GTP, gamma-GTP, LDH and alkaline-P may infrequently occur, close observation is required. If any abnormality if found, appropriate measures, e.g., discontinuation of manidipine tablet, should be taken.

Kidneys: Since elevation of BUN and serum creatinine may infrequently occur, close observation is required. If any abnormality is found, appropriate measures, e.g., discontinuation of this drug, should be taken.

Blood: Leukopenia and bleeding disorder may infrequently occur, close observation is required. If any abnormality is found, appropriate measures, e.g., discontinuation of this drug, should be taken.

Hypersensitivity: Rash or pruritus may infrequently occur. If such symptoms occur, manidipine tablet should be discontinued.

Cardiovascular: Facial hot flushed, feeling of warmth, conjunctival congestion, palpitation or tachycardia may infrequently occur. Chest pain may rarely occur.

Psychoneurologic: Dizziness, dizziness on standing up, headache, dull headache, sleepiness or numbness may infrequently occur.

Gastrointestinal: Nausea, vomiting, anorexia, stomach discomfort, heartburn, enlarged feeling of abdomen, abdominal pain, diarrhea, constipation or oral dryness may infrequently occur.

Others: General malaise, weakness, edema, pollakiuria, and elevation of total serum cholesterol, uric acid or triglyceride may infrequently occur.

4.9 Overdose

~~**Overdose**~~

Severe hypertension due to vasodilation and tachycardia are the most likely manifestations of overdosage.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Manidipine is a lipophilic, third-generation, long-acting dihydropyridine calcium channel blocker. Manidipine inhibits L- and T-type calcium channels on smooth muscle cells resulting in peripheral vasodilation and reduced blood pressure (BP).

The onset of inhibition of calcium influx is gradual and is maintained for prolonged periods after washout in *in vitro* and *in vivo* studies, with the effects maintained for the 24 hours dose interval in hypertensive patients.

Manidipine is highly selective for the vasculature and has negligible cardiodepressant action. With recommended dosages of manidipine, there were no clinically relevant effects on heart rate or electrocardiographical parameters in clinical trials in hypertensive patients.

Therapeutic dosages of manidipine in hypertensive patients did not significantly affect norepinephrine levels, suggesting a lack of sympathetic activation.

Manidipine had beneficial effects on renal function in hypertensive patients, including those with coexisting renal impairment and/or type 2 diabetes. Moreover, both efferent and afferent renal arterioles are dilated with manidipine, and in a 12-week study of hypertensive patients with chronic renal impairment, creatinine clearance was significantly increased, and

creatinine blood levels significantly decreased, with manidipine 10 or 20 mg once daily but both parameters were unchanged with nifedipine 30 or 60 mg once daily.

Therapeutic dosages of manidipine had neutral effects on glucose and lipid metabolism in hypertensive patients with or without diabetes.

5.2 Pharmacokinetic properties

Absorption

Manidipine is rapidly absorbed. Mean maximum plasma concentrations in the fasted and fed state were 6.2 and 7.8 ng/ml and were attained in a median of 1-4 hours. Hence the drug should be taken just after a meal.

Distribution

The drug undergoes a high degree of plasma protein binding (99%) and is widely distributed to the tissues. Accumulation dose not occur after repeated administration.

Metabolism and Elimination

Oral manidipine undergoes extensive first-pass hepatic metabolism, with 63% of the drug eliminated in the feces and 31% in the urine. In healthy volunteers, the mean terminal elimination half-lives after a single oral dose of manidipine 5, 10, 20 mg ranged from 3.9 to 7.95 hours. Elimination is significantly delayed in patients with severe hepatic impairment.

5.3 Preclinical safety data

The results of repeated dose toxicity studies have shown only toxic signs linked to the exacerbation of the pharmacological effects.

The toxicological profile of manidipine on reproduction has not been sufficiently evaluated in studies on animals, although the studies which have been carried out do not suggest an increased risk of teratogenic effects. In peri/postnatal reproduction studies in rats, the following adverse effects were observed at high doses: increase in the duration of pregnancy, dystocia, increase in fetal death, neonatal mortality.

Preclinical studies did not show any harmful effect for humans in terms of mutagenicity, carcinogenicity, antigenicity or adverse effects on fertility.

6. Pharmaceutical Particulars

6.1 List of excipients

- Betacyclodextrin

- Lactose monohydrate
- Corn starch
- Povidone K30
- Purified water
- Polyethylene glycol 6000
- Yellow iron oxide
- Sodium starch glycolate
- Colloidal silicon dioxide
- Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30 ^{O}C and protect from light.

6.5 Nature and contents of container

PVC-aluminum blister pack or aluminum-aluminum blister pack of 10, 12 and 14 tablets packed in paper box of 1, 3, 5 and 10 packs.

7. Manufacturer

Millimed Co., Ltd.
193 Moo 1 Suksawad rd., Pak Khlong Bang Plakot, Phra Samut Chedi,
Samut Prakan 10290, Thailand
Tel +66 2461 1027

8. Marketing authorization number(s)

XXXXXXXX

9. Date of first authorization/renewal of the authorization

XX.XX.XX

10. Date of revision of the text

21 December 2020