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Tel. : 95250 - 2455801 / 2452714 / 2453525 • Fax : 95250 - 2452074 (0091 - 250 - 2452074) • Email : agog@vsnl.net & agogpharma@rediffmail.com

Brand Name : **AGOMIDE TABLETS** **Generic Name** : Furosemide Tablets BP 40 mg		2021
Module 1 **1.5**	Administrative Information and Product Information Product Information	**Confidential**

1.5 PRODUCT INFORMATION

1.5.1 Prescribing information (Summary of products characteristics)

SUMMARY PRODUCT CHARACTERISTICS

1. Name of drug product:

AGOMIDE TABLETS (Furosemide Tablets BP 40 mg)

2. Qualitative and Quantitative Composition:

Each uncoated tablet contains: Furosemide BP 40 mg

3. Pharmaceutical form:

White, round, flat, uncoated tablets, having break line on one side and other side plain of each tablets.

4. Clinical particulars:

4.1 Therapeutic Indications:

.1 Therapeutic indications

Furosemide is a diuretic recommended for use in all indications where a prompt and effective diuresis is required.

1) The treatment of oedema associated with congestive heart failure, cirrhosis of the liver, renal disease including nephrotic syndrome and pulmonary oedema.

2) The treatment of peripheral oedema due to mechanical obstruction, venous insufficiency, mild to moderate hypertension.

4.2 Posology and method of administration

Posology

Adults and children over 12 years:

Oedema: Initially 40mg daily in the morning; ordinarily a prompt diuresis ensues and the starting dose can then be maintained or even reduced. Diuresis lasts for approximately four hours following administration and hence the time of administration can be adjusted to suit the patient's requirements. Maintenance dose is 20mg daily or 40mg on alternate days, increased in resistant oedema to 80mg daily.

Hypertension: 20-40mg twice daily; if 40mg twice daily does not lead to a clinically satisfactory response, the addition of other antihypertensive agents, rather than an increase in the dose of furosemide should be considered.

Children under 12 years: A more suitable dosage form should be used in this age group.

Elderly: Furosemide is generally eliminated more slowly. The dosage should be titrated until the required response is achieved.

Method of Administration

For oral administration.

Dosage adjustment may be required (see also section 4.4)

Dosage adjustment may be necessary in patients with

• hypoproteinaemia

• liver congestion/dysfunction

Concomitant administration of the following with furosemide should be considered (see section 4.4):

Colestyramine and colestipol - Administer 2 to 3 hours apart.

4.3 Contraindications

Furosemide is contraindicated in the following circumstances

• Hypersensitivity to furosemide, any of its excipients, sulfonamides, sulfonamide derivatives/amiloride

• Anuria and impaired renal function (creatinine clearance below 30mL/min per 1.73 m2 body surface area) and renal failure resulting from poisoning by nephrotoxic and/or hepatotoxic agents

• Electrolyte disturbances (severe hyponatraemia: severe hypokalaemia, hypovolaemia), dehydration and/or hypotension (see section 4.4)

• Concomitant potassium supplements or potassium sparing diuretics (see section 4.5)

• Pre-coma/coma associated with hepatic cirrhosis or encephalopathy

• Addison's disease

• Digitalis intoxication (see also section 4.5)

• Breast-feeding women (see section 4.6)

4.4 Special warnings and precautions for use

Hypotension and/or hypovolaemia (see also section 4.3)

These and any acid-base disturbances should be corrected before furosemide is started

Symptomatic hypotension leading to dizziness, fainting or loss of consciousness can occur in patients treated with furosemide, particularly in the elderly, patients on other medications which can cause hypotension and patients with other medical conditions that are risks for hypotension.

Dose titration/adjustment (see section 4.2)

• Patients with hypoproteinaemia (such as that associated with the nephotic syndrome) require careful dose titration (reduced furosemide effect: increased risk of ototoxicity)

• In moderate liver congestion dosage adjustment may be needed

Caution required:

Caution needed in the following circumstances

• impaired hepatic function (see sections 4.2 & 4.3 and below – monitoring required)

• impaired renal function and hepato-renal syndrome (see section 4.3 and below –monitoring required)

• diabetes mellitus (latent diabetes may become overt: insulin requirements in established diabetes may increase)

• elderly patients

• difficulty with micturition/potential obstruction in the urinary tract including prostatic hypertrophy (increased risk of acute retention).

• gout (increased risk of hyperuricaemia)

• patients at risk of pronounced falls in blood pressure

Clinical monitoring requirements (see also section 4.8):

Regular monitoring for

• blood dyscrasias. If these occur, stop furosemide immediately

• liver damage

• idiosyncratic reactions

In premature infants there is a risk of development of nephrocalcinosis/nephrolithiasis. Renal function must be monitored and renal ultrasonography performed.

Laboratory monitoring requirements:

• frequent BUN in first few months of treatment, periodically thereafter

• serum electrolytes with replacement as appropriate

Other alterations in lab values

• Serum creatinine and urea levels tend to rise during treatment

• Serum cholesterol and triglycerides may rise but usually return to normal within 6 months of starting furosemide

• Furosemide should be discontinued before a glucose tolerance test

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Antihypertensives – enhanced hypotensive effect possible with all types. Concurrent use with ACEinhibitors can result in marked falls in blood pressure. Furosemide should be stopped or the dose reduced before starting an ACE-inhibitor. There is a risk of a first-dose effect with post-synaptic alphablockers eg prazosin. Furosemide may interact with ACE inhibitors causing impaired renal function.

Antipsychotics – furosemide-induced hypokalaemia increases the risk of cardiac toxicity. Avoid concurrent use with pimozide. Increased risk of ventricular arrhythmias with amisulpride or sertindole. Enhanced hypotensive effect with phenothiazines.

Anti-arrhythmics (including amiodarone, disopyramide, flecanaide and sotalol) - risk of cardiac toxicity (because of furosemide-induced hypokalaemia). The effects of lidocaine, tocainide or mexiletine may be antagonised by furosemide.

Drugs associated with QT prolongation – cardiac toxicity may be increased by furosemide-induced hypokalaemia and/or hypomagnesaemia.

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Cardiac glycosides – hypokalaemia and electrolyte disturbances (including magnesium) increases the risk of cardiac toxicity.

Vasodilators – enhanced hypotensive effect with moxisylyte (thymoxamine) or hydralazine.

Renin inhibitors – aliskiren reduces plasma concentrations of furosemide.

Nitrates – enhanced hypotensive effect.

Lithium - Furosemide reduces lithium excretion with increased plasma lithium concentrations (risk of toxicity). Avoid concomitant administration unless plasma levels are monitored.

Chelating agents – sucralfate may decrease the gastro-intestinal absorption of furosemide – the 2 drugs should be taken at least 2 hours apart.

Lipid regulating drugs – Bile acid sequestrants (eg colestyramine: colestipol) – reduced absorption of furosemide – administer 2 to 3 hours apart.

NSAIDs – increased risk of nephrotoxicity (especially if there is hypovolaemia). Indometacin and ketorolac may antagonise the effects of furosemide. In patients with dehydration or hypovolaemia, NSAIDs may cause acute renal insufficiency.

Salicylates – effects may be potentiated by furosemide.

Antibiotics – increased risk of ototoxicity with aminoglycosides, polymixins or vancomycin. Increased risk of nephrotoxicity with aminoglycosides or cefaloridine. Furosemide can decrease vancomycin serum levels after cardiac surgery.

Antidepressants – enhanced hypotensive effect with MAOIs. Increased risk of postural hypotension with TCAs (tricyclic antidepressants). Possible increased risk of hypokalaemia with reboxetine.

Antidiabetics – hypoglycaemic effects antagonised by furosemide.

Insulin - requirements may be increased (see section 4.4).

Antiepileptics – increased risk of hyponatraemia with carbamazepine. Diuretic effect reduced by phenytoin.

Antihistamines – hypokalaemia with increased risk of cardiac toxicity.

Antifungals – increased risk of hypokalaemia with amphoterecin.

Anxiolytics and hypnotics – enhanced hypotensive effect. Chloral or triclorfos may displace thyroid hormone from binding site.

CNS stimulants (drugs used for ADHD) – hypokalaemia increases the risk of ventricular arrhythmias.

Corticosteroids – diuretic effect antagonised (sodium retention) and increased risk of hypokalaemia.

Cytotoxics – increased risk of nephrotoxicity and ototoxicity with platinum compounds.

Other diuretics – profound diuresis possible when furosemide given with metolazone. Increased risk of hypokalaemia with thiazides.

Dopaminergics – enhanced hypotensive effect with levodopa.

Immunomodulators – enhanced hypotensive effect with aldesleukin.

Muscle relaxants – enhanced hypotensive effect with baclofen or tizanidine (see also Anaesthetic agents below – curare).

Oestrogens and progestogens – diuretic effect antagonized.

Prostaglandins – enhanced hypotensive effect with alprostadil.

Sympathomimetics – increased risk of hypokalaemia with high doses of beta2 sympathomimetics (such as bambuterol, femoterol, salbutamol, salmeterol and terbutaline).

Theophylline – enhanced hypotensive effect.

Probenecid – reduced renal clearance of furosemide and decreased diuretic effect.

Anaesthetic agents – general anaesthetic agents may enhance the hypotensive effects of furosemide. The effects of curare may be enhanced by furosemide.

Alcohol – enhanced hypotensive effect.

Laxative abuse - increases the risk of potassium loss.

Liquorice - excess intake may increase the risk of hypokalaemia.

4.6 Pregnancy and lactation

The teratogenic and embryotoxic potential of furosemide in humans is unknown. There is little evidence of safety of high-dose furosemide in human pregnancy, although the results of animal work, in general, show no hazardous effects.

The drug should not be used in pregnant women unless the benefits to the patient outweigh the possible risk to the foetus which includes persistence of patent ductus arteriosus (section 4.8).

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Furosemide may inhibit lactation or may pass into the breast milk, it should therefore be used with caution in nursing mothers.

4.7 Effects on ability to drive and use machines

Patients should be warned that reduced mental alertness may impair ability to drive or operate dangerous machinery.

4.8 Undesirable effects

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 (<1/10,000); Frequency not known (cannot be estimated from the available data).

Blood and lymphatic system disorders:

Uncommon:

aplastic anaemia

Rare:

bone marrow depression (necessitates withdrawal of treatment), eosinophilia, leucopenia.

Very rare:

haemolytic anaemia, agranulocytosis, thrombocytopenia

Metabolism and nutritional disorders:

Very common:

dehydration, hyponatraemia, hypochloremic metabolic alkalosis, hypocalcaemia, hypomagnesemia (incidences of the last three are reduced by triamterene)

Common:

Hypovolaemia, hypochloraemia

Uncommon:

impaired glucose tolerance (by hypokalaemia) hyperuricaemia, gout, reduction of serum HDL-cholesterol, elevation of serum LDL-cholesterol, elevation of serum triglycerides, hyperglycaemia

Very rare:

tetany

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Frequency not known:

aggravated pre-existing metabolic alkalosis (in decompensated cirrhosis of the liver), fluid and electrolyte disturbances, excretion of potassium increased*

Psychiatric disorder:

Rare:

psychiatric disorder NOC

Nervous system disorders:

Rare:

paraesthesia, confusion, headache

Not known:

dizziness, fainting and loss of consciousness (caused by symptomatic hypotension)

Eye disorders:

Uncommon:

visual disturbance, blurred vision, yellow vision.

Ear and labyrinth disorders:

Uncommon:

deafness (sometimes irreversible)

Rare:

tinnitus and reversible or irreversible loss of hearing (although usually transitory, particularly in patients with renal failure, hypoproteinaemia (e.g. in nephritic syndrome)

Cardiac disorders:

Uncommon:

orthostatic intolerance, cardiac arrhythmias, increased risk or persistence of patent ductus arteriosus in premature infants.

Vascular disorders:

Very common:

hypotension, (which, if pronounced may cause signs and symptoms such as impairment of concentration and reactions, light-headedness, sensations of pressure in the head, headache, drowsiness, weakness, disorders of vision, dry mouth, orthostatic intolerance).

Rare:

vasculitis, thrombosis, shock

Gastrointestinal disorders:

Uncommon:

dry mouth, thirst, nausea, bowel motility disturbances, vomiting, diarrhoea, constipation

Rare:

acute pancreatitis (in long-term diuretic treatment, including furosemide).

Hepatobiliary disorders:

Rare:

pure intrahepatic cholestasis (jaundice), hepatic function abnormal.

Skin and subcutaneous tissue disorders:

Rare:

rash, pruritus, photosensitivity, toxic epidermal necrolysis.

Frequency not known:

urticaria, erythema multiforme, purpura, exfoliative dermatitis, itching, allergic reactions, such as skin rashes, various forms of dermatitis including urticaria, bullous lesions, acute generalised exanthematous pustulosis (AGEP). When these occur treatment should be withdrawn, Stevens-Johnson syndrome.

Musculoskeletal and connective tissue disorders:

Uncommon:

muscle cramps, muscle weakness.

Renal and urinary disorders:

Very common:

nephrocalcinosis in infants

Uncommon:

reduced diuresis, urinary incontinence, urinary obstruction (in patients with hyperplasia of the prostate, bladder inability to empty, urethral stricture unspecified).

Rare:

acute renal failure.

Very rare:

interstitial nephritis

Congenital, familial and genetic disorders:

Rare:

patent ductus arteriosus

General disorders and administration site conditions:

Uncommon:

Fatigue

Rare:

malaise, fever, severe anaphylactoid or anaphylactic reactions (e.g. with shock).

Investigations:

Common:

creatinine increased, blood urea increased

Rare:

Transaminases increased, blood

*Potassium deficiency manifests itself in neuromuscular symptoms (muscular weakness, paralysis), intestinal symptoms (vomiting, constipation, meterorism), renal symptoms (polyuria) or cardiac symptoms. Severe potassium depletion can result in paralytic ileus or confusion, which can result in coma.

Reporting of suspected adverse reactions

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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 Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard

4.9 Overdose

Symptoms include dehydration and electrolyte depletion due to excessive diuresis. In cirrhotic patients, overdosage may precipitate hepatic coma.

Treatment should be aimed at fluid replacement and correction of the electrolyte imbalance. The drug should be discontinued and electrolyte and water replacement instituted immediately; adjustment should be on the basis of careful monitoring.

5. Pharmacological properties

5.1 Pharmacodynamic properties
ATC code: CO3C A01

The evidence from many experimental studies suggests that furosemide acts along the entire nephron with the exception of the distal exchange site. The main effect is on the ascending limb of the loop of Henley with a complex effect on renal circulation. Blood-flow is diverted from the juxta-medullary region to the outer cortex.

The principle renal action of furosemide is to inhibit active chloride transport in the thick ascending limb. Re-absorption of sodium chloride from the nephron is reduced and a hypotonic or isotonic urine produced.

It has been established that prostaglandin (PG) biosynthesis and the renin-angiotensin system are affected by furosemide administration and that furosemide alters the renal permeability of the glomerulus to serum proteins.

5.2 Pharmacokinetic properties

Furosemide is a weak carboxylic acid which exists mainly in the dissociated form in the gastrointestinal tract. Furosemide is rapidly but incompletely absorbed (60-70%) on oral administration and its effect is largely over within 4 hours. The optimal absorption site is the upper duodenum at pH 5.0. Regardless of route of administration 69-97% of activity from a radio-labelled dose is excreted in the first 4 hours after the drug is given. Furosemide is bound to plasma albumin and little biotransformation takes place. Furosemide is mainly eliminated via the kidneys (80-90%); a small fraction of the dose undergoes biliary elimination and 10-15% of the activity can be recovered from the faeces.

In renal/ hepatic impairment

Where liver disease is present, biliary elimination is reduced up to 50%. Renal impairment has little effect on the elimination rate of furosemide, but less than 20% residual renal function increases the elimination time.

The elderly

The elimination of furosemide is delayed in the elderly where a certain degree of renal impairment is present.

New born

A sustained diuretic effect is seen in the newborn, possibly due to immature tubular function.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. Pharmaceutical particulars

6.1 List of excipients
Also contains: lactose, magnesium stearate, maize starch, stearic acid.

6.2 Incompatibilities
None known.

6.3 Shelf life
PVC/Aluminium Blister

4 years

All other containers

3 years

6.4 Special precautions for storage
Store below 25°C in a dry place.

Protect from light.

6.5 Nature and contents of container
The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene containers with polyfoam wad or polyethylene ullage filler and snap-on polyethylene lids; in case any supply difficulties should arise the alternative is amber glass containers with screw caps and polyfoam wad or cotton wool.

The product may also be supplied in blister packs and cartons:

a) Carton: Printed carton manufactured from white folding box board.

b) Blister pack: (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil with 5-6g/M2 PVC and PVdC compatible heat seal lacquer on the reverse side.

Pack sizes: 28s, 30s, 50s, 56s, 60s, 84s, 90s, 100s, 112s, 120s, 168s, 180s, 250s, 500s, 1000s

Product may also be supplied in bulk packs, for reassembly purposes only, in polybags contained in tins, skillets or polybuckets filled with suitable cushioning material. Bulk packs are included for temporary storage of the finished product before final packaging into the proposed marketing containers.

Maximum size of bulk packs: 25,000.

6.6 Special precautions for disposal and other handling
Not applicable.

Administrative Data

7. Marketing authorisation holder
Accord-UK Ltd

(Trading style: Accord)

Whiddon Valley

Barnstaple

Devon

EX32 8NS

8. Marketing authorisation number(s)
PL 0142/0371

9. Date of first authorisation/renewal of the authorisation
21.2.94

(Renewed: 11.3.99)

6. Pharmaceutical particulars:

6.1 List of Excipients:

Lactose	BP

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Colloidal silicon dioxide	BP
Sodium starch glycolate	BP
Maize starch	BP
Methyl paraben sodium	BP
Propyl paraben sodium	BP
Talcum	BP
Magnesium stearate	BP
Cross carmellose sodium	BP
Polyplasdone XL-10 (cross povidone)	USP

6.2 Incompatibilities:
None Reported

6.3 Shelf-Life:
36 months from the date of manufacture.

6.4 Special Precautions for Storage:
Store under normal storage conditions (15ºC-30ºC) Protect from light.

6.5 Nature and Contents of Container:
1000 tablets packed in one Jar. Such jar packed in unit jar along with its package insert. Such jar packed in export worthy shipper.

6.6 Special precautions for disposal:
None reported.

7. Registrant:
AGOG PHARMA LTD.
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8. Manufacturer:
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9. Date of revision of the text :

AGOG Pharma Ltd.

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