SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Liskonum® Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Liskonum Tablets are available in one strength. Each tablet contains 450 mg lithium carbonate (12.2 mmol Li^+) in controlled-release form.

Excipient with known effect:
Lactose
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

White, oblong, film-coated tablets, with convex faces and a breakline on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Liskonum is a controlled-release tablet, designed to reduce fluctuations in serum lithium levels and the likelihood of adverse reactions.
It is indicated for the treatment of acute episodes of mania or hypomania and for the prophylaxis of recurrent manic-depressive illness.

4.2 Posology and method of administration

Posology:

Adults only: Liskonum should be given twice a day.

Treatment of acute mania or hypomania
Patients should be started on one or one-and-a-half tablets twice a day. Dosage should then be adjusted to achieve a serum lithium level of 0.8 to a maximum of 1.5 mmol/l. Serum concentration of lithium should be measured after four to seven days' treatment and then at least once a week until dosage has remained constant for four weeks. When the acute symptoms have been controlled, recommendations for prophylaxis should be followed.

Prophylaxis: The usual starting dosage is one tablet twice a day. Dosage should then be adjusted until a serum level of 0.5 to 1.0 mmol/l is maintained. Serum concentration of lithium should be measured after four to seven days' treatment and then every week until dosage has remained constant for four

weeks. Frequency of monitoring may then be gradually decreased to a minimum of once every two months, but should be increased following any situation where changes in lithium levels are possible (see Section 4.4).

Blood samples for measurement of serum lithium concentration should be taken just before a dose is due and not less than 12 hours after the previous dose.

Levels of more than 2 mmol/l *must* be avoided.

Elderly: Use with caution. Start with half a tablet twice a day and adjust serum levels to the lower end of the above ranges (see also Section 4.4).

The full prophylactic effect of lithium may not be evident for six to 12 months, and treatment should be continued through any recurrence of the illness.

Paediatric population: The safety and efficacy of liskonum in children under 12 years of age have not yet been established and therefore is not recommended for use in this age group.

Method of Administration:

Oral.

Planned Discontinuation of Liskonum

Gradual withdrawal of lithium (over a period of at least 2 weeks) is recommended, as it may delay recurrence of the patient's underlying symptoms.

Discontinuation of Liskonum due to toxicity

On the first sign of toxicity, treatment should be immediately discontinued (see Section 4.4).

4.3 Contraindications

Do not use in patients with a history of hypersensitivity to lithium, or to any of the other excipients, listed in section 6.1.
Do not use in patients with impaired renal function, cardiac disease, untreated hypothyroidism, Brugada syndrome or family history of Brugada syndrome (see section 4.4). Lithium should not be given to patients with low body sodium levels, including, for example, dehydrated patients, those on low sodium diets, or those with Addison's disease.

4.4 Special Warnings and Precautions for Use

Vomiting, diarrhoea, intercurrent infection, fluid deprivation and drugs likely to upset electrolyte balance, such as diuretics, may all reduce lithium excretion

and thereby precipitate intoxication; reduction of dosage may be required. Use with care in elderly patients as lithium excretion may also be reduced.

The possibility of hypothyroidism and of renal dysfunction arising during prolonged treatment should be borne in mind and periodic assessments made.

Brugada syndrome
Lithium may unmask or aggravate Brugada syndrome, a hereditary disease of the cardiac sodium channel with characteristic electrocardiographic changes (right bundle branch block and ST segment elevation in right precordial leads), which may lead to cardiac arrest or sudden death. Lithium is not recommended in patients with known Brugada syndrome or a family history of Brugada syndrome (see Section 4.3). Caution is advised in patients with a family history of cardiac arrest or sudden death.

Histological changes (including tubulointerstitial nephropathy) have been reported after long-term treatment with lithium. These changes may lead to impaired renal function. It is unclear if these changes are always reversible on stopping lithium. It is advisable to monitor renal function periodically.

Lithium therapy may lower the seizure threshold and increase the risks of neurological adverse effects following electroconvulsive therapy (ECT). If ECT is administered to patients on lithium therapy, lithium levels should checked beforehand to ensure that they are moderate (around 0.4-1 mmol/l) and a low electrical dose at the first treatment should be considered.

Patients receiving neuroleptics concomitantly with lithium should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if symptoms appear. On extremely rare occasions, the concurrent administration of lithium with neuroleptics may result in an encephalopathic syndrome, (characterised by delirium, seizures or an increased incidence of extrapyramidal symptoms) which may be similar to or the same as neuroleptic malignant syndrome. In some instances, the syndrome was followed by irreversible brain damage. See section 4.5 (Interaction with Other Medicaments and Other Forms of Interaction)

Patients should be warned of the symptoms of impending intoxication (see Section 4.8), of the urgency of immediate action should these symptoms appear, and also of the need to maintain a constant and adequate salt and water intake. Outpatients should be warned to take their medication at the stipulated time. If a dose is missed, the patient should wait until the next scheduled time of dosing. A double dose to make up for the dose that has been missed should not be taken. Treatment should be discontinued immediately on the first signs of toxicity, which include cardiovascular, renal, neurological and gastrointestinal events (see Section 4.8). Acute renal failure has been reported rarely with lithium toxicity.

Renal tumours: Cases of microcysts, oncocytomas and collecting duct renal carcinoma have been reported in patients with severe renal impairment who received lithium for more than 10 years (see Section 4.8).

Patients with the rare hereditary galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take Liskonum.

In patients who have undergone bariatric surgery, a lower maintenance dose of lithium may be required. Lithium levels should be closely monitored due to the risk of lithium toxicity until weight has stabilized.

Lithium should be used with particular care in the elderly since this group may be particularly susceptible to toxicity due to decreasing renal function and hence elimination *(see Dosage and Administration).*

Patients with bipolar disorder may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking medications for bipolar disorder. Patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviours or thoughts of harming themselves and to seek medical advice immediately if these symptoms present.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Interactions which increase lithium concentrations:

- Metronidazole
- Non-steroidal anti-inflammatory drugs, including selective cyclo-oxygenase (COX) II inhibitors (monitor serum lithium concentrations more frequently if NSAID therapy is initiated or discontinued)
- ACE inhibitors
- Angiotensin II receptor antagonists.
- Diuretics (thiazides show a paradoxical antidiuretic effect resulting in possible water retention and lithium intoxication)

Interactions which decrease serum lithium concentrations:

- Dapagliflozin
- Empagliflozin
- Urea
- Xanthines
- Sodium bicarbonate containing products
- Diuretics (carbonic anhydrase inhibitors)

Interactions causing neurotoxicity:

- Neuroleptics
- Carbamazepine
- Methyldopa
- Selective Serotonin Re-uptake Inhibitors (e.g. fluvoxamine and fluoxetine) as this combination may precipitate a serotonergic syndrome.
- Calcium channel blockers
- Tri-cyclic antidepressants

Lithium may prolong the effects of neuromuscular blocking agents.

Topiramate
In healthy volunteers, there was an observed reduction (18% for AUC) in systemic exposure for lithium during concomitant administration with topiramate 200 mg/day. In patients with bipolar disorder, the pharmacokinetics of lithium were unaffected during treatment with topiramate at doses of 200 mg/day; however, there was an observed increase in systemic exposure (26% for AUC) following topiramate doses of up to 600 mg/day. There have been reports on lithium toxicity when concurrently administered with topiramate. Lithium levels should be closely monitored when co-administered with topiramate

4.6 Fertility, Pregnancy and lactation

Pregnancy:
Lithium crosses the placental barrier. In animal studies, lithium has been reported to interfere with fertility, gestation and foetal development. There is epidemiological evidence that the drug may be harmful in human pregnancy. Lithium therapy should not be used during pregnancy, especially during the first trimester, unless considered essential. In certain cases where a severe risk to the patient could exist if treatment were to be stopped, lithium has been continued during pregnancy. If given, however, serum levels should be measured frequently because of the changes in renal function associated with pregnancy and parturition.
Breast-feeding:
Since adequate human data on use during lactation and adequate animal reproduction studies are not available, bottle feeding is advisable.

4.7 Effects on ability to drive and use machines

As lithium may cause disturbances of the CNS, such as somnolence, dizziness or hallucinations, patients should be warned of the possible hazards when driving or operating machinery.

4.8 Undesirable Effects

Initial therapy: Fine tremor of the hands, polyuria thirst and nausea may occur.

The frequency classifications for these adverse reactions cannot be accurately estimated from the available clinical trial data.

Blood and lymphatic system disorders:	Leukocytosis
Endocrine disorders:	Euthyroid goitre, hypothyroidism, hyperthyroidism, hyperparathyroidism, parathyroid adenoma, parathyroid hyperplasia (frequency: not known) hypercalcaemia (frequency: very frequent)
Metabolism and nutrition disorders:	Hyperglycemia, hypercalcemia, weight gain, anorexia, polydipsia
Psychiatric disorders:	Hallucinations, somnolence, memory loss
Nervous system disorders:	Tremor, ataxia, peripheral sensorimotor neuropathy, hyperactive deep tendon reflexes, extrapyramidal symptoms, seizures, slurred speech, dizziness, vertigo, giddiness, nystagmus, stupor, coma, pseudotumor cerebri, dysgeusia, myasthenia gravis
Eye disorders:	Scotomata, blurred vision
Cardiac disorders:	Cardiac arrhythmia, of which bradycardia due to sinus node dysfunction is most frequent, and oedema. ECG changes: reversible flattening and inversion of T-waves. Brugada syndrome (Unmasking/aggravation) (frequency: not known)
Vascular disorders:	Peripheral circulatory collapse, hypotension, Raynaud's phenomena
Gastrointestinal disorders:	Nausea, vomiting, diarrhoea, gastritis, excessive salivation, dry mouth

Skin and subcutaneous tissue disorders:	Alopecia, folliculitis, pruritus, psoriasis exacerbation, rash and other signs of skin hypersensitivity, acneiform eruptions, papular skin disorder. Frequency not known: lichenoid drug reaction. Drug reaction with eosinophilia and systemic symptoms (DRESS) (frequency: not known)
Musculoskeletal and connective tissue disorders:	Muscle weakness, arthralgia, myalgia
Renal and urinary disorders:	Symptoms of nephrogenic diabetes insipidus, and after long-term therapy, histological renal changes (including tubulointerstitial nephropathy) and impaired renal function. Frequency unknown: Microcysts, oncocytoma and collecting duct renal carcinoma (in long-term therapy) (see Section 4.4).
Reproductive system and breast disorders:	Sexual dysfunction
General disorders and administration site conditions:	Oedema, dazed feeling

Intoxication (see 4.4): Cardiovascular events e.g. QT/QTc prolongation. Gastrointestinal events e.g. vomiting, diarrhoea. Neurological events e.g. drowsiness, lack of co-ordination and/or a coarse tremor of the extremities and lower jaw may occur, especially with serum levels above the therapeutic range. Ataxia, giddiness, blurred vision, dysarthria, tinnitus, muscle hyperirritability, choreoathetoid movements peripheral neuropathy, hypoactive or absent deep tendon reflexes, and toxic psychosis have also been described.

If any of the above symptoms appear, treatment should be stopped immediately and arrangements made for serum lithium measurement.

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

4.9 Overdose

The toxic concentrations for lithium are close to the therapeutic concentrations. Any overdose in a patient who has been taking chronic lithium therapy should be regarded as potentially serious. A single acute overdose usually carries low risk and patients tend to show mild symptoms only, irrespective of their serum lithium concentration. However more severe symptoms may occur after a delay if lithium elimination is reduced because of renal impairment, particularly if a slow-release preparation has been taken.

If an acute overdose has been taken by a patient on chronic lithium therapy, this can lead to serious toxicity occurring even after a modest overdose as the extravascular tissues are already saturated with lithium.

Symptoms

The onset of symptoms may be delayed, with peak effects not occurring for as long as 24 hours, especially in patients who are not receiving chronic lithium therapy, or following the use of a sustained release preparation.
Mild: Nausea, diarrhoea, vomiting, blurred vision, polyuria, light headedness, fine resting tremor, first degree heart block, muscular weakness and drowsiness.
Moderate: Increasing confusion, blackouts, fasciculation and increased deep tendon reflexes, myoclonic twitches and jerks, ataxia, choreoathetoid movements, urinary and faecal incontinence, increasing restlessness followed by stupor. Hypernatraemia.
Severe: Coma, convulsions, cerebellar signs, cardiac dysrhythmias including sino-atrial block, sinus and junctional bradycardia. Hypotension or rarely hypertension, circulatory collapse and renal failure.

Management

There is no known antidote. . Supportive and symptomatic treatment should be initiated. Correction of electrolyte balance and fluid resuscitation is critical Gut decontamination is not useful for chronic accumulation. Whole bowel irrigation may be helpful in patients ingesting large quantities of slow-release preparation.

NOTE: activated charcoal does not adsorb lithium.

Haemodialysis is the treatment of choice for severe poisoning and should be considered in all patients with marked neurological features. It is the most efficient method of lowering lithium concentrations rapidly but substantial rebound increases can be expected when dialysis is stopped, and prolonged, or repeated treatments may be required. It should be considered also in acute, acute on chronic or chronic overdose in patients with severe symptoms regardless of serum lithium concentration; discuss with your local poisons service.

NOTE: Clinical improvement generally takes longer than reduction of serum lithium concentrations regardless of the method used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, Lithium, ATC code: N05AN01

Lithium carbonate is used as a source of lithium ions. The mechanism by which it exerts its effect in affective disorders is not known but may be related to inhibition of neurotransmitter receptor mediated processes involving beta-adrenoceptors. It is used in the treatment of acute episodes of mania or hypomania and for prophylaxis of recurrent manic depressive illness.

5.2 Pharmacokinetic properties

Lithium is readily absorbed from the gastrointestinal tract, and is distributed throughout the body over a period of several hours. Lithium is excreted almost exclusively in the kidneys but can also be detected in sweat and saliva. It is not bound to plasma proteins. It crosses the placenta, and is excreted in breast milk. The half-life of non-sustained lithium varies considerably, but generally is considered to be about 12 to 24 hours following a single dose. It is however increased for example in those with renal impairment and with age, and may increase significantly during long-term therapy.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone
Maize Starch
Lactose
Gelatin
Calcium Carboxymethylcellulose
Talcum *(E553Cb)*
Calcium Arachinate
Titanium Dioxide (El 71)
Magnesium Stearate (E5 72)
Polyethylene Glycol 6000
Eudragit El*2.5*

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

'Liskonum' Tablets have a shelf-life of five years.

6.4 Special precautions for storage

Store below 250C.

6.5 Nature and Contents of Container

Opaque Blister Packs (OP) of 60 (3 x 20) tablets.

6.6 Special precautions for disposal and other handling

Tablets may be halved but should not be chewed or broken up.

7 MARKETING AUTHORISATION HOLDER

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