Provision of everolimus (Votubia®) for tuberous sclerosis complex in Wales

October 2022

Recommendation:
Everolimus (Votubia®) is recommended for use within NHS Wales for the treatment of:

- **adult patients with renal angiomyolipoma associated with tuberous sclerosis complex who are at risk of complications (based on factors such as tumour size or presence of aneurysm, or presence of multiple or bilateral tumours) but who do not require immediate surgery, and;**
- **patients with subependymal giant cell astrocytoma associated with tuberous sclerosis complex who require therapeutic intervention but are not amenable to surgery**

This recommendation applies only in circumstances where the approved Patient Access Scheme (PAS) is utilised or where the list/contract price is equivalent or lower than the PAS price.

Additional notes:
This recommendation applies to everolimus (Votubia®) 1 mg, 2 mg, 3 mg and 5 mg dispersible tablets and 2.5 mg, 5 mg and 10 mg tablets. Please refer to the Summary of Product Characteristics for the full licensed indication for each formulation.

Everolimus (Votubia®) has previously been recommended by AWMSG as an option for use in NHS Wales for the adjunctive treatment of patients aged 2 years and older whose refractory partial-onset seizures, with or without secondary generalisation, are associated with tuberous sclerosis complex (TSC) (Advice number 1121, September 2021).

It is anticipated that generic preparations of everolimus for the same licenced indications as Votubia® will be available during 2023. Once available, everolimus should be prescribed on the basis of lowest acquisition cost.

Background:
Tuberous sclerosis complex (TSC) is a rare autosomal dominant genetic disorder associated with mutations affecting the TSC1 and TSC2 genes. Deficiency of either leads to over-activation of the mammalian target of rapamycin (mTOR) pathway (specifically mTOR complex-1), resulting in abnormal cellular growth and proliferation, and protein synthesis, which can cause the development of non-cancerous growths in multiple organ systems throughout the body (kidney, brain, skin, eye, lung and heart). Where surgery is inappropriate or not suitable, treatment options are limited to best supportive care. Everolimus (Votubia®) is currently the only licensed treatment option for three clinical manifestations associated with TSC; subependymal giant cell astrocytoma (SEGA), renal angiomyolipoma (AML) and refractory partial onset seizures. Its use for the treatment of these is recommended in both UK and international guidelines.

In September 2015, in an agreement with the marketing authorisation holder (Novartis), Welsh Government announced funding for Votubia® within its licensed indications. The commercial arrangement was fixed for two years. Following the expiry of the contract, AWTTC encouraged the company to engage in the HTA appraisal process. In 2021, AWTTC secured a HTA submission for the seizures part of the licensed indication and AWMSG subsequently recommended Votubia® as a treatment option for TSC-associated epilepsy. However, patients with SEGA or AML are still only able to gain access via IPFR in contrast to patients in England where the routine commissioning of everolimus for all TSC indications has been available for a number of years.

Everolimus is considered established practice for the treatment of all three indications and is included in TSC UK guidelines. Patients and clinicians in Wales have continued to highlight the high unmet need for TSC patients with SEGA or AML and the potential inequity of access across Wales compared with England. Currently, clinicians must apply for IPFR funding, which requires additional NHS Wales resource to submit and process, and patients have to await a decision before they can commence treatment. Since 2015, all IPFR applications for patients with AML and SEGA have been successful.

Clinical efficacy and safety for the use of Votubia® in patients with TSC is based on a series of phase II trials and three randomised, double-blind, placebo-controlled pivotal phase III studies; EXIST-1 (for SEGA), EXIST-2 (for AML) and EXIST-3 (for seizures). The results of EXIST-1 and EXIST-2 were clinically meaningful with a statistically significant reduction in SEGA volume and AML response rate respectively. The safety profile of everolimus treatment is already well established in several cancer indications and no new safety concerns were highlighted for patients with TSC. Adverse reactions are typically mild to moderate in severity and are generally manageable with dose interruption, dose modification, and/or supportive intervention.

The International Tuberous Sclerosis Complex Consensus Group, comprising of clinicians worldwide specialising in the management of TSC, categorise the evidence supporting the use of everolimus for the treatment of SEGA and AML as Class 1 with a uniform consensus of opinion that the intervention is appropriate. UK TSC-specialist clinicians also reached the same consensus to produce agreed guidance for the management of patients with TSC in the UK. Therefore, everolimus is recommended in both the International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations and in the UK Guidelines for Management and Surveillance of Tuberous Sclerosis Complex and is considered an established treatment for both SEGA and AML.

There are no studies evaluating the cost-effectiveness of everolimus (Votubia®) for the treatment of either SEGA or AML. The appraisal by AWMSG in 2021 (for seizures) considered that Votubia® was eligible to be appraised as an orphan medicine ie. one used to treat a disease that is life-threatening or chronically debilitating with a prevalence of ≤ 1 in 2,000 people in Wales. There are approximately 70 patients overall eligible for treatment with everolimus (Votubia®) per year for all licenced TSC indications.

Currently, there are [confidential data figure removed] patients with SEGA and [confidential data figure removed] with AML receiving everolimus via IPFR. Clinical experts from the TSC Specialist Clinic in Cardiff estimate that 1 patient would start treatment for SEGA and 5 patients would start treatment for AML each year with a discontinuation rate of 6.5% and 12.5% respectively. Dosing of everolimus for SEGA is individualised and based on patient body surface area with a recommended daily starting dose of 4.5 mg/m^2 whereas for AML a standard daily dose of 10 mg is recommended. As the majority of SEGA cases are in people aged 20 years and younger, cost estimates are based using a 5 mg dose typical for a nine-year-old child. Therefore, an average estimated cost per patient per year based on medicine acquisition costs only and using the confidential PAS price for Votubia® is [commercial in confidence figure removed] for the treatment of SEGA and [commercial in confidence figure removed] for the treatment of AML. This would result in a total estimated medicine acquisition cost for the treatment of both SEGA and AML of [commercial in confidence figure removed] in Year 1 rising to [commercial in confidence figure removed] in Year 5. However, in reality the budget impact is likely to be lower given that a number of patients are already receiving treatment through IPFR. Also, this doesn't take into account patients receiving everolimus to treat more than one manifestation of TSC and so some patients may be double counted.

Everolimus (Votubia®) may be supplied by a home healthcare provider and an arrangement is already in place for Wales. Generic preparations for the tablet form of everolimus licensed for some cancer indications have been available since 2019. The exclusivity of Votubia® ends in September 2023 and it is anticipated generic everolimus preparations will also be licensed for the TSC indications, resulting in lower medicine acquisition costs.

References:

A full reference list is available on request.