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 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.

4.5 Interactions 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 (≥ 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 requiring special care:
Allopurinol:
Concomitant treatment with indapamide may increase the incidence of hypersensitivity reactions to allopurinol.

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 lactation

Pregnancy
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 effects

Summary 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 (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥1/10,000 to <1/1,000); very rare (≥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

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

{CARTON}

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains: indapamide 1.5 mg

3. LIST OF EXCIPIENTS

Contains lactose monhydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets
14 film-coated tablets
15 film-coated tablets
20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
60 film-coated tablets
90 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally.
For RMS (France):
Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex - France

12. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

To be completed nationally.
For RMS (France):
Fludex1.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

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

2. NAME OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally.
For RMS (France):
Les Laboratoires Servier

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

LOT {number}

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Fludex 1.5 mg prolonged-release film-coated tablets
Indapamide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Fludex 1.5 mg is and what it is used for

Fludex 1.5 mg is a prolonged-release film-coated tablet containing indapamide as active ingredient.
Indapamide is a diuretic. Most diuretics increase the amount of urine produced by the kidneys. However, indapamide is different from other diuretics, as it only causes a slight increase in the amount of urine produced.

This medicine is intended to reduce high blood pressure (hypertension) in adults.

2. What you need to know before you take Fludex 1.5 mg

Do not take Fludex 1.5 mg:
- if you are allergic to indapamide or any other sulphonamide or to any of the other ingredients of this medicine (listed in section 6),
- if you have severe kidney disease,
- if you have severe liver disease or suffer from a condition called hepatic encephalopathy (degenerative disease of the brain),
- if you have low potassium levels in your blood.

Warnings and precautions:
Talk to your doctor or pharmacist before taking Fludex 1.5 mg:
- if you have liver problems,
- if you have diabetes,
- if you suffer from gout,
- if you have any heart rhythm problems or problems with your kidneys,
- if you need to have a test to check how well your parathyroid gland is working.

You should tell your doctor if you had photosensitivity reactions.

Your doctor may give you blood tests to check for low sodium or potassium levels or high calcium levels.
If you think any of these situations may apply to you or you have any questions or doubts about taking your medicine, you should consult your doctor or pharmacist.
Athletes should be aware that this medicine contains an active ingredient, which may give a positive reaction in doping tests.

Other medicines and Fludex 1.5 mg:
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
You should not take Fludex 1.5 mg with lithium (used to treat depression) due to the risk of increased levels of lithium in the blood.
Make sure to tell your doctor if you are taking any of the following medicines, as special care may be required:
- medicines used for heart rhythm problems (e.g. quinidine, hydroquinidine, disopyramide, amiodarone, sotalol, ibutilide, dofetilide, digitalis),
- medicines used to treat mental disorders such as depression, anxiety, schizophrenia… (e.g. tricyclic antidepressants, antipsychotic drugs, neuroleptics),
- bepridil (used to treat angina pectoris, a condition causing chest pain),
- cisapride, diphemanil (used to treat gastro-intestinal problems),
- sparfloxacin, moxifloxacin, erythromycin by injection (antibiotics used to treat infections),
- vincamine by injection (used to treat symptomatic cognitive disorders in elderly including memory loss),
- halofantrine (antiparasitic drug used to treat certain types of malaria),
- pentamidine (used to treat certain types of pneumonia),
- mizolastine (used to treat allergic reactions, such as hay fever),
- non-steroidal anti-inflammatory drugs for pain relief (e.g. ibuprofen) or high doses of acetylsalicylic acid,
- angiotensin converting enzyme (ACE) inhibitors (used to treat high blood pressure and heart failure),
- amphotericin B by injection (anti-fungal medicines),
- oral corticosteroids used to treat various conditions including severe asthma and rheumatoid arthritis,
- stimulant laxatives,
- baclofen (to treat muscle stiffness occurring in diseases such as multiple sclerosis),
- allopurinol (for the treatment of gout),
- potassium-sparing diuretics (amiloride, spironolactone, triamterene),
- metformin (to treat diabetes),
- iodinated contrast media (used for tests involving X-rays),
- calcium tablets or other calcium supplements,
- ciclosporin, tacrolimus or other medicines to depress the immune system after organ transplantation, to treat autoimmune diseases, or severe rheumatic or dermatological diseases,
- tetracosactide (to treat Crohn's disease).

Pregnancy and breast-feeding:
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking any medicine.
This medicine is not recommended during pregnancy. When a pregnancy is planned or confirmed, the switch to an alternative treatment should be initiated as soon as possible. Please tell your doctor if you are pregnant or wish to become pregnant**.**
The active ingredient is excreted in milk. Breastfeeding is not advisable if you are taking this medicine.

Driving and using machines:
This medicine can cause side effects due to lowering of the blood pressure such as dizziness or tiredness (see section 4). These side effects are more likely to occur after initiation of the treatment and after dose

increases. If this occurs, you should refrain from driving and other activities requiring alertness. However, under good control, these side effects are unlikely to occur.

Fludex 1.5mg contains lactose monohydrate.
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Fludex 1.5 mg

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
The recommended dose is one tablet each day, preferably in the morning.
The tablets can be taken irrespective of meals. They should be swallowed whole with water. Do not crush or chew them.
Treatment for high blood pressure is usually life-long.

If you take more Fludex 1.5 mg than you should:
If you have taken too many tablets, contact your doctor or pharmacist immediately.
A very large dose of Fludex 1.5 mg could cause nausea, vomiting, low blood pressure, cramps, dizziness, drowsiness, confusion and changes in the amount of urine produced by the kidneys.

If you forget to take Fludex 1.5 mg:
If you forget to take a dose of your medicine, take the next dose at the usual time.
Do not take a double dose to make up for a forgotten dose.

If you stop taking Fludex 1.5 mg:
As the treatment for high blood pressure is usually life-long, you should discuss with your doctor before stopping this medicinal product.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking the medicinal product and see a doctor immediately, if you experience any of the following side effects:
- Angioedema and/or urticaria. Angioedema is characterised by swelling of the skin of extremities or face, swelling of the lips or tongue, swelling of the mucous membranes of the throat or airways resulting in shortness of breath or difficulty of swallowing. If this occurs, contact your doctor immediately. (Very rare) (may affect up to 1 in 10,000 people)
- Severe skin reactions including intense skin rash, reddening of the skin over your whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of mucous membranes (Stevens Johnson Syndrome) or other allergic reactions, (Very rare) (may affect up to 1 in 10,000 people)
- Life-threatening irregular beat.(Not known)
- Inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell (Very rare) (may affect up to 1 in 10,000 people)
- Disease of the brain caused by liver illness (Hepatic encephalopathy) (Not known)
- Inflammation of the liver (Hepatitis) (Not known)

In decreasing order of frequency, other side effects can include:
Common (may affect up to 1 in 10 people):

- Red raised skin rash
- Allergic reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions.

Uncommon (may affect up to 1 in 100 people):
- Vomiting,
- Red pinpoints on skin (Purpura)

Rare (may affect up to 1 in 1000 people):
- Feeling of tiredness, headache, pins and needles (paresthesia), vertigo;
- Gastro-intestinal disorders (such as nausea, constipation), dry mouth;

Very rare (may affect up to 1 in 10,000 people):
- Changes in blood cells, such as thrombocytopenia (decrease in the number of platelets which causes easy bruising and nasal bleeding), leucopenia (decrease of white blood cells which may cause unexplained fever, soreness of the throat or other flu-like symptoms – if this occurs, contact your doctor) and anaemia (decrease in red blood cells);
- High level of calcium in blood;
- Heart rhythm irregularities, low blood pressure;
- Kidney disease;
- Abnormal hepatic function.

Not known:
- Fainting
- If you suffer from systemic lupus erythematous (a type of collagen disease), this might get worse.
- Cases of photosensitivity reactions (change in skin appearance) after exposure to the sun or artificial UVA have also been reported.
- Short sightedness (myopia).
- Blurred vision.
- Visual impairment.
- Changes may occur in your laboratory parameters (blood tests) and your doctor may need to give you blood tests to check your condition. The following changes in laboratory parameters may occur:
  . low potassium in the blood,
  . low sodium in the blood that may lead to dehydration and low blood pressure,
  . increase in uric acid, a substance which may cause or worsen gout (painful joint(s) especially in the feet),
  . increase in blood glucose levels in diabetic patients,
  . increased levels of liver enzymes.
- Abnormal ECG heart tracing

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist. This includes any possible side effects not listed in this leaflet.
You can also report side effects directly via the national reporting system listed in Appendix V*. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Fludex 1.5 mg

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and blister. The expiry date refers to the last day of that month.
Store below 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Fludex 1.5 mg contains:
The active substance is indapamide. Each tablet contains 1.5 mg of indapamide.
The other ingredients are:
- tablet core: anhydrous colloidal silica (E551), hypromellose (E464), lactose monohydrate, magnesium stearate (E470B), povidone
- film-coating: glycerol (E422), hypromellose (E464), macrogol 6000, magnesium stearate (E470B), titanium dioxide (E171).

What Fludex 1.5 mg looks like and contents of the pack:
This medicine is a white, round prolonged-release film-coated tablet.
The tablets are available in blisters of 10, 14, 15, 20, 30, 50, 60, 90 or 100 tablets packed in a cardboard box. Not all pack sizes may be marketed.

Marketing Authorisation Holder and manufacturer
Marketing Authorisation Holder :
<[To be completed nationally]>
For RMS (France):
Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex – France

Manufacturers :
Les Laboratoires Servier Industrie
905 route de Saran
45520 Gidy
FRANCE

and

Servier (Ireland) Industries Ltd
Gorey Road
Co. Wicklow – Arklow
IRELAND

and

ANPHARM Przedsiębiorstwo Farmaceutyczne S.A.
Ul. Annopol 6B - 03-236 Warszawa
POLAND

Manufacturer responsible for packaging and batch release (only for the Spanish market):
Laboratorios Servier S.L.
Avenida de Los Madroños, 33
28043 Madrid
SPAIN

Manufacturer responsible for packaging and batch release
Delpharm Bretigny
Usine du Petit Paris

91220 Bretigny sur Orge
FRANCE

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria	FLUDEX RETARD 1.5 mg
Belgium	FLUDEX 1.5 mg
Cyprus	FLUDEX 1.5 mg
Czech Republic	TERTENSIF SR
Denmark	NATRILIX RETARD
Estonia	TERTENSIF SR
Finland	NATRILIX RETARD 1.5 mg
France	FLUDEX 1.5 mg
Germany	NATRILIX SR 1.5 mg
Greece	FLUDEX 1.5 mg
Hungary	PRETANIX
Ireland	NATRILIX SR
Italy	NATRILIX LP 1.5 mg
Latvia	TERTENSIF SR
Lithuania	TERTENSIF SR
Luxembourg	FLUDEX 1.5 mg
Malta	NATRILIX SR
Netherlands	FLUDEX SR 1.5 mg
Poland	INDAPAMIDE 1.5 mg SR SERVIER
Portugal	FLUDEX LP
Slovakia	TERTENSIF SR
Slovenia	TERTENSIF SR
Spain	TERTENSIF RETARD
United Kingdom	NATRILIX SR

This leaflet was last revised in November 2015.
<[To be completed nationally]>

<Other sources of information>

<Detailed information on this medicine is available on the web site of {MA/Agency}>