Everolimus and Sirolimus for Renal Angiomyolipoma Associated with Tuberous Sclerosis

Sirolimus for renal angiomyolipoma associated with tuberous sclerosis **WILL BE** routinely funded on the NHS as an option in the treatment of renal angiomyolipoma associated with tuberous sclerosis.

**Everolimus for renal angiomyolipoma associated with tuberous sclerosis WILL NOT** be routinely funded on the NHS.

Renal angiomyolipomas (renal AML) are common in the kidneys of people with tuberous sclerosis (TS). The tumours can increase in size and cause problems due to bleeding within the tumours and/or reduced kidney function. These renal tumours are the major cause of morbidity and premature death in TS patients.

Everolimus and sirolimus are mTOR inhibitor drugs which can block the abnormal cell signalling pathways which lead to tumour growth in TS. Everolimus has marketing authorisation for use in TS, whilst sirolimus does not, but could be used ‘off label’. Everolimus is significantly more expensive than sirolimus and currently not affordable given other calls on DHSC resources. There is clinical consensus that sirolimus is similar to everolimus in terms of cost effectiveness and the cost is significantly lower. In order to make best use of limited resources, DHSC has, therefore, agreed funding for sirolimus to be used in this indication.

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<th>Strength of evidence</th>
<th>Clinical Effectiveness</th>
<th>Cost Effectiveness</th>
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<td>Evidence for clinical effectiveness comes from the EXIST-2 (^1) randomised, double blind, placebo-controlled trial. In this study, 118 adult patients with renal AML associated with TS were randomised to receive everolimus (n=79) or placebo (n=39). The primary efficacy endpoint was defined as confirmed AML response of at least a 50% reduction in total volume of the target AMLs relative to baseline. At 24 weeks of treatment, 42% of patients receiving everolimus had experienced a volume reduction of 50% or greater, compared with 0% of patients taking placebo. At 22 month of treatment, 3.8% of patients receiving everolimus had experienced AML progression, compared to 20.5% in the placebo arm (no confidence interval or p-value given so statistical significance uncertain). Outcomes for clinically significant events such as bleeding, decline in renal function and mortality were not reported and the study period was likely too short to demonstrate them.</td>
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Reason for requesting policy review:
Replaces the CRC Recommendation CRC16-08: Everolimus for renal angiomyolipoma associated with tuberous sclerosis.

The previous CRC Recommendations resulted from consideration of an individual funding request (rarity) in 2016. Funding for everolimus was declined and further work with the specialist clinician led to approval of funding for sirolimus in 2017.

Under the arrangements for ‘rarity consideration’, a policy has now been prepared reflecting this decision.

Summary of evidence

Sources of evidence: EXIST-2 study\(^1\) and EXIST-2\(^2\) extension study; NHS E Commissioning Policy\(^3\)


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<td>The EXIST-2 extension study(^2) was an open label continuation phase of the original study. During this period, the response rate increased to 54% after a median treatment period of 28.9 months. During follow up, no patients on everolimus experienced a renal bleed, compared to one patient on placebo.</td>
<td>There is expert clinical consensus that similar outcomes are seen from sirolimus, a much cheaper drug.</td>
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Where a patient is considered to have exceptional need for and capacity to benefit from a treatment that is not routinely funded, a request for individual funding may be made to the Individual Funding Requests Panel. The patient must be made aware that the Panel may not support the request and must not be given any expectation that they will be able to have the treatment until a decision to fund has been received in writing from the Panel.

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