Pharmacotherapeutic report on everolimus (Votubia®) for the indication 'treatment of patients aged 3 years and older with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC)'.

Medicine. Everolimus tablets; 2.5 and 5 mg; ATC-code L01XE10.

Therapeutic indications. For the treatment of patients aged 3 years and older with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC), who require therapeutic intervention but are not amenable to surgery.

Dose. The dose is determined on the basis of the blood concentration. Dosing should be titrated to attain trough concentrations of 5-15 nanogram/ml. The recommended starting dose is 2.5 mg with a body surface area (BSA) of ≤1.2 m^2; 5 mg with a BSA of 1.3-2.1 m^2 and 7.5 mg with a BSA of ≥ 2.2 m^2. Whole blood trough concentrations should be assessed 2 weeks after commencing treatment and adjusted every 2 weeks, if necessary, by 2.5 mg.

Mechanism of action. Everolimus, a rapamycine derivative, is a protein kinase inhibitor. Everolimus binds to the intracellular protein FKBP-12, forming a complex that inhibits mTOR complex-1 (mTORC1) activity. mTOR is a key serine-threonine kinase, the activity of which is known to be up-regulated in a number of human cancers. The growth and proliferation of tumour cells is also reduced by reducing the mTOR activity.

Remarks. Votubia® was registered as an orphan drug under a „conditional approval" scheme. Everolimus is also marketed under other brand names: Certican® is registered for use as an immunosuppressant following transplantation and Afinitor® is indicated for the treatment of renal cell carcinoma and pancreatic tumours.

Summary of the therapeutic value

Intended effects. The efficacy of everolimus in patients with TSC-associated SEGA was investigated in an open-label, non-randomized phase 2 study with 28 patients. Unpublished data from a phase 3 trial supported this study. The most important intended effect is reduction in the SEGA volume. After 6 months of everolimus treatment, the median volume of the SEGA had declined from 1.74 cm^3 to 0.93 cm^3, a reduction of 0.80 cm^3 (95% CI: 0.4 to 1.2; p <0.001). In 75% of the patients studied, the SEGA volume was decreased at least by 30% and in 32% of the patients the decline was more than 50%. The clinical relevance of these tumour reductions is unclear: a possible improvement in disease-related symptoms could not be demonstrated in the two studies. Secondary outcomes measured were: change in seizure frequency, quality of life, effect on facial angiofibromas, neuropsychological and cognitive effects. In the phase 2 study, a reduction in the seizure frequency was measured (-0.99, range from -17.0 to 10.8). Whether this effect should be ascribed to everolimus or to an improved antiepileptic treatment is not clear. In the supportive phase 3 study, these findings could not be confirmed. An effect of everolimus on the other secondary outcome measures could not be demonstrated either.

Unintended effects. The main adverse effects of everolimus in patients with TSC-associated SEGA are infections and stomatitis, which are known side effects of everolimus and are regarded as manageable.
Experience. Experience with everolimus in patients with TSC-associated SEGA is limited.
Applicability. Everolimus is indicated for the treatment of children aged 3 years and older with TSC-associated SEGA. The patients should be regularly checked to maintain the target trough concentrations of 5-15 nanogram/ml. Concomitant use of potent inhibitors of CYP3A4 and/or PGP can lead to a drastically increased blood levels and is therefore not recommended. Seizures were observed in 80-90% of TSC patients. CYP3A4-inducing anticonvulsants such as carbamazepine, phenytoin and phenobarbital may decrease the blood concentrations of everolimus and should therefore be properly monitored.
Ease of use. Everolimus is administered orally.

Final conclusion. The use of everolimus for the treatment of patients aged 3 years and older with subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex (TSC), who require therapeutic intervention but are not amenable to surgery, has a therapeutic added value in comparison with best supportive care.