SCHEDULING STATUS: S3

PROPRIETARY NAME (AND DOSAGE FORM):

MYLAN INDAPAMIDE 2,5 mg (film-coated tablet)

COMPOSITION:

Each film-coated tablet contains 2,5 mg indapamide hemihydrate.

Contains sugar.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1 Hypotensives.

PHARMACOLOGICAL ACTION:

Indapamide hemihydrate is an indole derivative of chlorosulphonamide diuretics and is related to the thiazide group of diuretics in its structure and actions. The mechanism of action in hypertensive patients includes reduction in peripheral arterial resistance and decrease of vascular hyper-reactivity.

Pharmacokinetics:

Indapamide hemihydrate is rapidly and completely absorbed from the gastro-intestinal tract. Elimination is biphasic with a half-life in whole blood of about 14 hours.

Indapamide hemihydrate is strongly bound to red blood cells. It is extensively metabolised. About 60 to 70 % of the dose has been reported to be excreted in the urine; only about 5 % to 7 % is excreted unchanged. About 16 to 23 % of the administered dose is excreted in the faeces.

Indapamide is not removed by haemodialysis.

INDICATIONS:

For the treatment of mild to moderate hypertension. **MYLAN INDAPAMIDE 2,5 mg** may be used as sole therapy or combined with other non-thiazide antihypertensive agents.

CONTRA-INDICATIONS:

- Hypersensitivity to any of the components of **MYLAN INDAPAMIDE 2,5 mg**.
- **MYLAN INDAPAMIDE 2,5 mg** is not recommended in patients who are hypersensitive to sulphonamide derivatives.
- Recent cerebrovascular accident.
- Severe impairment of hepatic function or severe renal insufficiency and hepatic encephalopathy.
- Hypokalaemia.
- Pregnancy and Lactation (See Pregnancy and Lactation).

WARNINGS:

Use in children

There is no experience of the use of this medication in children.

Effects on Ability to Drive and Use Machines

MYLAN INDAPAMIDE 2,5 mg may affect the ability to drive or operate machines to a small or moderated extent because of adverse effects, especially at the beginning of treatment.

Caution should be exercised when administering **MYLAN INDAPAMIDE 2,5 mg** to patients with severe renal impairment. If renal insufficiency worsens, treatment should be stopped.

Serum potassium and urate levels should be regularly monitored in patients who may be likely to suffer from or are sensitive to hypokalaemia or hyperuricaemia (cardiac patients receiving cardiac glycosides, the elderly, patients with hyperaldosteronism or patients predisposed to or suffering from gout).

Treatment with **MYLAN INDAPAMIDE 2,5 mg** should be stopped if hypercalcaemia occurs in patients with hyperparathyroidism.

In case of hepatic impairment thiazide-related diuretics may cause hepatic encephalopathy. If hepatic encephalopathy occurs **MYLAN INDAPAMIDE 2,5 mg** should be withdrawn.

Plasma sodium

Plasma sodium should be measured before treatment is initiated and subsequently at regular intervals. A drop in plasma sodium may be asymptomatic in the beginning. Therefore, regular monitoring is important and should be carried out more frequently in elderly patients and in cirrhotic patients.

Plasma potassium

Hypokalaemia constitutes the greatest risk in the treatment with thiazides and related diuretics including **MYLAN INDAPAMIDE 2,5 mg**. Plasma potassium should be measured during the first week of treatment and subsequently at regular intervals, especially in the below mentioned risk patients. If hypokalaemia (< 3,4 mmol potassium) should develop, it must be treated and it should be prevented in risk patients.

Risk patients include e.g.:

Elderly, malnourished patients, patients taking medicines interacting with **MYLAN INDAPAMIDE 2,5 mg**, cirrhosis patients with oedema and ascites, patients with coronary artery disease, cardiac patients as hypokalaemia increases the sensitivity to digoxin and the risk of arrhythmia, patients suffering from long QT interval. Hypokalaemia is a predisposing factor of severe arrhythmia, especially potentially life-threatening torsade de pointes.

Plasma calcium

MYLAN INDAPAMIDE 2,5 mg may inhibit the excretion of calcium and cause a temporary increase in plasma calcium.

Blood glucose

Blood glucose should be monitored in diabetic patients, especially in the case of hypokalaemia.

Uric acid

Serum urate should be monitored in patients with gout because of the risk of an attack.

Renal function

MYLAN INDAPAMIDE 2,5 mg only has the optimal effect at normal or only insignificantly impaired renal function (plasma creatinine < 220 umol/L (25 mg/L) in adults). In elderly patients the plasma creatinine values should be adjusted according to age, body weight and sex.

Secondary hypovolaemia as a result of loss of water and sodium in the beginning of treatment results in reduced glomerular filtration which may increase plasma concentrations of creatinine.

Sports, doping

The presence of indapamide in urine at doping testing results in disqualification of the athlete.

Lactose

Contains lactose and should not be used in patients with hereditary galactose intolerance, a special kind of hereditary lactase deficiency (Lapp lactase deficiency) or glucose/galactose malabsorption.

INTERACTIONS:

- **MYLAN INDAPAMIDE 2,5 mg** may enhance the toxicity of digitalis glycosides by depleting serum-potassium concentrations.

- The neuromuscular blocking action of competitive muscle relaxants such as tubocurarine may be enhanced.

- The effect of antihypertensive agents may be enhanced.

- Postural hypotension may be enhanced by concomitant ingestion of alcohol, barbiturates or opioids.

- The potassium-depleting effect may be enhanced by corticosteroids, corticotrophin or carbenoxolone.

- Hypokalaemia can occur if **MYLAN INDAPAMIDE 2,5 mg** is co-administered with carbenoxolone or diuretics, cardiac glycosides, antiarrhythmics (eg Quinidine derivatives), corticoids and laxatives.

- **Lithium**

Co-administration of **MYLAN INDAPAMIDE 2,5 mg** with lithium can lead to a decrease in lithium excretion.

MYLAN INDAPAMIDE 2,5 mg should not be administered with lithium as this may lead to toxic blood concentrations of lithium.

MYLAN INDAPAMIDE 2,5 mg lowers lithium clearance and thus increases plasma lithium and the risk of overdose. If concomitant treatment with **MYLAN INDAPAMIDE 2,5 mg** is indicated, plasma lithium should be monitored and, if necessary, the dose of lithium should be adjusted.

- **Medicinal products which may lead to torsades de pointes tachycardia**
  - antiarrhythmia. group 1a (quinidine)
  - antiarrhythmia, group III (amiodarone, sotalol)
  - certain antipsychotics:

    phenothiazines (chlorpromazine, levomepromazine)

    benzamides (amisulpride, sulpiride)

    butyrophenones (droperidol, haloperidol)
  - Others: erythromycin IV, mizolastine, pentamidine, moxifloxacine

    Increased risk of ventricular arrhythmia, especially *torsade de pointes* (hypokalaemia is a predisposing factor). Plasma potassium should be monitored and corrected if necessary before introducing this combination. Monitoring of the QT interval.

    The use of medicines which can cause torsade de pointes in the presence of hypokalaemia should be avoided.

- **Digoxin**

  Hypokalaemia increases the sensitivity to digoxin. Plasma potassium should be monitored, ECG should be carried out and, if necessary, the treatment with digoxin should be adjusted.

  Systemic non-steroidal anti-inflammatory drugs (NSAID's) including selective COX-2-inhibitors and large doses of acetylsalicylic acid (≥ 3 g daily).
  NSAID's may reduce the hypotensive effect of **MYLAN INDAPAMIDE 2,5 mg** and increase the risk of acute renal failure in dehydrated patients (reduced glomerular filtration). The patient should be hydrated and the renal function should be monitored when treatment with NSAID's is initiated.

- **Angiotensin-converting enzyme (ACE) inhibitors**

  Risk of acute hypotension and/or renal failure when treatment with ACE inhibitors is initiated, especially in patients with low serum sodium level. Prior to treatment with ACE inhibitors the patients should have a normal serum sodium level and be well hydrated. If possible, treatment with **MYLAN INDAPAMIDE 2,5 mg** should be withdrawn 3 days before treatment with ACE inhibitors. Alternatively, treatment should be initiated with a small dose of an ACE inhibitor. If diuretics are needed on a continuous basis a potassium saving diuretic should be used. The renal function (serum creatinine) should be monitored during the first weeks.

- **Medicinal products which are predisposing factors of hypokalemia (amphotericin B (iv), systemic glucocorticoids and mineral corticoids, tetracosactide**

  Increased risk of hypokalaemia (additive effect). Because of water/sodium retention the glucocorticoids, mineral corticoids and tetracosactide may reduce the antihypertensive

effect. Plasma potassium should be monitored and, if necessary, treatment should be adjusted. Do not use non-stimulating laxatives.

- **Baclofen**

  Intensified antihypertensive effect. The patients will become dehydrated. The renal function should be monitored when treatment is initiated.

- **Potassium saving diuretics (amiloride, spironolactone)**

  The combinations do not exclude the risk of hypokalaemia. There is a risk of hyperkalaemia, especially in patients with renal insufficiency or diabetes. Serum potassium should be monitored and, if necessary, ECG should be carried out. Treatment may be revised.

- **Metformin**

  There is an increased risk of lactic acidosis during metformin treatment because of reduced glomerular filtration. Metformin should not be used if serum creatinine exceeds 135 umol/L (15 mg/L) in men and 110 umol/L (12 mg/L) in women.

- **Iodine-containing contrast media**

  Dehydration poses the risk of acute renal failure when applying large doses of iodine-containing contrasts. The patient should be rehydrated prior to the administration of iodine-containing contrasts.

- **Tricyclic antidepressants, typical antipsychotics**

  Additive antihypertensive effect; risk of orthostatic hypotension.

- **Ciclosporin, tacrolimus**

  Risk of increased serum creatinine with unchanged concentrations of immunosuppressives, even at normal serum sodium level.

PREGNANCY AND LACTATION:

MYLAN INDAPAMIDE 2,5 mg should not be used during pregnancy due to the risk of foetal placental ischemia and reduced foetal growth.

MYLAN INDAPAMIDE 2,5 mg should not be taken by breast-feeding mothers, as it is excreted in mother's milk and may cause electrolyte disturbance and create hypersensitivity to sulphonamide in the child. The quantity of milk may be reduced.

DOSAGE AND DIRECTIONS FOR USE:

Adults:

The dosage is one **MYLAN INDAPAMIDE 2,5 mg** tablet daily to be taken in the morning.

The action of **MYLAN INDAPAMIDE 2,5 mg** is progressive and the reduction in blood pressure may continue and not reach a maximum until several months after the start of therapy. A larger dose than 2,5 mg **MYLAN INDAPAMIDE 2,5 mg** daily is not recommended as there is not appreciable additional antihypertensive effect, but a diuretic effect may become apparent. If a single daily tablet of **MYLAN INDAPAMIDE 2,5 mg** does not achieve a sufficient reduction in blood pressure, another antihypertensive agent may be added; those which have been used in combination with **MYLAN INDAPAMIDE 2,5 mg** include beta-blockers, ACE inhibitors, methyldopa, clonidine and other adrenergic blocking agents. The co-administration of **MYLAN INDAPAMIDE 2,5 mg** with other diuretics, which may cause hypokalaemia, is not recommended.

Elderly:

The elimination time of indapamide hemihydrate may be prolonged in the elderly, as they are more susceptible to electrolyte imbalance and fluid loss. It is advisable to monitor these patients frequently for evidence of such effects.

Children:

Should not be taken by children as there is insufficient experience of the use in children.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:

Nervous system disorders:

The following side-effects have been reported and frequencies are unknown:

Drowsiness, dizziness, headache, paraesthesia, fatigue

Metabolism and nutrition disorders:

The following side-effects have been reported and frequencies are unknown:

Nausea, constipation, dry mouth, gastric irritation, pancreatitis, hypokalaemia. Hyponatraemia with hypovolemia and the risk of dehydration and orthostatic hypotension. Concomitant loss of chloride ions may lead to secondary compensatory metabolic alkaloses. Increased serum urate. Increased blood glucose, hypercalcemia, glucosuria. Loss of weight.

Vascular disorders:

The following side-effects have been reported and frequencies are unknown:

Postural hypotension, orthostatic hypotension, arrhythmia, syncope.

Skin and subcutaneous tissue disorders:

The following side-effects have been reported and frequencies are unknown:

Maculopapular rash. Purpura, possible exacerbation of acute systemic lupus erythematosus, erythema multiforme and toxic epidermal necrolysis.

Hepatobiliary disorders:

The following side-effects have been reported and frequencies are unknown:

Abnormal liver function tests, hepatic encephalopathy with patients with impaired liver function, cholestatic jaundice and pancreatitis.

Blood and lymphatic system disorders:

The following side-effects have been reported and frequencies are unknown:

Thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia.

Musculoskeletal and connective tissue disorders:

The following side-effects have been reported and frequencies are unknown:

Muscular cramps.

Reproductive system and breast disorders:

The following side-effects have been reported and frequencies are unknown:

Impotence.

Other:

The following side-effects have been reported and frequencies are unknown:

Photosensitivity reactions.

Precautions:

Signs of electrolyte imbalance include dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain and cramps.

It may cause hyperglycaemia and aggravate or unmask diabetes mellitus. Blood-glucose concentrations should be monitored in patients taking antidiabetic agents since requirements may change.

This medicine should not be given to patients with Addison's disease.
All patients should be observed for signs of fluid and electrolyte imbalance, especially in the presence of vomiting or during parenteral fluid therapy. Hyponatraemia may occur in patients with severe congestive heart failure who are very oedematous, particularly with large doses in conjunction with restricted salt in the diet. It should not be given to patients with existing hypercalcaemia. Elderly patients are particularly susceptible to electrolyte imbalance.
Systemic lupus erythematosus may be exacerbated or activated in susceptible patients.

***Withdrawal*:**

Usually, there is no rebound hypertension on withdrawal of **MYLAN INDAPAMIDE 2,5 mg** treatment.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF TREATMENT:

Symptoms of overdosage would be those associated with a diuretic effect, electrolyte imbalance (hyponatraemia, hypokalaemia); hypotension, gastrointestinal disturbances, dizziness and muscular weakness. Polyuria or oliguria, possibly anuria.

Treatment:

Treatment should be symptomatic and supportive with particular emphasis on correcting the electrolyte abnormalities and gastric decontamination.

In cases of recent ingestion, emesis or gastric lavage should be considered.

Note: Indapamide is not removed by haemodialysis.

IDENTIFICATION:

White, round, biconvex, film-coated tablets.

PRESENTATION:

Securitainers or blister packs containing 30 or 300 tablets.

STORAGE INSTRUCTIONS:

Store below 25 °C in a dry place.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

29/7.1/0590

NAME AND BUSINESS ADDRESS OF HOLDER OF THE CERTIFICATE OF REGISTRATION:

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