

ESPRIT

Efficacy and **S**afety of **P**Rescribing In **T**ransplantation

Implications of Generic Immunosuppressants for Transplant Patients

The ESPRIT Group is constituted as an independent company limited by guarantee, full name ESPRIT Partnership Ltd., registered in England and Wales no. 06971971. Registered office: 6 Baldwin Crescent, London, SE5 9LQ. Its 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.

Agenda

- Background to the ESPRIT Group
- Licensing of generic medicines and implications in transplantation
- Generic immunosuppressants – ESPRIT recommendations
 - Ciclosporin
 - Tacrolimus
 - Mycophenolates
- Other recommendations and guidance
- Implications and actions

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Background to the **ESPRIT** Group

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ESPRIT Group

- Independent, multidisciplinary group of healthcare professionals in transplant – plus an expert patient
- Committed to ensuring the continued, effective and safe treatment of transplant patients
- First formed in 2000 to educate healthcare professionals and patients
- Produces various educational items, including patient resources – all loaded on central website www.esprit.org.uk
- Published specific recommendations based on latest evidence on generic immunosuppressants
 - Inputting to latest official discussions



ESPRIT Group Members

- **Ms Heather Black, Senior Renal Pharmacist, Glasgow**
- **Miss Laura Buist, Director of Renal Transplantation & Consultant Surgeon, Glasgow**
- **Ms Dawn Chapman, Pancreas Transplant Nurse Specialist, Cardiff**
- **Professor Atholl Johnston, Clinical Pharmacologist, London**
- **Professor Deirdre Kelly, Professor of Paediatric Hepatology, Birmingham**
- **Ms Sue Lyon, Kidney Transplant Recipient, London**
- **Ms Jane Moffatt, PCT Head of Medicines Management, Brighton**
- **Mr Stephen Pollard, Transplant Surgeon, Leeds**
- **Dr Michael Tredger, Consultant Clinical Scientist, London**

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**Licensing of Generic Medicines and
Implications in Transplantation**

***Licensed Bioequivalence DOES NOT
equal Clinical Equivalence***

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Bioavailability and Bioequivalence

- **Bioavailability:**

The rate and extent to which a drug is absorbed from a pharmaceutical form and becomes available at the site of action

- **Bioequivalence:**

“A drug shall be considered to be bioequivalent to a listed drug if the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of the listed drug”
(FDA)

Potential Issues Arising as a Result of the Regulations

The limitations of the bioequivalence criteria

Tested in healthy volunteers only	Ciclosporin pharmacokinetics can be different in transplant patients compared to healthy volunteers ¹
No testing in different subpopulations	There are important pharmacokinetic variations between different groups e.g. children versus adults ² ethnic origin ³ , diabetics ³
Generally tested under fasting conditions	Food affects absorption of ciclosporin from different formulations to different extents ^{4,5}
No testing of therapeutic equivalence	Any clinical impact of pharmacokinetic differences between formulations is not assessed
Average population	FDA / CHMP criteria based on averages rather than individuals' results

1. Ptachcinski RJ et al. J Clin Pharmacol 1987; 27: 243-248
2. Cooney GF et al. Clin Pharmacokinet 1997; 32: 481-495
3. Schroeder TJ et al. Transplant Proc 1995; 27: 837-839
4. Mueller EA et al. Pharm Res 1994; 11(1): 151-155
5. Kees F et al. Transplant Proc. 2004; 36(10): 3234-3238

Bioequivalence Requirements - Based on Average Results

- Criteria set by FDA/ CHMP are based on average population data rather than individual results
- Average ratio of the maximum concentration of drug in plasma or serum (C_{max}) and area under the curve (AUC) must fall between 80% and 125% of that of the reference product¹
- These criteria recognised to be insufficient for critical-dose drugs, so requirements for such medicines changed in 2010 to 90–111% of that of the reference product²

1. US Department of Health and Human Services. Guidance for industry: bioequivalence recommendations for specific products. Silver Spring, MD: FDA, 2010. Available from: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072872 (accessed 4 January 2011).

2. European Medicines Agency. Generic/hybrid applications Q&A: introduction. London: European Medicines Agency, 2011. Available from http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000179.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580022717 (accessed 10 January 2011).

Features of Critical Dose Drugs¹

- Narrow therapeutic window
- Indicated for critical patient/condition
- Serious consequences of sub- or supra-optimal dosing
- Wide intra- and inter-patient pharmacokinetic variability
- Limited or erratic absorption (i.e. bile dependent/slow)
- Routine blood level monitoring needed
- Formulation-dependent bioavailability/dissolution
- Individualised dosing

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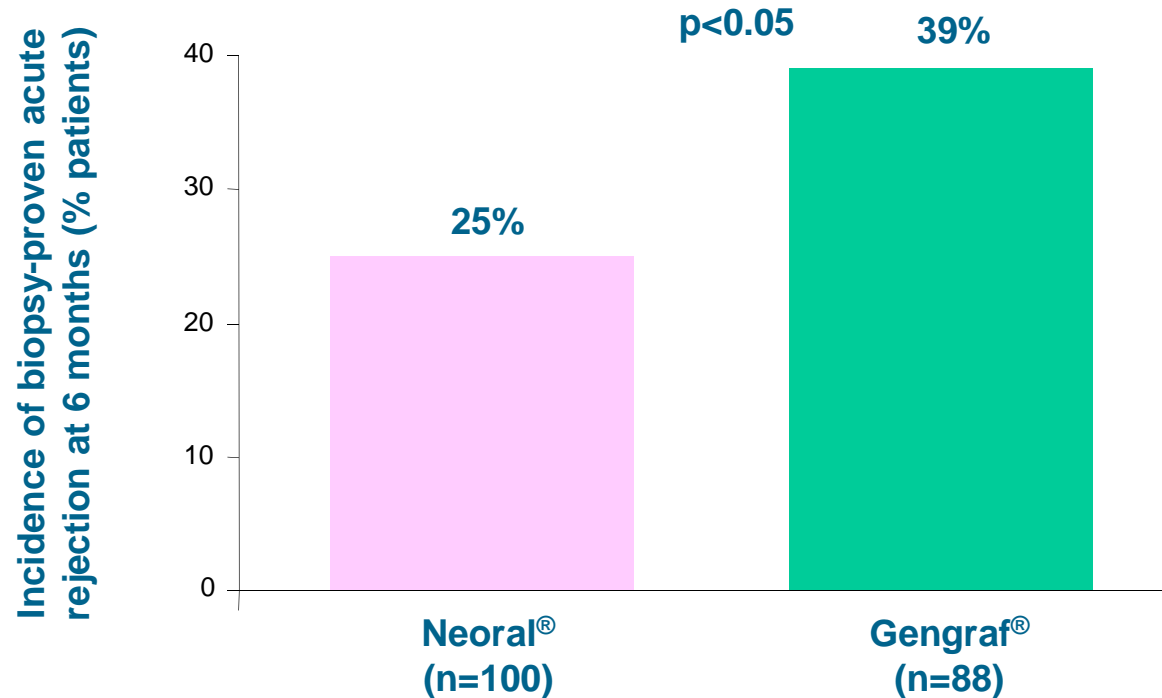
ESPRIT Recommendations on Generic Immunosuppressants

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Ciclosporin

- Ciclosporin is a pre-eminent example of a critical dose drug, and should always be prescribed and dispensed by brand, as also advocated by the BNF, MHRA, MIMS and other professional bodies, in order to avoid inadvertent switches between different formulations
- Switching should only ever be contemplated in the specialist hospital setting, with appropriate monitoring

Risk of Acute Rejection

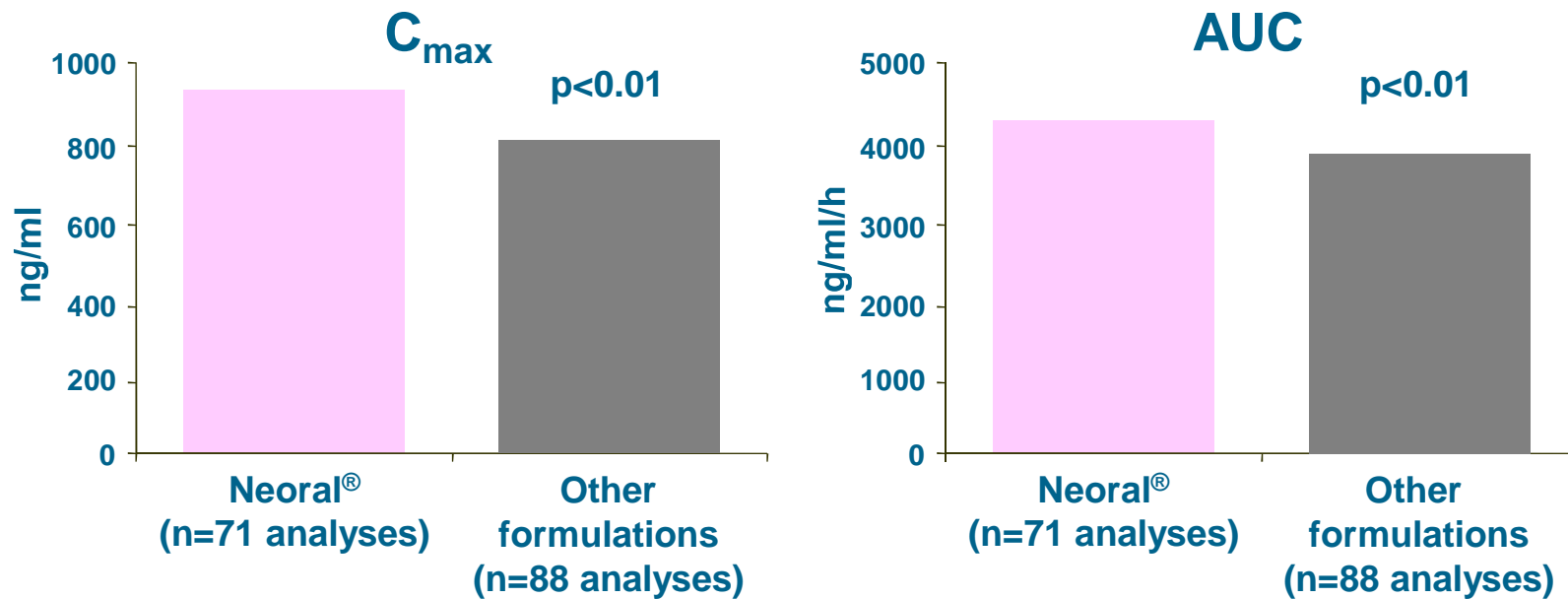


Higher incidence of acute rejection with generic formulation of ciclosporin compared to Neoral®

Data from retrospective study of *de novo* renal transplant patients receiving MMF, steroids and either the Neoral® or Gengraf® formulation of ciclosporin at a single centre
Taber DJ et al. Transplantation 2005; 80(11): 1633-1635

Overall Clinical Outcomes

Retrospective analysis of pharmacokinetic parameters and clinical efficacy of various bioequivalent ciclosporin formulations (mainly Consupren[®]) in comparison with Neoral[®]



Clinical outcomes with generic (n=195) compared with Neoral[®] (n=234):

- Biopsy Proven Acute Rejection rate considerably higher (10.6% vs 4.1%) $p < 0.05$
- Chronic allograft dysfunction higher (24% vs 14%) $p < 0.05$
- 3-year graft survival lower (90% vs 96%) $p = 0.05$

Tacrolimus

- All tacrolimus prescriptions should be written by brand to avoid inadvertent switches, and ensure that patients are maintained on the formulation on which they were stabilised in the transplant unit
- As with ciclosporin, switching should only be contemplated in the specialist transplant setting with appropriate monitoring
 - Similar drug (same class of calcineurin inhibitors) to ciclosporin and essentially the same critical indications in transplantation
 - No evidence that different immediate-release tacrolimus products can be safely interchanged
 - Situation further complicated by the *original* availability of three different forms of tacrolimus (immediate-release Prograf, prolonged-release Advagraf and Modigraf granules)
 - confusion occurred before the advent of generics
 - IR Adoport[®] is easily confused with o.d. Advagraf[®]
 - Only clinical evidence to date suggests a real need to monitor patients undergoing switching

Evidence of Need for Monitoring

- Forty-one mixed transplant patients switched to generic tacrolimus - 43% of patients had change in blood concentration >20%. The authors felt it *'prudent to measure tacrolimus levels when patients are switched to generic product'*¹
- Fifty-five patients with kidney, liver or multi-organ transplants switched in four centres²
 - Dose titrated in 17 (31%) patients: 10 downward, seven upward
 - Authors recommended post-conversion monitoring, given one in 3-4 patients may need dose titration
- Four inadvertent switches occurred from Prograf[®] to generic tacrolimus in paediatric renal transplant programme³
 - Three patients had no significant changes in creatinine levels
 - The fourth had biopsy-proven acute rejection

1.Venkatamaranan, R et al, Abstract no. 1741, Poster presented at ATC, San Diego, May 4th 2010

2.McDevitt, L.M et al, Abstract no.459, presented at Concurrent Session 63, ATC, San Diego, May 4th 2010

3.Abdulnour, HA et al, *Pediatr. Transplant.*, 2010, Aug 31 [Epub]

Mycophenolate Mofetil (MMF)

Important: only generic forms of MMF are available, **not** of enteric-coated mycophenolate sodium (ECMPS)

MMF vs ECMPS

- Definite differences apparent between MMF and ECMPS, most notably in terms of interactions with proton pump inhibitors (PPIs), which affect the pharmacokinetics of MMFs, but not ECMPS. Important difference, given almost universal use of PPIs post-transplant
- Consequently, **not** recommended that ECMPS and MMF products are interchanged. ECMPS should be prescribed by brand and patients made aware they are different

Mycophenolate Mofetil (MMF)

MMF vs MMF

- MMF formulations should only be changed in collaboration with the transplant unit as no real evidence that different MMF products can be safely interchanged
- High degree of variability apparent with MMF formulations, both in PK and reported side effects
- Evidence on whether mycophenolate is a critical dose drug or not is equivocal
- Monitoring of blood levels not routinely recommended, but some evidence it may be desirable on certain occasions
- Patients should be fully informed of potential changes in MMF formulations and encouraged to report any changes experienced (especially adverse events) to their transplant unit
- Patients should also be aware they can self-report adverse events via yellow cards, in discussion with transplant unit

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Other Recommendations and Guidance

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What the *British National Formulary* Says

bnf.org

“Different formulations of the same immunosuppressant may vary in bioavailability and to avoid reduced effect or excessive side-effects, it is important not to change formulation except on the advice of a transplant specialist”

What the *British Transplantation Society* Says



“Clinical members of the Society will be aware that over the last year there has been an increase in the number of generic immunosuppressive agents available. Owing to cost pressures in the NHS many units are needing to consider this option. There are potential patient safety issues, particularly with switching cyclosporine and tacrolimus preparations outside close clinical supervision, that have been highlighted by the ESPRIT Group”

What the *National Kidney Federation* Says



“The lesson is clear, if the drug you are being prescribed, or handed, is not identical to the drug you are used to taking – DON’T TAKE IT without getting advice from your own renal consultant.

*This applies even if the person is your GP, Chemist, Nurse or other Physician. See **ESPRIT Group Recommendations**”*

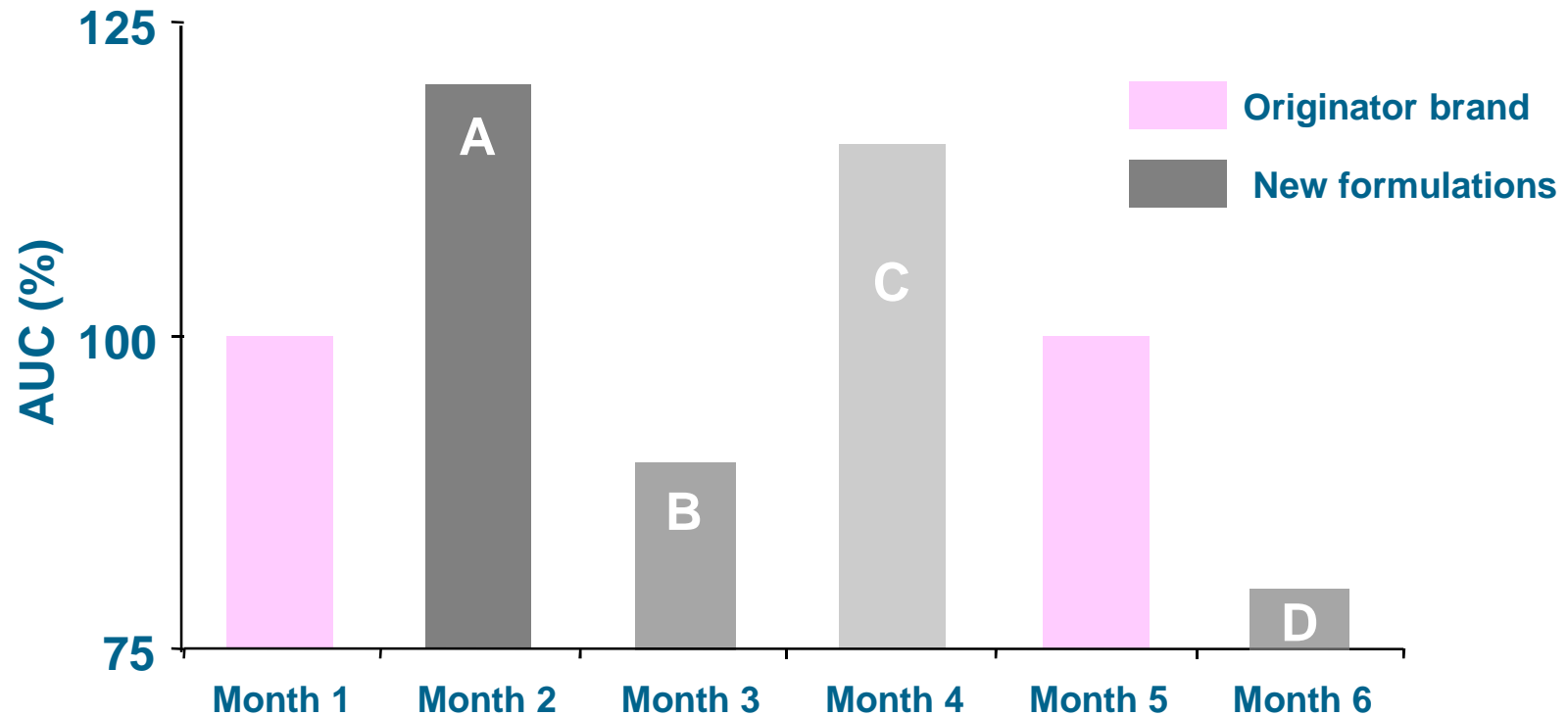
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Implications and Actions

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Multiple Different Formulations could be Received over Time



This could lead to clinically relevant differences in exposure. There is also a risk of partial switching or brand mixing where different formulations are mixed in the same dose

NB current bioequivalence limits are between 80% to 125% so the axis for AUC would never extend to zero

Potential Financial Implications

- Cost of immunosuppressant drugs? *c. £5,000 per patient per annum – of which 20-30% could potentially be saved using generic immunosuppressants*
- Cost of monitoring? *£250 for blood tests*
- Cost of managing acute rejection? *c£8,750 if steroid-responsive*
- Cost of return to dialysis? *£31,000 per annum*
- Cost of retransplant? *£17,000 per annum*

NHS Blood and Transplant. Cost-effectiveness of transplantation. Bristol: NHS Blood and Transplant, 2009. Available from: www.uktransplant.org.uk/ukt/newsroom/fact_sheets/cost_effectiveness_of_transplantation.jsp (accessed 22 March 2010).

.Woodroffe R, Yao GL, Meads C, et al. Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study. Chapter 6: Economic analysis. Health Technology Assessment 2005;9(21):37–62.

At the Core of all Prescribing and Dispensing Decisions...



Action Needed at all Levels to Avoid Inadvertent Switching

Tertiary/ Secondary Care

- Information should be included in discharge / referral letters to GPs and / or referring hospitals regarding the importance of prescribing immunosuppressants by brand
- Information for patients in clinics/ patient reminder resources

Primary Care

- All GP prescriptions for transplant immunosuppressants to be prescribed by brand
- Community pharmacists and technicians to be aware of risks of inadvertent switching

Patients and Carers

- Need to understand clearly to query if any different formulation is prescribed or dispensed to them
- Encouraged to report any effects from new formulations to their transplant unit and on yellow card

Summary

- FDA/CHMP bioequivalence criteria used for licensing generics may be insufficient for critical dose drugs such as those used post-transplantation
- There may be clinical implications of switching patients to generic formulations of immunosuppressant – drug toxicity or organ rejections
- These adverse outcomes could incur far greater NHS costs than any direct cost savings made from generic drug purchase
- Switching should only therefore be contemplated in the specialist hospital setting with appropriate monitoring
- Immunosuppressants should be prescribed and dispensed by brand, so as to ensure that patients are maintained on the formulation on which they have been stabilised
- Action is required at all levels to ensure patients on ciclosporin therapy receive a consistent formulation

See www.esprit.org.uk

The screenshot shows a Windows Internet Explorer browser window displaying the website <http://www.esprit.org.uk/>. The browser's address bar shows the URL, and the Norton Safe Search toolbar is visible. The website's header includes the ESPRIT logo and the tagline "EFFICACY AND SAFETY OF PRESCRIBING IN TRANSPLANTATION". A navigation menu contains links for Home, News, Resources, Contact, and Members. The main content area features a large blue banner with the text "Welcome to ESPRIT" and a detailed paragraph about the organization's mission. To the right, a section titled "Access ESPRIT Resources" provides a link to access documents. The Windows taskbar at the bottom shows the Start button, several open applications, and the system tray with the time 15:29.

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PRESCRIBING IN TRANSPLANTATION

Home | News | Resources | Contact | Members

Welcome to ESPRIT

ESPRIT stands for **E**fficacy and **S**afety of **P**rescribing In **T**ransplantation. As a multi-disciplinary group, comprised of transplantation clinicians, pharmacists, and primary care representatives, we share a common commitment to ensure the continued, effective and safe treatment of patients through education of healthcare professionals and patients. We first convened in 2000, and our aims are supported by the National Kidney Federation and the British Liver Trust.

All our materials can be accessed on this website. For further information, please e-mail the ESPRIT Group Secretariat on info@esprit.org.uk

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Access ESPRIT Resources

To access the resource documents, please [click here](#)

24 of 24 - Clipboard Item collected.

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Questions?

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