

# **SUMMARY OF PRODUCT CHARACTERISTICS**

## **1 NAME OF THE MEDICINAL PRODUCT**

Indapamide Hemihydrate 2.5mg Tablets  
Natramid/Opumide

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 2.5mg of Indapamide Hemihydrate.

## **3. PHARMACEUTICAL FORM**

Pink sugar-coated tablets intended for oral administration to human beings.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

For the treatment of essential hypertension, either as sole therapy or in combination with other antihypertensive agents.

### **4.2 Posology and method of administration**

For oral administration.

*Adults:* The dosage is one tablet, containing 2.5mg indapamide hemihydrate, daily to be taken in the morning. The action of indapamide is progressive and the maximum reduction in blood pressure may not be reached until several months after commencing therapy. A dose larger than 2.5mg daily is not recommended as there is no appreciable additional anti-hypertensive effect, but a diuretic effect may become apparent.

If one indapamide tablet daily does not achieve the required reduction in blood pressure, another antihypertensive agent may be added; those which have been used in combination with indapamide include beta-blockers, ACE inhibitors, methyl dopa, clonidine and other adrenergic blocking agents. Co-administration of indapamide with diuretics may cause hypokalaemia and, therefore, is not recommended.

There is no evidence of rebound hypertension following withdrawal of indapamide.

*Elderly:* There are no significant changes in the pharmacokinetics of indapamide in the elderly. The dosage recommendations for adults (above) apply also to elderly patients.

*Children:* There is no experience of the use of this drug in children.

### **4.3 Contraindications**

Indapamide is contraindicated in patients with:

- Hypersensitivity to indapamide, to sulphonamide derivatives or to any of the excipients in the tablet
- Recent cerebrovascular accident
- Severe hepatic failure or hepatic encephalopathy
- Hypokalaemia.
- Severe renal failure.

### **4.4 Special warnings and precautions for use**

#### *Special warnings*

Indapamide is not dialysable but has not demonstrated evidence of accumulation in patients with impaired renal function.

Although indapamide 2.5mg daily can be safely administered to hypertensive patients in whom renal function is impaired, therapy should be discontinued if there are signs of increasing renal insufficiency.

When liver function is impaired, thiazide-related diuretics may cause hepatic encephalopathy, particularly in case of electrolyte imbalance.

Administration of the diuretic must be stopped immediately if this occurs.

#### Photosensitivity:

Cases of photosensitivity reactions have been reported with thiazides and thiazide-related diuretics. If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

#### Excipients:

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

#### Special precautions for use

##### - Water and electrolyte balance:

###### • Plasma sodium:

This must be measured before starting treatment, then at regular intervals subsequently. Any diuretic treatment may cause hyponatraemia, sometimes with very serious consequences. The fall in plasma sodium may be asymptomatic initially and regular monitoring is therefore essential, and should be even more frequent in the elderly and cirrhotic patients.

###### • Plasma potassium:

Potassium depletion with hypokalaemia is the major risk of thiazide and related diuretics. The risk of onset of hypokalaemia (< 3.4 mmol/l) must be prevented in certain high risk populations, i.e. the elderly, malnourished and/or polymedicated, cirrhotic patients with oedema and ascites, coronary artery disease and cardiac failure patients. In this situation, hypokalaemia increases the cardiac toxicity of digitalis preparations and the risks of arrhythmias.

Individuals with a long QT interval are also at risk, whether the origin is congenital or iatrogenic. Hypokalaemia, as well as bradycardia, is then a predisposing factor to the onset of severe arrhythmias, in particular, potentially fatal torsades de pointes.

More frequent monitoring of plasma potassium is required in all the situations indicated above. The first measurement of plasma potassium should be obtained during the first week following the start of treatment.

Detection of hypokalaemia requires its correction.

##### Plasma calcium:

Thiazide and related diuretics may decrease urinary calcium excretion and cause a slight and transitory rise in plasma calcium. Frank hypercalcaemia may be due to previously unrecognised hyperparathyroidism.

Treatment should be withdrawn before the investigation of parathyroid function.

##### - Blood glucose:

Monitoring of blood glucose is important in diabetics, in particular in the presence of hypokalaemia.

##### - Uric acid:

Tendency to gout attacks may be increased in hyperuricaemic patients.

##### - Renal function and diuretics:

Thiazide and related diuretics are fully effective only when renal function is normal or only minimally impaired (plasma creatinine below levels of the order of 25 mg/l, i.e. 220 µmol/l in an adult). In the elderly, this plasma creatinine must be adjusted in relation to age, weight and gender.

Hypovolaemia, secondary to the loss of water and sodium induced by the diuretic at the start of treatment causes a reduction in glomerular filtration. This may lead to an increase in blood urea and plasma creatinine. This transitory functional renal insufficiency is of no consequence in individuals with normal renal function but may worsen preexisting renal insufficiency.

##### - Athletes:

The attention of athletes is drawn to the fact that this medicinal product contains a drug substance, which may give a positive reaction in doping tests.

If pre-existing renal insufficiency is aggravated, indapamide therapy should be discontinued. Indapamide should also be discontinued if hypercalcaemia occurs in patients with hyperparathyroidism.

The label should state the following: Protect from light.

Do not store above 25°C

## 4.5 Interaction with other medicinal products and other forms of interaction

### Combinations that are not recommended:

#### **Lithium:**

Increased plasma lithium with signs of overdosage, as with a salt-free diet (decreased urinary lithium excretion). However, if the use of diuretics is necessary, careful monitoring of plasma lithium and dose adjustment are required.

### Combinations requiring precautions for use:

#### **Torsades de pointes-inducing drugs:**

- class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide),
- class III antiarrhythmics (amiodarone, sotalol, dofetilide, ibutilide),
- some antipsychotics :

phenothiazines (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine),

benzamides (amisulpride, sulpiride, sultopride, tiapride)

butyrophenones (droperidol, haloperidol)

others: bepridil, cisapride, diphemanil, erythromycin IV, halofantrine, mizolastine, pentamidine, sparfloxacin, moxifloxacin, vincamine IV.

Increased risk of ventricular arrhythmias, particularly *torsades de pointes* (hypokalaemia is a risk factor).

Monitor for hypokalaemia and correct, if required, before introducing this combination. Clinical, plasma electrolytes and ECG monitoring.

*Use substances which do not have the disadvantage of causing torsades de pointes in the presence of hypokalaemia.*

#### **N.S.A.I.Ds. (systemic route) including COX-2 selective inhibitors, high dose salicylic acid ( $\geq 3$ g/day):**

Possible reduction in the antihypertensive effect of indapamide.

Risk of acute renal failure in dehydrated patients (decreased glomerular filtration).

Hydrate the patient; monitor renal function at the start of treatment.

#### **Angiotensin converting enzyme (A.C.E.) inhibitors:**

Risk of sudden hypotension and/or acute renal failure when treatment with an A.C.E. is initiated in the presence of preexisting sodium depletion (particularly in patients with renal artery stenosis).

*In hypertension*, when prior diuretic treatment may have caused sodium depletion, it is necessary:

- either to stop the diuretic 3 days before starting treatment with the A.C.E. inhibitor, and restart a hypokalaemic diuretic if necessary;
- or give low initial doses of the A.C.E. inhibitor and increase the dose gradually.

*In congestive heart failure*, start with a very low dose of A.C.E. inhibitor, possibly after a reduction in the dose of the concomitant hypokalaemic diuretic.

*In all cases*, monitor renal function (plasma creatinine) during the first weeks of treatment with an A.C.E. inhibitor.

#### **Other compounds causing hypokalaemia: amphotericin B (IV), gluco- and mineralo-corticoids (systemic route), tetracosactide, stimulant laxatives:**

Increased risk of hypokalaemia (additive effect).

Monitoring of plasma potassium and correction if required. Must be particularly borne in mind in case of concomitant digitalis treatment. Use non-stimulant laxatives.

**Baclofen:**

Increased antihypertensive effect.

Hydrate the patient; monitor renal function at the start of treatment.

**Digitalis preparations:**

Hypokalaemia predisposing to the toxic effects of digitalis.

Monitoring of plasma potassium and ECG and, if necessary, adjust the treatment.

*Combinations to be taken into consideration:*

**Potassium-sparing diuretics (amiloride, spironolactone, triamterene):**

Whilst rational combinations are useful in some patients, hypokalaemia (particularly in patients with renal failure or diabetes) or hyperkalaemia may still occur. Plasma potassium and ECG should be monitored and, if necessary, treatment reviewed.

**Metformin:**

Increased risk of metformin induced lactic acidosis due to the possibility of functional renal failure associated with diuretics and more particularly with loop diuretics. Do not use metformin when plasma creatinine exceeds 15 mg/l (135 µmol/l) in men and 12 mg/l (110 µmol/l) in women.

**Iodinated contrast media:**

In the presence of dehydration caused by diuretics, increased risk of acute renal failure, in particular when large doses of iodinated contrast media are used.

Rehydration before administration of the iodinated compound.

**Imipramine-like antidepressants, neuroleptics:**

Antihypertensive effect and increased risk of orthostatic hypotension increased (additive effect).

**Calcium (salts):**

Risk of hypercalcaemia resulting from decreased urinary elimination of calcium.

**Ciclosporin, tacrolimus:**

Risk of increased plasma creatinine without any change in circulating cyclosporin levels, even in the absence of water/sodium depletion.

**Corticosteroids, tetracosactide (systemic route):**

Decreased antihypertensive effect (water/sodium retention due to corticosteroids).

## 4.6 Pregnancy and lactation

**Pregnancy:**

As a general rule, the administration of diuretics should be avoided in pregnant women and should never be used to treat physiological oedema of pregnancy. Diuretics can cause foetoplacental ischaemia, with a risk of impaired foetal growth.

**Lactation:**

Breast-feeding is inadvisable (Indapamide is excreted in human milk).

#### **4.7 Effects on ability to drive and use machines**

Indapamide does not affect vigilance but different reactions in relation with the decrease in blood pressure may occur in individual cases, especially at the start of the treatment or when another antihypertensive agent is added.

As a result the ability to drive vehicles or to operate machinery may be impaired.

#### **4.8 Undesirable effects**

The majority of adverse reactions concerning clinical or laboratory parameters are dose-dependent.

Thiazide-related diuretics, including indapamide, may cause the following undesirable effects ranked under the following frequency:

Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10000, <1/1000), very rare (<1/10000), frequency not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders:

Very rare: thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia.

Metabolism and nutrition disorders:

Rare: metabolic alkalosis, hyperglycaemia, increased blood urate levels

Nervous system disorders:

Common: dizziness.

Rare: vertigo fatigue, headache, paresthesia

Eye disorders:

Rare: reversible acute myopia.

Cardiac disorders:

Very rare: arrhythmia, hypotension (orthostatic)

Gastrointestinal disorders:

Common: anorexia, diarrhoea, dyspepsia.

Uncommon: vomiting,

Rare: dry mouth, nausea, constipation,

Very rare: pancreatitis

Renal and urinary disorders:

Very rare: renal failure.

Reproductive system:

Rare: impotence

Hepato-biliary disorders:

Very rare: abnormal hepatic function

Not known: possibility of onset of hepatic encephalopathy in case of hepatic insufficiency.

Skin and subcutaneous tissue disorders:

Hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions:

- Common: maculopapular rashes
  - Uncommon: purpura
  - Rare: erythema multiforme, epidermal necrolysis, photosensitivity
  - Very rare: angioneurotic oedema and/or urticaria, Steven Johnson syndrome.
- Not known: possible worsening of pre-existing acute disseminated lupus erythematosus.

Cases of photosensitivity reactions have been reported.

Musculoskeletal, connective and bone disorders:

Common: muscle cramps

Investigations:

During clinical trials, hypokalaemia (plasma potassium <3.4 mmol/l) was seen in 10 % of patients and < 3.2 mmol/l in 4 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.23 mmol/l.

Very rare: Hypercalcaemia

Not known:

- Potassium depletion with hypokalaemia, particularly serious in certain high risk populations (see section 4.4).
- Hyponatraemia with hypovolaemia responsible for dehydration and orthostatic hypotension. Concomitant loss of chloride ions may lead to secondary compensatory metabolic alkalosis: the incidence and degree of this effect are slight.

Increase in plasma uric acid and blood glucose during treatment: appropriateness of these diuretics must be very carefully weighed in patients with gout or diabetes.

## **4.9 Overdose**

Indapamide has been found free of toxicity at up to 40 mg, i.e. 27 times the therapeutic dose.

Signs of acute poisoning take the form above all of water/electrolyte disturbances (hyponatraemia, hypokalaemia). Clinically, possibility of nausea, vomiting, hypotension, cramps, vertigo, drowsiness, confusion, polyuria or oliguria possibly to the point of anuria (by hypovolaemia).

There is no specific antidote. The stomach should be emptied by gastric aspiration and lavage or by emesis. Treatment should be symptomatic and supportive and particular attention should be directed at correcting electrolyte and fluid imbalances

## **5. PHARMACOLOGICAL PROPERTIES**

## **5.1 Pharmacodynamic properties**

Indapamide is a non-thiazide indole derivative of chlorosulphonamide. Indapamide exerts an antihypertensive effect and its mode of action includes reduction in peripheral arterial resistance and normalisation of vascular hyper-reactivity.

The action of indapamide is progressive and the maximum reduction in blood pressure may not be reached until several months after commencing therapy.

A dose larger than 2.5mg daily is not recommended as there is no appreciable additional antihypertensive effect but a diuretic effect may become apparent.

## **5.2 Pharmacokinetic properties**

Indapamide is rapidly and completely absorbed from the gastro-intestinal tract. The drug is preferentially and reversibly taken up by red blood cells and is about 71 to 79% bound to plasma proteins. Metabolism of indapamide is extensive. About 60 to 70% of the dose has been reported to be excreted in urine and only about 5% is excreted unchanged; approximately 16 to 23% is excreted in the faeces. Elimination is biphasic with a terminal half-life of 14 to 18 hours. There is no significant accumulation of indapamide in patients with impaired renal function. Indapamide is not dialysable.

## **5.3 Preclinical safety data**

No further relevant information other than that which is included in other sections of the Summary of Product Characteristics.

# **6. PHARMACEUTICAL PARTICULARS**

## **6.1 List of excipients**

Lactose B.P.  
Di-basic Calcium Phosphate B.P  
Maize Starch B.P  
(Purified Water B.P)\*  
Magnesium Stearate B.P  
Croscarmellose Sodium (Type A) N.F  
CS7 Shellac Solution dilute:-  
Shellac (1963) B.P.C.  
Castor Oil (No. 1) B.P./Ph.Eur.

(Industrial Methylated Spirits) \*  
CS4 White Coating Paste:-  
Coating Paste C53  
Titanium Dioxide B.P (E171)  
Coating Paste C53.-  
Sugar Syrup C31  
Acacia Gum CS83  
Talc B.P  
Sugar Syrup CSI  
Sucrose B.P  
(Purified Water B.P)\*  
Preservative Solution CS26  
Preservative Solution CS26:-  
Methylhydroxybenzoate B.P  
Propylhydroxybenzoate B.P  
(Industrial Methylated Spirits)  
Acacia Gum CS83.-  
Acacia B.P.  
(Purified Water B.P)\*  
(Chloroform BP) \*  
Pink Sugar Syrup CS116:-  
Opalux AS-F- 1312  
Sugar Syrup 70% CSS4  
Sugar Syrup 70% CSS4:-  
(Purified Water B.P)  
Sucrose B.P  
CS9 Polyethylene Glycol Polishing Solution:-  
Polyethylene Glycol 6000 B.P  
(Industrial Methylated Spirits)

## **6.2 Incompatibilities**

None known.

## **6.3 Shelf life**

36 months

## **6.4 Special precautions for storage**

Protect from light.  
Do not store above 25°C.

**6.5 Nature and contents of container**

Blister packs which consist of strips made from hard PVC with a foil lid.  
Pack sizes 28 tablets in blister packs of 14 (2 x 14); 30 tablets in blister packs of 15 (2 x 15); 56 tablets in blister packs of 14(4 x 14) and 60 tablets in blister packs of 15 (4 x 15).

**6.6 Instructions for use/handling**

Not applicable.

**ADMINISTRATION DETAILS**

**7. MARKETING AUTHORISATION HOLDER**

Goldshield Pharmaceuticals Ltd  
NLA Tower  
12-16 Addiscombe Road  
Croydon  
Surrey  
CR0 0XT  
United Kingdom

**8. MARKETING AUTHORISATION NUMBER**

PL 12762/0120

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

25<sup>th</sup> July 2001

**10 DATE OF REVISION OF THE TEXT**

30/09/2010