

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Diurelix XL 1.5 mg Prolonged-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 1.5 mg of indapamide.

Excipient with known effect

Each prolonged-release tablet contains 93.7 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

White, round, biconvex film-coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Diurelix XL 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 Diurelix XL when renal function is normal or only minimally impaired.

Paediatric population

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

Method of administration

For 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 precautions for use

Special warnings

Hepatic impairment

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.

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 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.

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. Hypokalaemia found in association with low serum magnesium concentration can be refractory to treatment unless serum magnesium is corrected.

Plasma magnesium

Thiazides and related diuretics including indapamide have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia (see section 4.5 and 4.8).

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 micromol/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.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma

Sulphonamide or sulphonamide derivative medicinal products can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of medicinal product initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue medicinal product intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

Athletes

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

Diurelix XL contains lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction 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 medicinal products

- 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.

NSAIDs (systemic route) including COX-2 selective inhibitors, high-dose salicylic acid ($\geq 3\text{g/day}$)

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 (ACE) inhibitors

Risk of sudden hypotension and/or acute renal failure when treatment with an ACE inhibitor 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 ACE inhibitor, and restart a hypokalaemic diuretic if necessary,
- or give low initial doses of the ACE inhibitor and increase the dose gradually.

In *congestive heart failure*, start with a very low dose of ACE 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 ACE inhibitor.

Other compounds causing hypokalaemia: amphotericin B (IV route), gluco- and mineralocorticoids (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 and/or hypomagnesaemia predispose to the toxic effects of digitalis.

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

Combinations requiring special care

Allopurinol

Concomitant treatment with indapamide can 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 micromol/l) in men and 12 mg/l (110 micromol/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

Increased antihypertensive effect and increased risk of orthostatic hypotension (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 ciclosporin 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 hypokalaemia, hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions and maculopapular rashes.

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 ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1000$, $< 1/100$); rare ($\geq 1/10000$, $< 1/1000$); very rare ($< 1/10000$); not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

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

Metabolism and nutrition disorders

Common: hypokalaemia (see section 4.4)

Uncommon: hyponatraemia (see section 4.4)

Rare: hypochloraemia, hypomagnesaemia

Very rare: hypercalcaemia

Nervous system disorders

Rare: vertigo, fatigue, headache, paraesthesia

Not known: syncope

Eye disorders

Not known: choroidal effusion, transient myopia, secondary angle-closure glaucoma

Cardiac disorders

Very rare: arrhythmia

Not known: Torsade de pointes (potentially fatal) (see sections 4.4 and 4.5)

Vascular disorders

Very rare: hypotension

Gastrointestinal disorders

Uncommon: vomiting

Rare: nausea, constipation, dry mouth

Very rare: pancreatitis

Hepatobiliary 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

- *Common:* hypersensitivity reactions, maculopapular rashes
- *Uncommon:* purpura
- *Very rare:* angioedema, urticaria, toxic epidermic necrolysis, Steven Johnson syndrome
- *Not known:* possible worsening of preexisting acute disseminated lupus erythematosus, photosensitivity reactions (see section 4.4)

Renal and urinary disorders

Very rare: renal failure

Reproductive system and breast disorders

Uncommon: erectile dysfunction

Investigations

Not known:

- Electrocardiogram QT prolonged (see sections 4.4 and 4.5)
- Blood glucose increased and blood uric acid increased (see section 4.4)
- Elevated liver enzyme levels

Description of selected adverse reactions

During phase II and III studies comparing indapamide 1.5mg and 2.5mg, plasma potassium analysis showed a dose-dependent effect of indapamide:

- Indapamide 1.5mg: 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.
- Indapamide 2.5 mg: Plasma potassium <3.4 mmol/l was seen in 25 % of patients and < 3.2 mmol/l in 10 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.41 mmol/l.

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 Yellow Card Scheme:

www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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: C03BA11

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 events 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

Diurelix XL is supplied in a prolonged release dosage based on a matrix system in which the active 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 active substance 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 protein 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.

Biotransformation

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

Renal failure

Pharmacokinetic parameters are unchanged in renal failure patients.

5.3 Preclinical safety data

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.

Indapamide has been tested negative concerning mutagenic and carcinogenic

properties.

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 core:

Lactose monohydrate

Povidone K30

Hypromellose

Silica, colloidal anhydrous

Cellulose, microcrystalline

Magnesium stearate

Film coating:

Hypromellose

Macrogol 6000

Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25 °C. Store in the original package to protect from moisture.

6.5 Nature and contents of container

The prolonged-release tablets are packed in PVC/PVDC/Alu blister or Alu/Alu blister and inserted in a carton.

Pack sizes:

10, 14, 15, 20, 28, 30, 50, 60, 90, 100 prolonged-release tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
Frimley Business Park,
Frimley,
Camberley,
Surrey,
GU16 7SR.
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/0942

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 November 2009

10 DATE OF REVISION OF THE TEXT

03/12/2021