Summary of Product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Ospolot® 200 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ospolot® 200 mg
1 film-coated tablet contains 200 mg sulthiame.
Excipient(s) with known effect: one tablet contains 50.0 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
Ospolot® 200 mg
White, round, slightly domed film-coated tablet with a dividing groove on one side and marked "200" on the other side. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of epilepsy in adults and in treatment of the so called focal benign epilepsy of children, when other medication was not adequate.

Note:
Treatment with *Ospolot*® should only be conducted by a paediatric neurologist with sufficient experience in treating epilepsy.
Efficacy and safety of *Ospolot*® in the above-mentioned indication have not been investigated in controlled studies. Prior to starting treatment with sulthiame, a thorough differential diagnostic procedure regarding other types of childhood epilepsies is indicated. Rolandic epilepsies demonstrate a high percentage of spontaneous remissions – even without drug treatment – and usually show a favourable course of disease and a good prognosis.

4.2 Posology and method of administration

Posology
The dosage must be established and monitored by the doctor on an individual basis. The maintenance dose is about 5 to 10 mg/kg body weight/day. It should be built up step-wise (tapered in) over a one-week period. *Ospolot® 200 mg* film-coated tablets have a dividing groove.
Due to the short half-life of sulthiame, the daily dose should as far as possible be spread over three single doses. If the daily dose is spread over the day in this way, constant plasma levels are to be expected after five to six days. Therapeutic plasma concentrations of sulthiame have not yet been determined.

Method of administration
The film-coated tablets should be swallowed whole (unchewed) with plenty of liquid (approx. one glass of water), as far as possible spread over 3 single doses.

A change from another medication or from combination treatment should be done gradually. *Ospolot*® should not be discontinued abruptly. A paediatric neurologist experienced in treating epilepsy should decide on dose adjustment, the duration of treatment and discontinuation on an individual basis.
If therapy is not successful, treatment with sulthiame should be discontinued after about one to two months.

It is recommendable to monitor the blood count, liver enzymes and renal function parameters before treatment with *Ospolot*®, then at weekly intervals in the first month of treatment, and thereafter at monthly intervals. After six months of treatment, two to four checks per year are sufficient.

4.3 Contraindications

Ospolot® may not be used in cases of
- known hypersensitivity to sulthiame, other sulphonamides or to any of the excipients listed in section 6.1.

Sulthiame should not be used in patients with
- known acute porphyria
- hyperthyroidism or arterial hypertension.

4.4 Special warnings and precautions for use

Sulthiame should not be administered, or only administered with special caution and adequate monitoring
- in patients with impaired renal function
- in patients with a history of psychiatric disorders

Note:
The patient respectively the parentsshould be instructed to consult the attending doctor immediately if fever, sore throat, allergic skin reactions with lymph node swelling and/or flu-like symptoms occur during treatment with Ospolot. Progressive thrombocytopenias or leukopenias that are accompanied by clinical symptoms, such as fever or sore throat, require interruption of treatment. In cases of severe allergic reactions, Ospolot must be discontinued immediately. Treatment should also be interrupted if a lasting increase in creatinine occurs. The blood count, liver enzymes and urine should be checked regularly (see also section 4.2).

Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take Ospolot®.

Suicidal ideation and suicidal behaviour
Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for sulthiame.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.
Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take *Ospolot*®.

4.5 Interaction with other medicinal products and other forms of interaction

Prior to starting treatment with *Ospolot*®, the patient should be asked about other medicines, including OTC products, he/she is using.

Influence of other medicinal products on sulthiame

Primidone
If sulthiame is combined with primidone, the intensity of undesirable effects of sulthiame may increase; especially in children, dizziness, unstable gait, drowsiness may occur.

Carbamzepine
There are indications that sulthiame serum levels may decrease if carbamazepine is taken concomitantly.

Influence of sulthiame other medicinal products

Phenytoin
If sulthiame is combined with phenytoin, the plasma levels of phenytoin can be markedly elevated. This combination requires especially strict monitoring and frequent controls of phenytoin plasma levels, particularly in the case of impaired renal function.

Lamotrigine
In combination with lamotrigine, an elevation of lamotrigine levels in the blood has also been observed in individual cases. Therefore, lamotrigine levels should be checked more frequently at the beginning of such a treatment.

Carboanhydrase-Inhibitors
Concomitant use of sulthiame and other carbonic anhydrase inhibitors (e.g. topiramate, acetazolamide) may increase the risk of undesirable effects due to carbonic anhydrase inhibition (see also section 4.8).

Alcohol
During treatment with sulthiame, the patient should abstain from alcohol, since sulphonamides have an effect similar to that of disulfiram, and sulthiame, as a sulphonamide derivative, can theoretically have a similar effect. These symptoms include a very unpleasant, although generally self-limiting systemic reaction caused by vasodilatation, with pulsating headache, respiratory depression, nausea, vomiting, tachycardia, hypotension, amblyopia, confusion, shock reactions, arrhythmias, loss of consciousness and seizures. The degree and duration of these symptoms can vary to a great extent.

4.6 Fertility, pregnancy and lactation

Pregnancy
No systematically gained experience on administration of sulthiame in humans during pregnancy is available. In experimental animal studies, embryotoxic effects have been revealed (see also section 5.3). In general, an increased risk of malformations has been observed after administration of antiepileptic drugs, which can be increased by the simultaneous administration of different antiepileptic drugs. Therefore, the administration of *Ospolot*® during pregnancy and in women of childbearing age, who do not use contraception, is not recommended.
In case of pregnancy, the lowest seizure-controlling dose of Ospolot should be given, as far as possible in monotherapy. Prenatal diagnostic measures for the early detection of damage (high-resolution ultrasound and alpha-fetoprotein determination) are recommended. In no case treatment with antiepileptic drugs should be discontinued without medical advice, as uncontrolled seizures can have serious consequences for both the mother and the unborn child.

Lactation

It is not known if sulthiame passes into breast milk. Since a risk for the newborn cannot be excluded, sulthiame should not be used during lactation

4.7 Effects on ability to drive and use machines

Even when used as directed, these medicinal products can affect reactions to such an extent - especially at the start of treatment - that the ability to drive a vehicle or use machines may be impaired. This applies to a greater extent in combination with alcohol.

4.8 Undesirable effects

The following frequency categories are used for the evaluation of 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)
Not known (frequency cannot be estimated from the available data)	

Metabolism and nutrition disorders
Common: weight loss, lack of appetite

Psychiatric disorders
Uncommon: hallucinations, anxiety, lack of drive
Not known: depressive mood/depression, personality change and behavioural anomaly (e.g. aggressiveness, irritability, mood swings)

Nervous system disorders
Common: paraesthesias in the extremities and in the face*, dizziness, headache
Uncommon: myasthenic phenomena, grand-mal status, increased seizure activity
Not known: polyneuritis

Eye disorders
Common: double vision

Cardiac disorders
Common: stenocardia, tachycardia

Respiratory, thoracic and mediastinal disorders
Common: tachypnoea*, hyperpnoea*, dyspnoea, singultus

Gastrointestinal disorders
Very common: gastric complaints like e.g. nausea, vomiting (in about 10% of patients)
Not known: diarrhoea

Hepatobiliary disorders
Not known: hepatotoxic reactions, increase of liver enzymes

Skin and subcutaneous disorders

Not Known: Stevens-Johnson syndrome, Lyell's syndrome

Musculoskeletal and connective tissue disorders
Uncommon: joint pain

Renal and urinary disorders
Not known: acute renal failure

*Dose-dependent, if necessary the dose has to be adapted.

In one case, administration of *Ospolot*® led to progressive weakness of the limbs, hypersalivation, slurred speech, increasing drowsiness up to coma. The symptoms abated within hours of *Ospolot*® being discontinued.

Sulthiame is a carbonic anhydrase inhibitor. Therefore, undesirable effects of carbonic anhydrase inhibition, such as renal stone formation, metabolic acidosis, tiredness/exhaustion, haemodilution and changes in serum electrolyte values (e.g. hypocalcaemia), may occur during administration of sulthiame (see also section 4.5).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

Symptoms of intoxication
Headache, dizziness, ataxia, impaired consciousness, metabolic acidosis, crystals in the urine. Sulthiame has a low toxicity. Overdoses of 4 to 5 g sulthiame have been survived. The intake of about 20 g sulthiame by adults with the intention of committing suicide was fatal in one case. In another case, a *restitutio ad integrum* was achieved.

Treatment of intoxications
A specific antidote is not known. The standard measures (gastric lavage and active charcoal) for minimising absorption and for maintaining vital functions should be taken. Sodium bicarbonate can be infused to treat acidosis. Alkalising diuretic therapy is recommended for preventing renal damage and crystalluria.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics
ATC code: N03AX03

Sulthiame belongs to the group of carbonic anhydrase inhibitors and displays an anticonvulsant effect in the electroconvulsion test (rat and mouse) and in the convulsion test with pentamethylene tetrazole (mouse).

5.2 Pharmacokinetic properties

Sulthiame pharmacokinetics were not systematically investigated in different age categories in children and adolescents.

Absorption
After oral administration, sulthiame is rapidly and completely absorbed, predominantly from the upper section of the small intestine. Peak plasma concentrations are measured after 1 - 5 hours.

In a single dose pharmacokinetic study with 16 probands, the influence of food intake on the absorption of Ospolot 200 mg tablets was examined. The results show that intake of Ospolot with food leads to a moderately reduced bioavailability of sulthiame.

Distribution
About 29% of the active substance is bound to plasma proteins.

Elimination
80 to 90% is eliminated with the urine and 10 to 20% with the faeces after biliary secretion. Within 24 hours, 32% of the administered dose is excreted unchanged via the kidneys. In a single dose pharmacokinetic study with 16 healthy adult probands, a half-life of approximately 12 h was determined. Based on published pharmacokinetic studies, a shorter half-life is assumed in children.

5.3 Preclinical safety data

Based on the conventional studies on repeated dose toxicity, preclinical data do not reveal any particular hazard to humans.

Carcinogenic and mutagenic potential
In three different *in vivo* and *in vitro* experimental models, no mutagenic potential of sulthiame has been revealed. Long-term carcinogenicity studies have not been conducted.

Reproductive toxicity
Reproductive toxic properties of sulthiame are not sufficiently investigated. In an embryotoxicity study on rats, embryotoxic effects have been revealed at the lowest investigated dose (30 mg/kg/day). Studies on fertility disorders and effects on peri- and postnatal development of the off-spring are lacking.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

maize starch, lactose monohydrate, talc, colloidal anhydrous silica, hypromellose, gelatin, magnesium stearate, macrogol 4000, titanium dioxide.

One tablet contains 50.0 mg lactose monohydrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Keep the container tightly closed.
Store below 25˚c
Use this medicine within 12 weeks after first opening

6.5 Nature and contents of container

Folding boxes containing 200 film-coated tablets in brown glass bottles with a child-proof polyethylene stopper.

Folding boxes containing 200 film-coated tablets in polyethylene containers with a child-proof polypropylene screw cap.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MANUFACTURER

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Weg beim Jäger 214
22335 Hamburg
Germany

8. LICENSE HOLDER

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Isreael

9. MARKETING AUTHORISATION NUMBER
066-04-28222

10. REVIEWED ON
September 2020