What is the evidence for the use of generics in renal transplant patients

Kate Webb
Renal Pharmacist Practitioner
University Hospital of North Midlands
Summary of Presentation

- Generics Overview
- Pharmacokinetics
- Renal Transplant medications
  - Evidence for Generics
  - Prednisolone / Azathioprine
  - Mycophenolate Mofetil
  - Ciclosporin
  - Tacrolimus
- Conclusion
Generics Overview

- Proprietary v’s Generics

- Benefits:
  - Greater n° of preparations in market place
  - Reduction in price
  - Pharmaceutical Industry more competitive
Generics Overview

- Generics are licensed Pharmaceuticals
  - EMEA
  - MHRA

- Ensure...
  - Contains the same active ingredients
  - Treats the same medical condition
  - Identical in strength, purity, quality, dosage form & route of admin.
  - Absorbs into the bloodstream at a similar rate & over the same period of time
Generics Overview

Examples:

- Lipitor®
  atorvastatin calcium tablets

- Plavix®
  (clopidogrel bisulfate) 75mg tablets

- Seretide™
  salmeterol/fluticasone propionate

- Clozaril®
  Clozapine

- ZTAS®
  Zaronex Treatment Access System®
Pharmacokinetics

- Drug \[?\] Effect
- In the right place
- At the right concentration
- For the right amount of time
Steady State
- Attained after approximately four half-times
- Time to steady state independent of dosage

Steady State Concentrations
Pharmacokinetics:

- Bioavailability: -

  *Fraction of drug absorbed into the drug stream (F)*

  - Absorption
  - Distribution
  - 1st pass metabolism
Pharmacokinetics:

- Therapeutic Window: -
Renal Transplant Medications
National Guidance

- **EMA:**
  - Narrowed acceptable differences in AUC

- **CHM:**
  - Changes Intentional TDM

- **ESPIRIT:**
  - Potential savings must be weighed against pt safety & costs of inadvertent savings
Evidence

- Goodman et al, Meta-analysis: -
  - Acute rejection rare
  - Risks did not differ
  - Bioequivalent conventional criteria but not EMA stricter criteria

“Bigger & better studies with longer follow-up are still required”
Evidence

- Molnar et al, Meta-analysis:
  - Acute rejection rare & did not differ
  - Pooling of results ltd by inconsistent study methods & reporting of outcomes
  - Not bioequivalent according to EMA criteria

“High quality data lacking. Well designed studies on bioequivalence are needed”
Prednisolone / Azathioprine

- Generics utilised effectively:
  - Meticorten® /
  - Deltacortril®
  - Imuran®

- 1955: 1st Available
- 1957: Generic
- 1996:
Mycophenolate Mofetil:

Brand: Cellcept®

Generic: Myfenax / Accord / Mylan

Mycophenolate mofetil

Enteric coated mycophenolate sodium

Interchangeable

Not interchangeable
Ciclosporin: -

- Narrow Therapeutic Window
- Bioavailability 30% (range 8% - 60%)
- Requirement for TDM

<table>
<thead>
<tr>
<th>Brand</th>
<th>Generic</th>
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<tbody>
<tr>
<td>Neoral®</td>
<td>Capimune</td>
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<td></td>
<td>Deximune</td>
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<td>Capsorin</td>
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<td>Vanquoral</td>
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**Tacrolimus:**

- **Narrow Therapeutic Window**
- **Bioavailability 25% (variable)**
- **Requirement for TDM**

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Brand</th>
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<tr>
<td>Immediate Release</td>
<td>Prograf®</td>
<td>Adoport</td>
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<td></td>
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<td>Vivadex</td>
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<td>Capexion</td>
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<td>Prolonged Release</td>
<td>Advagraf®</td>
<td>Envarsus</td>
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<tr>
<td>Granules</td>
<td>Modigraf®</td>
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Envarsus®

European Medicines Agency

Envarsus
tacrolimus

About Authorisation details Product Information Assessment history

This is a summary of the European public assessment report (EPAR) for Envarsus. It explains how the Agency assessed the medicine to recommend its authorisation in the EU and its conditions of use. It is not intended to provide practical advice on how to use Envarsus.

For practical information about using Envarsus, patients should read the package leaflet or contact their doctor or pharmacist.

1. What is Envarsus and what is it used for?
2. How is Envarsus used?
3. How does Envarsus work?
4. What benefits of Envarsus have been shown in studies?
5. What are the risks associated with Envarsus?


*EMA ➔ EPAR*
Envarsus®

NICE
STM:
Conclusion

- Generics
  - Highly Divisive
  - Hugely Beneficial
  - Managed appropriately
References

2. Duff G. Oral Tacrolimus Products should be prescribed & dispensed by brand name to avoid the risk of medication errors. Commission of Human Medicines (CHM), May 2012.
5. Winter M. Basic Clinical Pharmacokinetics. Lippincott Williams & Wilkins 2010;5th Edition:250-267
Questions