NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Everolimus for preventing organ rejection in liver transplantation

Your name: on behalf of The Efficacy and Safety of PRescribing In Transplantation (ESPRIT) Group

The ESPRIT Group is a totally independent group of multidisciplinary healthcare professionals, dedicated to the safety and well-being of transplant patients. Our activities are open to support by educational grants from interested parties. Currently these include Novartis Pharmaceuticals UK Ltd., Astellas Pharma Ltd., Mylan and Sandoz Ltd. However, as an independent group, we do not advocate any particular product and our opinions, recommendations and activities are all our own. For further information see www.esprit.org.uk .

As such we cannot contribute to NICE's assessment of the comparative efficacy and cost-effectiveness of the specific immunosuppressant included in the STA. However, where we feel that we have an important contribution to make is in relation to the efficacy and safety implications of the introduction of generic versions of immunosuppressant medications *per se*.

We note that the NICE Epilepsy Guidance (Guideline 137) says:
1.9.1.4 Consistent supply to the child, young person or adult with epilepsy of a particular manufacturer's AED preparation is recommended, unless the prescriber, in consultation with the child, young person, adult and their family and/or carers as appropriate, considers that this is not a concern. Different preparations of some AEDs may vary in bioavailability or pharmacokinetic profiles and care needs to be taken to avoid reduced effect or excessive side effects. Consult the summary of product characteristics (SPC) and 'British national formulary' (BNF; available at http://bnf.org) on the bioavailability and pharmacokinetic profiles of individual AEDs, but note that these do not give information on comparing bioavailability of different generic preparations[11],[12]. [New 2012] [1]

We would urge NICE to issue similar guidance for the immunosuppressants used in transplant patients.

In the final scope for this current STA, reference was made to the fact that 'The Commission on Human Medicines advises that all oral tacrolimus medicines in the UK should be prescribed and dispensed by brand name only'. We presume that this has arisen as a result of the specific national warning distributed about this particular immunosuppressant by the MHRA in 2012. However, as part of this technology assessment we would urge you to widen this recommendation, in line with the UK Medicines Information inclusions in Q&A 247.2, issued in July 2013.[2] In light of a systematic review of the literature, they recommended that switching between formulations of ciclosporin, mycophenolate and tacrolimus should be avoided.

The only way to guarantee this in practice is to prescribe and dispense by brand name. Where *branded* generic products do not exist e.g. in the case of the generic mycophenolate mofetil products, then it is prudent to specify the manufacturer.

The majority of the new generic immunosuppressants have been introduced in the past five years and, as yet, there is relatively little documented evidence on their use in practice in transplant patients. Indeed, in the absence of a central registry this is something which the ESPRIT Group is seeking to address in 2014 by way of systematic research. However, a simple review of the publicly-available bioequivalence assessments[3] shows that the currently available products are *different* - e.g. Adoport is quite a different formulation from the other branded generic tacrolimus products – and this may well translate into clinical differences. Generics are licensed on the basis of bioequivalence in healthy volunteers, which does not necessarily translate into clinical equivalence in individual patients. Indeed, recent studies have shown bioequivalence differences in practice in both elderly and paediatric renal transplant patients. [4,5]. This is the fundamental reason why it is recommended that switches to new generic products only take place under specialist-controlled conditions with appropriate monitoring. In a recent pilot survey amongst transplant patients who had been switched, around 30% of patients required a change of dose before they were stabilised on their new immunosuppressant, and 13% reported that they had to be switched back to their original product.[6]

Undoubtedly, there will be more new generic immunosuppressants introduced in the coming years and within the lifespan of this assessment – including generic sirolimus products, and everolimus, the specific subject of this current STA. It seems utterly sensible to establish a 'Good Generic Practice' *now* for immunosuppressants used in the very specialist transplant population. Immunosuppressants should be prescribed and dispensed by brand and switches should only be carried out in the specialist hospital setting with appropriate monitoring. Not only can this help ensure the efficacy and safety of use of generic immunosuppressants, it can also be cost-effective; inadvertent switches can lead to unwanted side effects, acute rejections, hospitalisations, retransplants and returns to dialysis, all with associated costs.

Finally, at a time when the campaign to encourage increased organ donation is fully underway, and there are patients dying on the waiting list for organs, it would seem expedient not to do anything which could put these precious commodities at risk.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Everolimus for preventing organ rejection in liver transplantation

References

1. NICE Epilepsy Guidance (Guideline 137). Clause 1.9.1.4. Accessed via www.**nice**.org.uk/**guidance**/cg137

2. UK Medicines Information. Q&A 247.2, July 2013. Accessed via NICE Evidence Search at www.evidence.nhs.uk

3. ESPRIT Group compilation of bioequivalence assessments. Accessed via www.esprit.org.uk/resources.cfm?category=Esprit

4. Robertsen, I et al, Transplantation 2014. Accessed via PubMed http://www.ncbi.nlm.nih.gov/pubmed?term=%22Transplantation%22%5BJour%5D+AND+robertsen+I+%5Bfirst+author%5D+AND+generic+tacrolimus&TransSchema=title&cmd=detailssearch

5. Jacobo-Cabral CO et al, Pediatric Transplantation 2014. Accessed via PubMed http://www.ncbi.nlm.nih.gov/pubmed?term=%22Pediatric+transplantation%22%5BJour%5D+AND+jacobo-Cabral%5Bauthor%5D&cmd=detailssearch

6. Pollard S and Johnston A on behalf of the Efficacy and Safety of PRescribing In Transplantation (ESPRIT) Group. Poster P169 presented at the British Transplantation Society Annual Meeting, 26th February 2014, Glasgow