SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FLUDEX LP, sustained release film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Indapamide .....1.50 mg

For a sustained release film-coated tablet.

Excipient : 124.5 mg lactose monohydrate

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sustained release film-coated tablet.

Round, white, film-coated tablet.

4. CLINICAL DATA

4.1 Therapeutic indications

Essential hypertension.

4.2 Posology and method of administration

Oral route.

One tablet per 24 hrs, preferably in the morning.

The tablet should be taken whole with water and should not be chewed.

Higher doses do not improve the antihypertensive action of indapamide; rather, they increase the salidiuretic effect.

Renal failure (see sections 4.3 and 4.4):
In severe renal failure (creatinine clearance below 30 ml/min), treatment is contraindicated.
Thiazide and related diuretics are fully effective only when renal function is normal or only minimally impaired.

Elderly (see section 4.4):
In the elderly, the plasma creatinine must be adjusted in relation to age, weight and gender. Elderly patients can be treated with FLUDEX LP when renal function is normal or only minimally impaired.

Patients with hepatic impairment (see sections 4.3 and 4.4):
In severe hepatic impairment, treatment is contraindicated.

Children and adolescents:
FLUDEX LP is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

4.3 Contraindications

- Hypersensitivity to indapamide, to other sulfonamides or to any of the excipients.
- Severe renal failure.
- Hepatic encephalopathy or severe liver failure.
- Hypokalemia.

4.4 Special warnings and special precautions for use

Special warnings

When liver function is impaired, thiazide-related diuretics may cause hepatic encephalopathy particularly in the event 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 (see section 4.8). 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

This medicinal product contains lactose. Its use is not recommended in patients with problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption (rare hereditary diseases).

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 hyponatremia, sometimes with very serious consequences. The fall in plasma sodium may be asymptomatic initially and regular monitoring is therefore essential, and should be carried out even more frequently in the elderly and cirrhotic patients (see sections 4.8 and 4.9).

Plasma potassium

Potassium depletion with hypokalemia is the major risk of thiazide and related diuretics. The risk of the onset of hypokalemia (< 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, hypokalemia increases the cardiac toxicity of digitalis preparations and the risk of arrhythmias.

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

More frequent monitoring of plasma potassium is required in all the situations indicated above. The first measurement of plasma potassium should be carried out during the first week following the start of treatment.
Detection of hypokalemia should be followed by its correction.

Plasma calcium
Thiazide and related diuretics may decrease urinary calcium excretion and cause a slight and transitory rise in plasma calcium. Frank hypercalcemia may be due to previously unrecognised hyperparathyroidism. Treatment should be withdrawn before the investigation of parathyroid function.

Blood glucose:
Monitoring blood glucose is important in diabetics, in particular in the presence of hypokalemia.

Uric acid:
Tendency to gout attacks may be increased in hyperuricemic 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 value must be adjusted in relation to age, weight and sex.
Hypovolemia, 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 plasma 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 drug contains an active ingredient that may induce a positive reaction during anti-doping control tests.

4.5 Interactions with other medicinal products and other forms of interaction

Inadvisable combination

+ **Lithium**
Increased blood lithium concentrations with signs of overdosage, as during a sodium-free diet (reduction in urinary lithium excretion). However, if the use of diuretics is required, the blood lithium levels should be strictly monitored and the dosage adjusted.

Combinations requiring precautions for use

+ **Drugs causing wave burst arrhythmias**
- 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 arrhythmia, in particular wave burst arrhythmias (hypokalemia is a risk factor).

Hypokalemia should be monitored and corrected if necessary, before starting a combination. Clinical signs, plasma electrolytes and the ECG should be monitored.

Use substances without the disadvantage of causing wave burst arrhythmia in the case of hypokalemia.

+ N.S.A.I.D. (systemic), ***including selective COX-2 inhibitors, and high dose salicylates (>3 g/day)***
Possible decrease in the antihypertensive effect of indapamide.
Risk of acute renal failure in dehydrated patients (decreased glomerular filtration).
Hydrate the patient; monitor the renal function at the start of treatment.

+ Angiotensin converting enzyme (ACE) inhibitors
Risk of sudden hypotension and/or acute renal failure at the start of treatment by a converting enzyme inhibitor if there is preexisting sodium depletion (in particular in patients with renal artery stenosis).

In essential hypertension, when an earlier diuretic treatment may have involved a depletion of sodium, it is necessary to:
- either stop the diuretic 3 days before the start of the ACE inhibitor treatment and reintroduce a potassium-lowering diuretic if necessary ;
- or initially administer low doses of the ACE inhibitor and then increase the dose gradually.

In congestive heart failure, begin with a very low dose of ACE inhibitor possibly after reducing the dose of associated potassium-lowering diuretic.

In all cases, monitor renal function (plasma creatinine) during the first few weeks of treatment with the ACE inhibitor.

+ Other hypokalemic compounds: amphotericin B (IV), gluco- and mineralocorticoids (oral), tetracosactide, stimulant laxatives
Increased risk of hypokalemia (additive effect).
Monitoring of plasma potassium and correction, if required, must be particularly borne in mind in the 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
Hypokalemia predisposes to the toxic effects of digitalis.
Monitor the plasma potassium, ECG and, if necessary, review the treatment.

Combinations to be taken into account

+ Hyperkalemic diuretics (amiloride, spironolactone, triamterene)
In the case of a rational combinations, useful for certain patients, the possibility of hypokalemia or hyperkalemia (in particular in renal failure and diabetic patients) is not eliminated. Monitor plasma potassium and ECG and review treatment if necessary.

+ Metformin
An increased risk of the appearance of lactic acidosis due to metformin, triggered by possible functional renal failure related to diuretics and more particularly to loop diuretics.
Do not use metformin when blood creatinine levels exceed 15 mg/liter (135 micromoles/liter) in men and 12 mg/liter (110 micromoles/liter) in women.

+ Iodinated contrast media
In cases of dehydration caused by diuretics, there is an increased risk of acute renal failure, in particular when high doses of iodinated contrast media are used.
Rehydration before the administration of the iodinated compound.

+ Imipramine antidepressants (tricyclics), neuroleptics
Antihypertensive effect and increased risk of orthostatic hypotension (additive effect).

+ Calcium (salts)
Risk of hypercalcemia resulting from decreased urinary calcium elimination.

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

+ Corticosteroids, tetracosactide (oral route)
Decreased antihypertensive effect (water/sodium retention of corticosteroids).

4.6 Pregnancy and lactation

Pregnancy

As a general rule, the administration of thiazide and related diuretics should be avoided in pregnant women and should never be used to treat the physiological edema of pregnancy. Diuretics can cause fetoplacental ischemia, with a risk of fetal hypotrophy.

Lactation

Breast-feeding is inadvisable (passage into the breast milk).

4.7 Effects on the ability to drive vehicles and use machines

FLUDEX LP does not affect alertness, but individual reactions in relation to the decrease in blood pressure may occur in certain patients, especially at the start of treatment or in combination with another antihypertensive drug.
Consequently, the ability to drive vehicles or to use machinery may be diminished.

4.8 Side 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), not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders:
- Very rare: thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia

Nervous system disorders:
- Rare: vertigo, fatigue, headache, paresthesia
- Not known: syncope

Cardiac disorders:
- Very rare: arrhythmia, hypotension.
- Not known: *torsades de pointes* (potentially fatal) (see sections 4.4 and 4.5)

Gastrointestinal disorders:
- Uncommon: vomiting
- Rare: nausea, constipation, dry mouth
- Very rare: pancreatitis

Renal and urinary disorders:
- Very rare: renal failure

Hepato-biliary disorders:
- Very rare: abnormal hepatic function
- Not known: possibility of onset of hepatic encephalopathy in case of hepatic insufficiency (see sections 4.3 and 4.4), hepatitis

Skin and subcutaneous tissue disorders:
- Hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions:
- Common: maculopapular rashes
- Uncommon: purpura
- Very rare: angioneurotic oedema and/or urticaria, toxic epidermic necrolysis, Steven Johnson syndrome
- Not known: possible worsening of pre-existing acute disseminated lupus erythematosus.
- Cases of photosensitivity reactions have been reported (see section 4.4).

Investigations
- Not known:
    - Electrocardiogram QT prolonged (see sections 4.4 and 4.5)
    - Blood glucose increased and blood uric acid increased during treatment: appropriateness of these diuretics must be very carefully weighed in patients with gout or diabetes
    - Elevated liver enzyme levels

Metabolism and nutrition disorder:
- 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.

4.9 Overdosage

Indapamide has not shown any toxicity at doses of up to 40 mg, i.e. 27 times the therapeutic dose.

Above all, signs of acute poisoning take the form of water and electrolyte disturbances (hyponatremia and hypokalemia). Clinically, they include possible nausea, vomiting, hypotension, cramps, vertigo, drowsiness, confusional states, polyuria or oliguria up to the extent of anuria (due to hypovolemia).

Initial measures taken involve the rapid elimination of the product(s) ingested by gastric lavage and/or the administration of activated charcoal, followed by restoration of the fluid and the electrolyte balance to normal in a specialized center.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

DIURETIC ACTING ON THE CORTICAL DILUTION SEGMENT
ATC Code: CO3 BA 11 (Cardiovascular System)

Indapamide is a sulfonamide derivative with an indol ring, which is pharmacologically related to the thiazide diuretics, which act by inhibiting the reabsorption of sodium in the cortical dilution segment. It increases the urinary excretion of sodium and chlorides and, to a lesser extent, the excretion of potassium and magnesium, thereby increasing urine output and having an antihypertensive action.

Phase II and III studies using monotherapy have demonstrated an antihypertensive effect lasting 24 hrs. This was present at doses where the diuretic effect was of mild intensity.

Its antihypertensive activity is related to an improvement in arterial compliance and a reduction in arteriolar and total peripheral resistance.

Indapamide reduces left ventricular hypertrophy.

Thiazide and related diuretics have a plateau therapeutic effect beyond a certain dose, while adverse effects continue to increase. The dose should not be increased if treatment is ineffective.

It has also been shown in the short-, medium- and long-term in hypertensive patients, that Indapamide:
- does not interfere with lipid metabolism: triglycerides, LDL-cholesterol and HDL-cholesterol,
- does not interfere with carbohydrate metabolism, even in the diabetic hypertensive patient.

5.2 Pharmacokinetic properties

FLUDEX LP is supplied in a sustained release dosage form based on a matrix system in which the active substance is dispersed in a support which allows sustained release of Indapamide.

Absorption

The fraction of Indapamide released is rapidly and totally absorbed via the gastrointestinal digestive tract.

Eating slightly increases the speed of absorption but has no influence on the amount of drug absorbed.

The peak serum level following a single dose occurs about 12 hrs after ingestion, repeated administration reduces the variation in serum levels between two doses.

Intra-individual variability exists.

Distribution

The binding of indapamide to plasma proteins is 79%;

The plasma elimination half-life is 14 to 24 hrs (mean = 18 hrs).

State of equilibrium is achieved after 7 days.

Repeated administration does not lead to accumulation.

Metabolism
Elimination is essentially urinary (70% of the dose) and fecal (22%) in the form of inactive metabolites.

Populations at-risk

Pharmacokinetic parameters are unchanged in renal failure patients.

5.3 Preclinical safety data

The highest doses administered in different animal species by the oral route (40 to 8000 times the therapeutic dose) have shown an exacerbation of the diuretic properties of indapamide. The main symptoms from acute toxicity studies with indapamide administered by the intravenous or intraperitoneal route are related to the pharmacological activity of indapamide, i.e. bradypnea and peripheral vasodilation.
Mutagenicity and carcinogenicity tests on indapamide are negative.

6. PHARMACEUTICAL DATA

6.1 List of excipients

Uncoated tablet: anhydrous colloidal silica, hypromellose, lactose monohydrate, magnesium stearate, povidone.

Film-coating: glycerol, hypromellose, macrogol 6000, magnesium stearate, titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years

6.4 Special storage precautions

Store below 30°C.