Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Arelix 6mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 6 mg piretanide.

For full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Yellow-white, oblong scored tablets imprinted on one side with the Hoechst logo and having the identifying code ARE imprinted on the unscored side.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Arelix is a diuretic for the management of fluid retention and treatment of mild to moderate hypertension.

4.2 Posology and method of administration

Adults:

Oedema: The usual initial adult dose is 6mg daily, adjusted according to response to a maximum of 30mg. An initial dose of 3mg may be sufficient in some patients.

Hypertension: The usual initial adult dose is 6mg daily in mild to moderate hypertension. This dose should be continued for 2-4 weeks then increased if necessary at 2-4 week intervals to a maximum of 18mg daily. The maintenance dose is usually 6mg daily.

Children:

There is at present insufficient experience of the use of this product in children to enable dosage recommendations to be made.

Elderly:

Piretanide may be excreted more slowly in the elderly. It may be appropriate to use a low (3mg) initial dose in the elderly.

4.3 Contraindications

Arelix must not be used in the following circumstances:

- hypersensitivity to piretanide or sulphonamide derivatives or any of the excipients
- renal failure with anuria
- coma and hepatic pre-coma
- severe hypokalaemia

- severe hyponatraemia
- hypovolaemia
- breast-feeding women

Arelix must not be used during the first trimester of a pregnancy (see section 4.6).

As there is insufficient experience in children, Arelix must not be used for this group of patients.

4.4 Special warnings and precautions for use

- hypotension
- patients with manifest or latent diabetes mellitus (regular blood sugar checks)
- patients with gout (regular check of serum levels of uric acid)
- patients with obstructed urinary flow (e.g. prostatic hypertrophy, hydronephrosis, ureteric stenosis)
- patients with cirrhosis of the liver accompanied by renal impairment
- patients with hypoproteinaemia, e.g. in nephrotic syndrome
- advanced cerebral and/or coronary sclerosis.

Piretanide should only be given to patients with impaired micturition (e.g. patients with prostatic hyperplasia) if free urinary flow is ensured because a sudden flood of urine can lead to urinary retention with over-distension of the bladder.

During prolonged treatment, serum levels of creatinine, urea and uric acid as well as glucose and electrolyte concentrations, particularly potassium, sodium, calcium, chloride and bicarbonate, should be checked regularly.

In the event of potassium loss (e.g. as a result of vomiting, diarrhoea, laxative abuse) or potassium deficiency resulting from concomitant diseases (e.g. cirrhosis of the liver) or concurrent medication (e.g. laxatives), a potassium-rich diet or potassium replacement medication is indicated. Generally speaking, a potassium-rich diet (lean meat, potatoes, bananas, tomatoes, spinach, cauliflower, dried fruit) with moderate salt restriction is recommended during treatment.

The weight loss caused by increased urinary excretion should not exceed 1 kg/day, irrespective of the extent of urinary excretion.

In nephrotic syndrome, the dose should be carefully selected because of the risk of increased side effects.

A dose adjustment is not usually necessary for elderly patients, but it is important to watch for possible impairment of renal function.

The use of Arelix can produce positive results in doping tests. In addition, the use of Arelix as a doping agent can endanger health.

Patients with the rare hereditary condition of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase deficiency should not take Arelix 6 mg prolonged-release capsules because they contain sucrose.

4.5 Interaction with other medicinal products and other forms of interaction

Based on experience with diuretics, the following interactions should be taken into consideration:

The nephrotoxic effects of certain antibiotics (e.g. aminoglycosides, cephalosporins, polymyxins) and the ototoxic effects of aminoglycosides (e.g. kanamycin, gentamicin, tobramycin) may be enhanced if piretanide is given concurrently. Resulting hearing impairment may be irreversible. Concurrent administration of the aforementioned medicinal products should therefore be avoided.

If cisplatin and piretanide are given simultaneously, there is a possibility of hearing damage. Forced diuresis with low-dose piretanide following cisplatin treatment should only be carried out while there is a positive fluid balance; otherwise, the nephrotoxicity of cisplatin may be enhanced.

If digitalis is administered concurrently, it is important to remember that potassium and magnesium deficiency increases the sensitivity of the myocardium to digitalis, which can result in cardiac arrhythmias.

If administration of piretanide is accompanied by the use of glucocorticosteroids, laxatives or carbenoxolone or frequent consumption of liquorice, it is important to bear in mind that these substances can lower the serum potassium level.

The hypotensive effect of other medicines may be potentiated. Particularly in patients who develop dehydration or salt deficiency on piretanide, concurrent administration of an ACE inhibitor may cause a blood pressure decrease (possibly even shock) and/or renal impairment (possibly even acute renal failure).

It may be necessary to increase the dose of concurrent antidiabetic drugs for patients in a diabetic metabolic condition.

There have been reports that diuretics may cause latent diabetes to become manifest or may necessitate adjustment of the dosage of concurrently administered hypoglycaemic agents.

The effect of salicylates and curare-type muscle relaxants may be increased and the effect of pressor amines (e.g. adrenaline, noradrenaline) may be reduced. The excretion of lithium via the kidneys may be reduced and hence its cardiotoxicity and neurotoxicity enhanced.

Non-steroidal anti-inflammatory drugs (e.g. indomethacin, aspirin) may weaken the efficacy of piretanide and lead to renal failure in patients with pre-existing hypovolaemia.

Probenecid may weaken the effect of piretanide.

In common with all thiazide and loop diuretics, Arelix can cause hypokalaemia.
In patients with severe liver disease, Arelix may precipitate hepatic coma; the use of potassium-sparing diuretics may be preferable in the first instance in these patients.

Caution should be observed in patients liable to electrolyte imbalance; the levels of serum potassium should be monitored where cardiac glycosides or corticosteroids are to be administered and in patients with liver disease.

4.6 Fertility, pregnancy and lactation

Arelix must not be used during the first trimester of pregnancy. There is insufficient experience to assess the safety of its use in the later phases of pregnancy.

Arelix must not be administered to breast-feeding women because the active substance piretanide is excreted in breast milk. If necessary, weaning should take place.

4.7 Effects on ability to drive and use machines

Treatment with this medicinal product requires regular medical checks. In individual cases reduced mental alertness may impair the ability to drive or operate dangerous machinery. This is most likely at the beginning of treatment, when there is a dose increase or a change of drug and in interaction with alcohol.

4.8 Undesirable effects

The adverse reactions for piretanide are listed below. The frequencies for these reactions are unknown.

Blood and lymphatic system disorders	thrombocytopenia, leucopenia, haemoconcentration
Metabolism and nutrition disorders	dehydration, hypovolemia, hypokalaemia, hyponatraemia, hypocalcaemia, hypomagnesaemia, decrease of glucose tolerance, latent diabetes mellitus may become manifest, deterioration of pre-existing metabolic alkalosis, increase in cholesterol and triglycerides serum

	levels, increase in blood creatinine and urea levels, increase in uric acid levels and attacks of gout
Vascular disorders	hypotension including orthostatic hypotension, tendency for thrombosis, vasculitis
Gastrointestinal disorders	nausea, vomiting, diarrhea, dyspepsia
Hepatobiliary disorders	cholangitis, intrahepatic cholestasis, increase in liver transaminases
Skin and subcutaneous tissue disorders	itching, urticaria, maculopapular exanthema and enanthema, erythema multiforme, photosensitivity
Renal and urinary disorders	symptoms of obstruction of urine flow may become manifest or exacerbated in patients with impaired micturation, e.g. in prostatic hypertrophy
Reproductive system and breast disorders	erectile impotence may occur as a result of blood pressure decrease
General disorders and administration site conditions	fever
Ear and labyrinth disorders	hearing disorders, such as tinnitus and deafness (sometimes irreversible)

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

a) Symptoms of intoxication
Severe diuresis with the risk of dehydration and, during prolonged use, hypokalaemia. The rapid water and electrolyte loss can lead to a state of delirium.

A sudden flood of urine can lead to urinary retention with acute over-distension of the bladder in cases of prostatic hypertrophy, for instance.

b) Measures to be taken in the event of intoxication
Fluid and electrolyte replacement as well as repeated checks of the water-electrolyte balance and metabolic functions are required.

For patients with impaired micturition (patients with prostatic hypertrophy, disturbances of consciousness, etc.), it is essential to ensure that urinary excreation is adequate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Piretanide is a loop diuretic.

5.2 Pharmacokinetic properties

Piretanide is readily absorbed from the gastrointestinal tract. The diuretic effect begins about 30 minutes after administration and lasts about 4-6 hours.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Microcrystalline cellulose
Magnesium stearate
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Aluminium/PVC blister packs of 20 or 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Ireland Ltd., T/A SANOFI
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0540/030/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 May 1983

Date of last renewal: 07 October 2010

10 DATE OF REVISION OF THE TEXT

March 2017