Impact of Generics and Biosimilars on Branded Drug Listing Decisions in Singapore

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OBJECTIVES

- To explore the impact of generics and biosimilars on Health Technology Assessment outcomes of branded originator products in Singapore.

BACKGROUND

- Previous research reported that price is a key consideration in the likelihood of a positive listing following Health Technology Assessment (HTA) by the Agency for Care Effectiveness (ACE) in Singapore.[1]
- Given the importance of price, this analysis aimed to investigate whether the inclusion of a generic or biosimilar product – both of which typically have lower costs compared to branded originator products – within the HTA evaluation framework impacted the outcome of HTA for branded products.

METHODS

- All appraisals published by ACE between March 2017–September 2019 were reviewed.[2]
- Appraisals where branded drug(s) and generic(s)/biosimilar(s) were in the HTA evaluation framework – regardless of whether the branded drug(s) and generic(s)/biosimilar(s) were the intervention, comparator or both – were included for analysis.
- Branded drug(s) and generic(s)/biosimilar(s) did not have to share the same active ingredient.
- A drug was categorised as a 'biosimilar' if described as such within the appraisal.
- Generic status was either determined by explicit mention within the appraisal, or if unclear, the availability of a generic was searched in other sources. Generic status was assumed if the drug met two of the following criteria: a non-branded drug was registered in Singapore; the branded drug patent had expired for more than five years; the product was on the Ministry of Health Standard Drug List. Where inclusion of generics was uncertain, the appraisal was excluded from the analysis.
- For each appraisal, drugs included in the evaluation framework (including their branded/generic/biosimilar status), indication and outcome of HTA evaluation were extracted.

RESULTS

- Amongst the 45 appraisals reviewed, 20 included generic(s)/biosimilar(s) in the evaluation framework (17 included generics; 3 included biosimilars) **(Table 1)**.
  - 10 of the 17 appraisals that included generic(s) favoured branded drug(s) (i.e. subsidy listing was awarded to branded drug[s]). The remaining seven appraisals favoured a generic (i.e. subsidy listing was awarded to a generic, or no subsidy listing was awarded to branded drugs as generic[s] were already available on the subsidy list).
  - All three appraisals that included a biosimilar favoured the biosimilar **(Figure 1)**.

Appraisals That Favoured Branded Drugs

- Amongst the 10 appraisals that favoured branded drug(s) over generic(s), subsidy listing was awarded to 7 of these on the basis of cost-effectiveness, where a higher price for a branded drug was deemed acceptable considering the clinical benefits offered over a generic.

1 Summary of appraisals including generics/biosimilars published by ACE (March 2017–September 2019)[2]

HTA evaluation framework		Indication evaluated	Changes to subsidy list
Intervention[§]	Comparator[#]		
Apixaban*, rivaroxaban*, dabigatran*	**Enoxaparin/warfarin***, warfarin[‡]	Deep vein thrombosis and pulmonary embolism	Rivaroxaban added (MAF)
Apixaban*, rivaroxaban*, dabigatran*	Warfarin[‡]	Preventing stroke and systemic embolism in patients with non-valvular atrial fibrillation	Rivaroxaban added (MAF)
Canagliflozin*, dapagliflozin*, empagliflozin*	Sulfonylureas[‡Δ], **dipeptidyl peptidase 4 inhibitors*[Δ]**	Type 2 diabetes mellitus	Dapaglifozin and empaglifozin added (both MAF)
Daptomycin*, linezolid[‡]	*Not reported*	Vancomycin-resistant enterococci bloodstream infections	Linezolid added (MAF)
Denosumab*	Zoledronic acid[‡], **pamidronate***	Prevention of skeletal-related events in adults with bone metastases from solid tumours	No change
Denosumab*	Zoledronic acid[‡]	Osteoporosis in post-menopausal women at high risk of fracture	Denosumab added (MAF)
Dutasteride/tamsulosin combination*, dutasteride*, tamsulosin*, alfuzosin[‡]	Finasteride[‡]	Benign prostatic hyperplasia	Alfuzosin added (SDL)
Ezetimibe/simvastatin combination*, ezetimibe[‡]	Simvastatin[‡], **statin therapy*[Δ]**	Primary hypercholesterolaemia	Ezetimibe added (SDL)
Febuxostat*	Allopurinol[‡]	Chronic hyperuricaemia in gout	No change
Infliximab biosimilar [Remsima][†]	**Infliximab originator [Remicade]***	Various immunological conditions	Remsima added (MAF); Remicade removed
Insulin glargine biosimilar [Basaglar][†]	**Insulin glargine originator [Lantus]***	Type 1 and type 2 diabetes mellitus	Basaglar added (SDL)
Long-acting muscarinic antagonists (LAMA): **Glycopyrronium*, tiotropium*, umeclidinium***	Ipratropium[‡]	Chronic obstructive pulmonary disease	Umeclidinium added (SDL)
LAMA and long-acting beta$_2$ agonists (LABA) combinations: **Indacaterol/glycopyrronium*, tiotropium/olodaterol*, umeclidinium/vilanterol***	**LAMA*, Inhaled corticosteroid/LABA combination*[Δ]**		Umeclidinium/vilanterol added (SDL)
Mycophenolate mofetil (MMF)[‡], **mycophenolate sodium (EC-MPS)***	**Cyclophosphamide***, azathioprine[‡]	Lupus nephritis	MMF and EC-MPS added (both MAF)
Omalizumab*	**Ciclosporin***, ciclosporin[‡]	Severe chronic spontaneous urticaria	Omalizumab added (MAF)
Rivastigmine*	Donepezil[‡]	Dementia associated with Parkinson's disease or Alzheimer's disease	Rivastigmine patch added (MAF)
Sacubitril/valsartan*	Enalapril[‡]	Chronic heart failure with reduced ejection fraction	No change
Second-generation antipsychotic injections **(paliperidone*, aripiprazole*)**	First-generation antipsychotic injection (haloperidol[‡])	Schizophrenia	No change
Ticagrelor*	Clopidogrel[‡]	Preventing thrombotic events in adults with acute coronary syndromes	Ticagrelor added (MAF)
Trastuzumab (intravenous)*, trastuzumab (subcutaneous)*	Taxane regimens (e.g. regimens containing docetaxel or paclitaxel)[‡Δ]	HER2-positive metastatic breast cancer	Intravenous trastuzumab added (MAF)
Vedolizumab*	Infliximab biosimilar [Remsima][†], **adalimumab***	Ulcerative colitis and Crohn's disease	No change

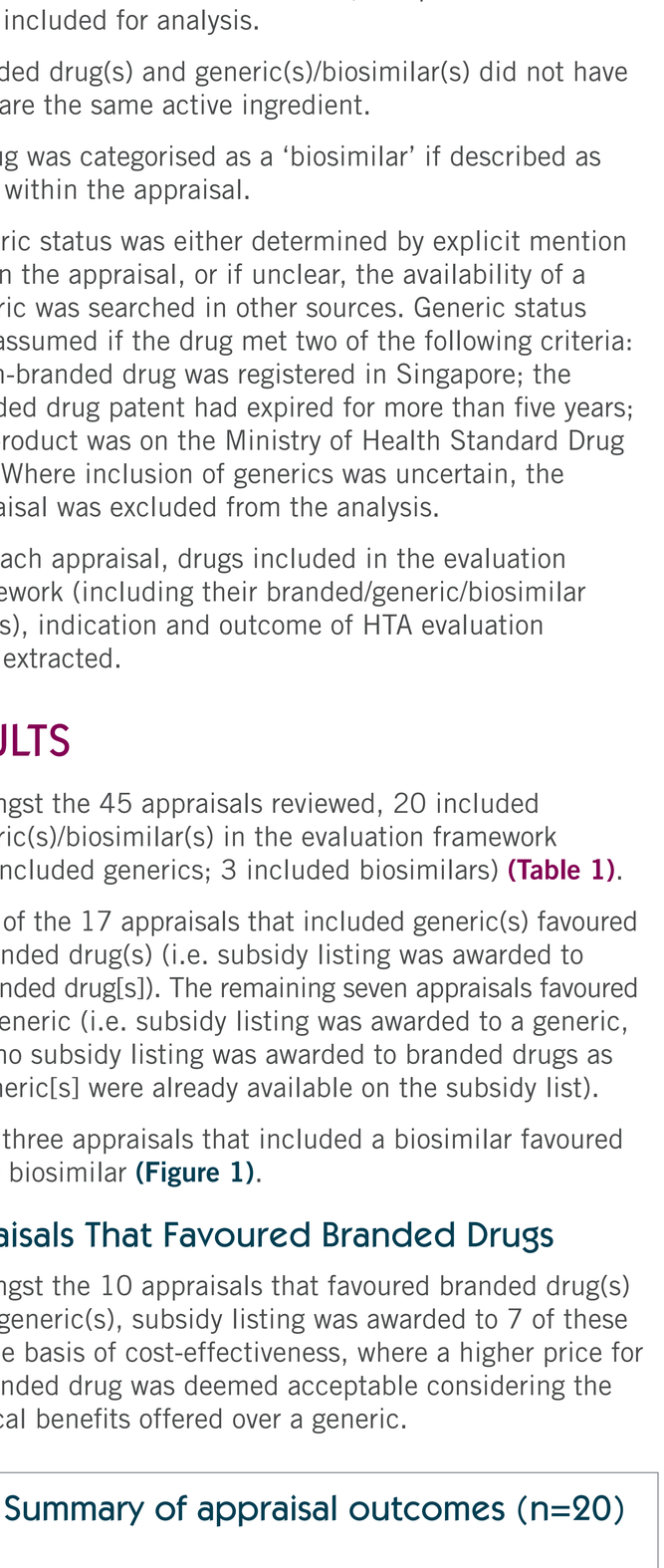
Blue: Appraisal favoured branded. **Green:** Appraisal favoured generic. **Coral:** Appraisal favoured biosimilar.

ACE: Agency for Care Effectiveness. EC-MPS: Mycophenolate sodium. HTA: Health Technology Assessment. LABA: Long-acting beta$_2$ agonists. LAMA: Long-acting muscarinic antagonists. MAF: Medication Assistance Fund. MMF: Mycophenolate mofetil. SDL: Standard Drug List.

Before HTA evaluation, drug was already on the subsidy list (Standard Drug List [SDL] or Medication Assistance Fund [MAF]) (based on the Ministry of Health Drug Subsidies List accessible via https://www.moh.gov.sg/cost-financing/healthcare-schemes-subsidies/drug-subsidies-schemes).

[§]A drug was considered an 'intervention' if it was reported in Section 1 (Technology Evaluation) of ACE's published guidance document as the technology being evaluated. [#]A drug was considered a 'comparator' if it was being compared to an intervention in Section 3 (Clinical Effectiveness) or Section 4 (Cost Effectiveness) of ACE's published guidance document. ***Branded**. [†]Biosimilar. [‡]Generic. [Δ]ACE's published guidance document reported class of drugs only; specific drugs being considered were not reported.

1 Summary of appraisal outcomes (n=20)



- The remaining three branded drugs received a positive recommendation for reasons other than cost-effectiveness compared to generic(s):
  - Branded rivastigmine patch was awarded subsidy listing due to its ease of administration, potential for improved adherence and reduced caregiver burden compared to oral generic donepezil.
  - Branded mycophenolate mofetil (250 mg) was awarded subsidy listing due to the clinical need for dose titration, which was not possible with the generic 500 mg tablet.
  - Branded omalizumab was awarded subsidy listing as it was cost-effective when compared to branded ciclosporin, rather than generic ciclosporin, which clinicians did not wish to stock in hospitals due to the risk of dispensing errors.
- Interestingly, while branded intravenous trastuzumab was subsidised, the branded subcutaneous formulation was not, because of the view that listing of the subcutaneous formulation would drive switching from the intravenous to the subcutaneous formulation, thereby limiting future cost-savings associated with the entry of intravenous biosimilars.

Appraisals That Favoured Generics/Biosimilars

- In all seven appraisals where generic(s) were favoured, this was due to the branded drug(s) being not cost-effective, or due to higher costs associated with the branded drug(s) if there was no clear clinical differentiation between the drugs.
- Amongst the three appraisals that favoured the biosimilar, two appraisals compared the biosimilar with the equivalent branded originator; both appraisals awarded subsidy listing to the biosimilar and the branded originator was also de-listed in one of these (infliximab).
- In the remaining appraisal, a biosimilar was compared to a *different* branded originator, with subsidy listing awarded to the biosimilar.

CONCLUSIONS

- Subsidy listing was awarded to branded drug(s) over generic(s) where the higher-cost branded drug(s) demonstrated clinical benefits when compared to a lower-cost generic.
- In some cases, non-cost benefits were considered when choosing a branded drug over a generic.
- Access to innovative medicines may be limited in cases where the clinical evidence base may be deemed insufficient to justify a higher price vs generic/biosimilar standard of care. Manufacturers should consider evidence generation plans in the context of this research.

References

1. Ghosh W. *et al.* Value in Health 2018;21(Suppl2):S9;
2. Agency for Care Effectiveness 2019. Drug Guidances. Available at: http://www.ace-hta.gov.sg/our-guidance.html [Last accessed 16 September 2019].

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