

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fludex 1.5 mg, prolonged-release film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One prolonged-release film-coated tablet contains 1.5 mg indapamide.

Excipient with known effect: 124.5 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

White, round, film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fludex 1.5 mg is indicated in essential hypertension in adults.

4.2 Posology and method of administration

Posology

One tablet per 24 hours, preferably in the morning, to be swallowed whole with water and not chewed. At higher doses the antihypertensive action of indapamide is not enhanced but the saluretic effect is increased.

Special populations

Renal impairment (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.

Hepatic impairment (see sections 4.3 and 4.4):

In severe hepatic impairment, treatment is contraindicated.

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 1.5 mg when renal function is normal or only minimally impaired.

Paediatric population:

The safety and efficacy of Fludex 1.5 mg in children and adolescents have not been established. No data are available.

Method of administration

Oral use

4.3 Contraindications

- Hypersensitivity to the active substance, to other sulfonamides or to any of the excipients listed in section 6.1.
- Severe renal failure.
- Hepatic encephalopathy or severe impairment of liver function.
- Hypokalaemia.

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 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 (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:

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. 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 (see sections 4.8 and 4.9). Any diuretic treatment may cause hyponatraemia, sometimes with very serious consequences. Hyponatraemia with hypovolaemia may be responsible of 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.

• 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 $\mu\text{mol/l}$ 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.

4.5 Interactions with other medicinal products and other forms of interaction

Combinations that are not recommended:

Lithium:

Increased plasma lithium with signs of overdose, 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 (≥ 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 or hyperkalaemia (particularly in patients with renal failure or diabetes) 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 Fertility, pregnancy and lactationPregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of indapamide in pregnant women. Prolonged exposure to thiazide during the third trimester of pregnancy can reduce maternal plasma volume as well as uteroplacental blood flow, which may cause a foeto-placental ischaemia and growth retardation.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Indapamide during pregnancy.

Breast-feeding

There is insufficient information on the excretion of indapamide/metabolites in human milk. Hypersensitivity to sulphonamide-derived medicines and hypokalaemia might occur. A risk to the newborns/infants cannot be excluded.

Indapamide is closely related to thiazide diuretics which have been associated, during breast-feeding, with decrease or even suppression of milk lactation.

Indapamide should not be used during breast-feeding.

Fertility

Reproductive toxicity studies showed no effect on fertility in female and male rats (see section 5.3).

No effects on human fertility are anticipated.

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 effectsSummary of safety profile

The most commonly reported adverse reactions are hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions and maculopapular rashes.

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.

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

Tabulated summary of adverse reactions

The following undesirable effects have been observed with indapamide during treatment ranked under the following frequency:

Very common ($\geq 1/10$); common ($\geq 1/100$ to $<1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $<1/1,000$); very rare ($\geq 1/100,000$ to $<1/10,000$), not known (cannot be estimated from the available data).

MedDRA System Organ Class	Undesirable Effects	Frequency
Blood and the lymphatic System Disorders	Agranulocytosis	Very rare
	Aplastic anaemia	Very rare
	Haemolytic anaemia	Very rare
	Leucopenia	Very rare
	Thrombocytopenia	Very rare
Metabolism and Nutrition Disorders	Hypercalcaemia	Very rare
	Potassium depletion with hypokalaemia, particularly serious in certain high risk populations (see section 4.4)	Not known
	Hyponatraemia (see section 4.4)	Not know
Nervous System disorders	Vertigo	Rare
	Fatigue	Rare
	Headache	Rare
	Paresthesia	Rare
	Syncope	Not known
Eye disorders	Myopia	Not known
	Blurred vision	Not known
	Visual impairment	Not known
Cardiac Disorders	Arrhythmia	Very rare
	Torsade de pointes (potentially fatal) (see sections 4.4 and 4.5)	Not known
Vascular Disorders	Hypotension	Very rare
Gastrointestinal Disorders	Vomiting	Uncommon
	Nausea	Rare
	Constipation	Rare
	Dry mouth	Rare
	Pancreatitis	Very rare
Hepatobiliary Disorders	Abnormal hepatic function	Very rare
	Possibility of onset of hepatic encephalopathy in case of hepatic insufficiency (see sections 4.3 and 4.4)	Not known
	Hepatitis	Not known
Skin and Subcutaneous Tissue Disorder	Hypersensitivity reactions	Common
	Maculopapular rashes	Common
	Purpura	Uncommon
	Angioedema	Very rare
	Urticaria	Very rare
	Toxic epidermic necrolysis	Very rare
	Stevens-Johnson Syndrome	Very rare
	Possible worsening of pre-existing acute disseminated lupus erythematosus	Not known
Photosensitivity reactions (see section 4.4)	Not known	
Renal and Urinary Disorders	Renal failure	Very rare
Investigations	Electrocardiogram QT prolonged (see sections 4.4 and 4.5)	Not known
	Blood glucose increased (see section 4.4)	Not known
	Blood uric acid increased (see section 4.4)	Not known
	Elevated liver enzyme levels	Not known

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

4.9 Overdose

Symptoms

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).

Management

Initial measures involve the rapid elimination of the ingested substance(s) by gastric wash-out and/or administration of activated charcoal, followed by restoration of water/electrolyte balance to normal in a specialised centre.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sulfonamides, plain, ATC code: C 03 BA 11

Mechanism of action

Indapamide is a sulphonamide derivative with an indole ring, pharmacologically related to thiazide diuretics, which acts 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.

Pharmacodynamic effects

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

The antihypertensive activity of indapamide 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-, mid- 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 diabetic hypertensive patients.

5.2 Pharmacokinetic properties

Indapamide 1.5 mg is supplied in a prolonged release dosage based on a matrix system in which the drug substance is dispersed within 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 rapidity of absorption but has no influence on the amount of the drug absorbed.

Peak serum level following a single dose occurs about 12 hours after ingestion, repeated administration reduces the variation in serum levels between 2 doses. Intra-individual variability exists.

Distribution:

Binding of indapamide to plasma proteins is 79%.

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

Steady state is achieved after 7 days.

Repeated administration does not lead to accumulation.

Metabolism:

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

High risk individuals:

Pharmacokinetic parameters are unchanged in renal failure patients.

5.3 Preclinical safety data

Indapamide has been tested negative concerning mutagenic and carcinogenic properties.

The highest doses administered orally to different animal species (40 to 8000 times the therapeutic dose) have shown an exacerbation of the diuretic properties of indapamide. The major symptoms of poisoning during acute toxicity studies with indapamide administered intravenously or intraperitoneally were related to the pharmacological action of indapamide, *i.e.* bradypnoea and peripheral vasodilation.

Reproductive toxicity studies have not shown embryotoxicity and teratogenicity.

Fertility was not impaired either in male or in female rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet:

Silica, colloidal anhydrous

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 precautions for storage

Store below 30°C.

6.5 Nature and contents of container

10, 14, 15, 20, 30, 50, 60, 90, 100 tablets in blisters (PVC/aluminium).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

To be completed nationally.

For RMS (France):

Les Laboratoires Servier

50, rue Carnot

92284 Suresnes cedex - France

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

27/11/2015