Repurposing Medicines Follow up consultation

Cancer Council Australia, Clinical Oncology Society of Australia, Medical Oncology Group of Australia.

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This submission has been prepared jointly between Cancer Council Australia (Cancer Council), the Clinical Oncology Society of Australia (COSA) and the Medical Oncology Group of Australia (MOGA).

Cancer Council is Australia's peak national non-government cancer control organisation and advises the Australian Government and other bodies on evidence-based practices and policies to help prevent, detect and treat cancer.

The Clinical Oncology Society of Australia is the peak national body representing health professionals from all disciplines whose work involves the care of cancer patients.

The Medical Oncology Group of Australia is the national, professional organisation for medical oncologists and the profession in Australia.

BCNA has reviewed the submission and supports it on behalf of those Australians diagnosed with breast cancer.

We acknowledge the traditional custodians of the lands on which we live and work. We pay respect to Aboriginal and Torres Strait Islander elders past, present and emerging and extend that respect to all other Aboriginal and Torres Strait Islander people.

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Introduction

Cancer Council, COSA and MOGA appreciate the opportunity to contribute to the important conversation of repurposing prescription medicines. This submission focuses specifically on the experience of repurposing prescription medicines in oncology but is likely applicable to other therapeutic areas.

We would welcome further discussion on this issue and be pleased to work with the Therapeutic Goods Administration (TGA) on solutions which enable people with cancer to access safe and effective registered products which can be considered for subsidy. Our organisations represent the impact on patients of the existing regulatory processes including the registration of medicines for new purposes, and the clinical experience of prescribing medicines.

A. Commercial and intellectual property (IP) Issues

Problem statement: *the obstacles relating to commercial and IP issues are different between medicines that are on-patent vs off-patent*

On Patent

1. What practical options may encourage an innovator to work with a third party to allow an on-patent medicine to be brought to market?

Our organisations are concerned with the challenges experienced by people affected by cancer when medicines require a repurposing process and so support a process that makes it as easy as possible for an innovator sponsor to offload a medicine to an interested third party. In the treatment of cancer, it is particularly challenging when medicines are off-patent, yet are part of usual care for patients, so we have commenced our submission at question 3.

2. How could product stewardship issues be managed in this circumstance?

Beyond the remit of Cancer Council, COSA and MOGA.

Genericised (Off- Patent)

3. What would be the most effective method to engage with potential non-traditional sponsors (such as non-profit groups, clinical colleges etc) where no interest is displayed by current sponsors of registered medicines?

The TGA would need to provide additional resourcing, including funding and a straightforward application process with clear criteria, to enable non-traditional sponsors to provide an application for off-patent medicines.

The current repurposing application process is not feasible for the vast majority of non-traditional sponsor organisations. Adjustments to criteria would need to include mechanisms to provide different types of evidence such as real-world data and evidence-based clinical guidelines, and support for non-traditional organisations to address the criteria, particularly on applications that are unappealing to traditional sponsors to progress. Such changes to current criteria would reduce the impact of submission application workloads for non-traditional sponsors and make it more likely they would be able to participate in the process.

Pharmacovigilance

The workload required to ensure appropriate pharmacovigilance is undertaken, particularly post- market surveillance, is an important factor in non-traditional sponsors currently being unable to participate in the processes for novel clinical use of existing medicines. Including additional post market surveillance for repurposed medicines that are on-patent is less impactful to pharmaceutical companies who are already required to take responsibility for this important role; however, most colleges, patient organisations and non-profit groups do not have capacity to conduct post market surveillance for off-patent medications in circumstances where traditional sponsors are hesitant to participate. Under the current system, pharmacological companies would need to be willing to do this work to support optimal cancer care through quality use of medicines. However, another solution could exist. If Australia were to implement a large scale pharmacovigilance program, underpinned by willing support and contributions from pharmaceutical companies, resources for post-market surveillance would be available when a medicine requires repurposing but sponsorship is not undertaken by a traditional sponsor. In this circumstance non-traditional organisations could contribute to the process and be comfortable in the knowledge that the broader aspects of the repurposing medicines process were overseen by the Department

4. How could product stewardship issues be managed in this circumstance?

There are a number of elements of product stewardship that do not fit within the remit of non-traditional sponsors, including pharmacovigilance and medicine supply chain factors. Non-traditional sponsors could only support repurposing medicines applications with a product stewardship process established for the Australian setting. Design or development of medicines will remain out of scope for the vast majority of non-traditional sponsors; however, they could provide support to the Department in the compilation of an appropriate level of evidence either through direct support or development of guidance documents for applicants. Stewardship needs to remain with one or a group of commercial sponsors, or the Department itself.

B. Identifying potential candidates

Problem Statement: *There is no central information collection or collation of off-label treatment options that could be used by the Department or others to identify potential medicines for repurposing.*
Four options could be used in combination and responders are invited to propose alternatives.

i. The Department could identify potential candidates through gap analysis of registered prescription medicines, comparing the indications registered in Australia to international registrations.
ii. The Department could identify potential candidates through analysis of Standards of Care and similar documents to find unregistered usages with Australia.
iii. Interested parties (patient advocacy groups, hospital drugs and therapeutics committees and/or colleges) could provide potential candidates that meet critical criteria for the Department to shortlist.
iv. Expert clinicians and/or independent advisory committees could recommend that the Department consider additional indications for a registered medicine through a coordinated approach. Additionally, clinicians could identify the quantity and quality of clinical evidence they hold.

5. Of these four options, which do you support, and why

All four opportunities to identify potential candidates have merit.
Options one and two require additional resourcing to ensure the Department is well equipped to analyse Standards of Care and clinical guidelines, as well as monitoring the gaps between Australian and international indications and registrations. A cancer specific example demonstrating how option one could work in practice is highlighted by the resource eviQ (www.eviq.org.au), an evidence-based, consensus driven source of cancer treatment protocols and information to be used at the point of care.

These resources already list off-label medicines and would be well placed to provide a valuable list of repurposed medicines already identified as having a role in optimal cancer care.

Clinical guidelines bring together the best available evidence to underpin scientifically valid recommendations for the prevention and diagnosis of cancer and the treatment and care of patients. However, guidelines are only helpful if there is investment to assist services to meet the minimum standards specified within them and when they are reviewed and updated regularly to ensure currency. Non-government organisations like Cancer Council, COSA and MOGA are owners of and contributors to these processes and understand that increasing access to cancer information, by providing the supportive environment to enable ongoing updates to clinical guidelines, will allow them to remain up to date, and to be well placed to provide the additional evidence to support the repurposing medicines process. This change alone will improve cancer outcomes and access to medicines in the proposed model.

Clinicians already informally assist and are well placed to identify medications that are routinely repurposed to ensure people affected by cancer receive and tolerate optimal treatment and therapies (recent examples include dacarbazine, lomustine, mitomycin, zoledronic acid, infliximab and valaciclovir), however it is unrealistic to expect clinicians or their colleges/societies to oversee management of an application. There remains an important role for the Department, either in sourcing sponsor(s) to take on the process or providing an alternative process for non-traditional sponsors that is less burdensome and facilitates their contribution in a manageable environment. Product stewardship must be the responsibility of a single or group of traditional sponsors regardless of who undertakes the application process and appropriate reimbursement needs to be designed to ensure this is an attractive option in the case of an off-label medication. Australia's National Medicines Policy places person centred care and optimal patient outcomes at the centre of medicines policy, and as such, patient needs must remain the driving force behind approaches to repurposing and reimbursement strategies, with the expectation that patient needs are as much of a consideration as commercial drivers.

6. Is there a combination of the above four options that would be most effective?

All four opportunities to identify potential candidates have merit and can be enhanced by stakeholder consultation to assist in speeding up considerations. Consumer organisations usually know which medications are causing their members financial distress and are a valuable source of information to assist prioritisation; however, it is important for the process to clearly identify those medicines listed in clinical guidelines, such as eviQ, rather than those in early access or compassionate access programs.

7. Are there other practical methods possible?

Option ii would be well supported by the creation of a Repurposing Subcommittee of TGA/PBAC which can actively review indications and passively receive requests for prioritisation of repurposed medicines review.

C. Prioritising candidates

Problem Statement: *There is a need for prioritising the 'right' medicines identified as candidates for potential repurposing to support an efficient pathway through regulation and reimbursement. It is recognised that different approaches would be required for on-patent and off-patent medicines.*

At this point, it is expected to follow at least four steps:
i. Criteria based requests:
ii. An independent expert committee prioritises these requests and recommends a range of candidates for progression at recurring meetings:

iii. A short-form assessment of existing information holdings is undertaken by the Department for the proposed candidates:
iv. An early assessment of probability for success will occur by the Department in conjunction with stakeholders:

8. What potential criteria or checks would support the intention to prioritise novel clinical uses over more traditional extension of indications

- Regularity of medicine use and number of novel purposes, including the necessity for the medicine to be used in multiple cycles of treatment. For example, olanzapine is used for the management of nausea and vomiting induced by chemotherapy used to treat multiple cancer types.
- Prioritisation of medicines by clinicians based on patient outcomes and best practice including the presence of medicines in clinical guidelines or standards of care, including those that prolong overall patient survival, or significantly improve a patient's quality of life or progression free survival in a cancer with few treatment options. The example of olanzapine highlighted above is recommended as best practice in clinical guidelines but is not registered or funded for the indication. If an indication for an older, cheaper medicine forms part of evidence-based care and is recognised in clinical guidelines it should just be added to the TGA/PBS listing.
- The type and quantity of out-of-pocket expenses borne by patients.

9. Would these criteria identify the most valuable candidates? Are there others that should be considered?

The criteria are reasonable; however, some additions and considerations would ensure the most valuable candidates for repurposing medicines are identified.

- The consumer voice needs to be included and would be of most benefit if they were included the independent expert committee.
- It would be helpful to consider different criteria for on-patent and off-patent medicines, or generically available medicines such as -:
    - On-patent medicines: It is imperative that commercial sponsors take responsibility for applying for extensions to indications especially where their medication is relatively new, is profitable and has become an internationally recognised standard of care. Clinical groups could play a role in developing guidance criteria when on-patent repurposing is required for truly rare cancers.
    - Off-patent medicines: the criteria suggested in the document with the inclusion of the criteria where a generic medicine is available or has been available in Australia.
- Whilst we support the changes presented in the repurposing medicines process it is important to consider the potential conflict of interest where the Department is providing additional support above and beyond what it ordinarily provides for registration or reimbursement as it could be seen to create a conflict. Policy design will need to ensure this can be managed.

10. In which phase should the patient perspective be a focus? What is the best process for this?

Patients have an important role to play across all phases of this process. There is increasing awareness amongst people affected by cancer of Food and Drug Administration (FDA) approvals of cancer medications. However, we are aware of a lack of understanding by people affected by cancer about how such FDA approvals relate to the Australian environment notably the TGA and PBS. Additionally, people affected by cancer tell Cancer Council, COSA, MOGA, and other consumer organisations they are confused and frustrated when medications, that are approved by the TGA for one purpose and subsequently recommended by evidence based clinical guidelines to provide optimal cancer care for their

circumstances, result in considerable out of pocket expenses as they cannot be reimbursed. Patients find this situation illogical, which often adds to the level of distress they already experience due to their cancer diagnosis and treatment. Patients often ask their clinicians and Cancer Council for clarity on why this occurs and are rarely satisfied with our explanations of Australia's medicines approval and reimbursement process. This situation is exacerbated when the medicine has been approved for use (and possibly reimbursement) for their indication by a similar international regulator. We find that directing patients to the TGA website is currently not helpful in meeting their needs, and that plain English and multimodal resources from the TGA, particularly addressing the Australian environment compared to international circumstances, would go some way to assisting in this situation.

Patients are well placed to assist in identifying and prioritising candidates for consideration of repurposing, however it is important to be inclusive of a broad range of patient experiences and input. Too often the same small number of consumers represent the patient experience to government organisations across policies and programs, and whilst their experience is valid, it is important for it to be enhanced by the experiences of people potentially less health literate, or with different and more diverse experiences, to gain a full insight into the issues faced by patients when they experience non-reimbursement issues with repurposed medicines. Strategies such as flexibility of engagement and timing, allowing patients to feed into decisions rather than only providing feedback, supporting the development of skills to engage with the process in priority or previously under-represented communities, and more work with non-traditional sponsors in community and healthcare will improve patient engagement in the process and provide a unique insight into real-world data. Codesigning engagement strategies with patients and more broadly, people affected by cancer, would increase the range and diversity of participants. The Medicines Australia agreement outlines a new process to incorporate patients' views and experiences early in the Pharmaceutical Benefits Advisory Committee (PBAC) assessment of medicines, which will help to make the full value of new medicines clear. In terms of what is important to patients, the repurposing medicines processes would benefit from strengthening the description of a patient centred approach.

11. At what stage should commercial factors be assessed? What is the best process for this?

The true cost of medicines with multiple reimbursable indications is not publicly known, and so the addition of another indication cannot be assessed with information currently in the public domain. Commercial factors are important and need to be considered in the context of improved patient outcomes; however, the detail regarding commercial factors is beyond the remit of Cancer Council, COSA and MOGA.

12. What type of skills/knowledge should an independent committee seek to have (noting not all areas of expertise can be available in a single committee)?

It is important for specialist clinicians, patients, and consumers to be included as members of an independent committee to provide real-world experience and evidence to enhance repurposing medicines applications.

Clinicians and clinician led organisations are well placed to provide information about quality use of medicines when they form part of clinical guidelines and best practice. A good example of this in practice is goserelin, a medicine used in prevention of early menopause. The improvement in cancer care was driven by clinicians who designed and implemented the clinical trial, effectively changing the clinical practice and improving patient outcomes. Clinicians have also been successful in lobbying for derestricting drugs. For example, in the case of the medicine pemetrexed, broadened access through the PBS allowed patients with lung cancer to be treated with the medicine as a first line treatment, and improved access to optimal cancer care.

This expertise allows clinical practice to inform equitable access to medicines to ensure people affected by cancer receive optimal cancer care. The skills clinicians bring include the articulation of countless impact stories of the patients they are treating, and the inequity they see in their practice settings. The

third consideration is the impact on clinician workload and patient time (the other hidden costs) when medicines need to be prescribed but are not reimbursable. One example of this is in the use of the granulocyte colony stimulating factor (G-CSF), a growth factor often used after chemotherapy to stimulate white blood cells or before or after stem cell treatment. The impact of G-CSF access on patients and clinicians is the added cost, time and in the supply and administration when treating Hodgkin lymphoma with dacarbazine based protocols (off-label use of dacarbazine in the two primary, dose dense treatment options for this curative cancer where G-CSF support is essential to avoid hospitalisation with febrile neutropenia and to maintain treatment intensity). Additionally, PBS restricted antiemetics such as aprepitant are also required for delivery of dacarbazine based protocols in Hodgkin lymphoma.

Patients and consumers (including people affected by cancer such as carers) are important members of a committee as they bring context to the decisions that are made at arm's length of the day-to-day impacts to Australians navigating our complex health system, burdened by a cancer diagnosis. The skills they would bring include the indirect impact of decision making, the experience of being required to choose between purchasing a medicine or meeting the daily living requirements for their families, and the ripple effect non-reimbursable medicines have on their household and wider community.

13. Should the Department (in conjunction with other groups) set priority therapeutic area foci?

Through review processes it would be logical for the Department to set priority therapeutic area foci, that is, particular focus in specific diseases where medicines are routinely repurposed to ensure patients receive best practice care. Clinicians and consumers are best paced to provide input into prioritisation, and it is important that rare diseases and cancers are a focus.

In cancer care there are many priorities and opportunities to make significant impacts with small changes, where medicines are already established as providing optimal cancer care in clinical guidelines. It may be helpful to divide medicines into categories such as curative (for example dacarbazine and mitomycin), adjuvant therapy (such as zoledronic acid) and key supportive care medicines that can save lives (such as infliximab used to treat immunotherapy toxicity).

D. Encouraging sponsors to apply by removing obstacles and/or providing incentives

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Problem statement: *There are obstacles for sponsors to overcome to register a new indication for a medicine. Provision of incentives are not the only actions required.*
The Department has identified the following actions it may take, based on the consultation to date and whether the produce is on-patent or off-patent

- *Provide priority review to enable a repurposed off-patent indication to be registered through an abridged application and evaluation process focusing on clinical efficacy, effectiveness and safety*
- *Waive or reduce application and evaluation fees where there is a limited commercial incentive to repurpose*
- *Provide regulatory exclusivity for a limited period to sponsor for repurposed indications for medicines that are on-patent*
- *Provide support to the development of a regulatory submission including early scientific advice and pre-submission meetings*
- *Provide coordinated support from the TGA and PBAC*
- *Collation of clinical evidence including real-world evidence, literature reviews, and sourcing reviews and dossiers form comparable overseas regulators and Health Technology Assessment (HTA).*

14. Are these actions the most important for sponsors?

Although Cancer Council, COSA and MOGA will not specifically comment on what is important to sponsors, we are united in supporting the introduction of a social licence to operate in the Australian health and medicines environment, where equitable patient access to optimal health care is put at the centre of decision making, incentivisation and other process requirements. Making repurposing medicines easier for sponsors by removing obstacles and providing appropriate incentives will benefit patients and improve equity of access. MOGA and COSA would be pleased to work with sponsors to ensure appropriate evidence is assembled, clinician input is provided, and patient needs and safety are considered.

15. What forms of coordination support from the TGA and PBAC would be most effective for sponsors?

As we have not acted as a sponsor, Cancer Council, COSA and MOGA are unable to provide advice on this question. It is a question appropriately addressed by sponsors.

16. Will giving an exclusivity period to a repurposed indication give incentive for sponsors to pursue a repurposing opportunity?

A question appropriately addressed by commercial sponsors.

17. How should they be funded?

Cancer Council, COSA and MOGA recommend that funding needs to be assessed in light of achieving optimal patient outcomes in Australia. The funding mechanisms is a matter that is outside the remit of our organisations.

18. Are there other options that should be considered?

We do not have further options to suggest.

19. Would there be interest in collaborative submissions by sponsors? Under what circumstances could this be attractive to sponsors?

With the goal of achieving optimal patient outcomes, COSA and MOGA would be willing to consider participation in a collaborative submission process should there be appropriate criteria and support in place to assist our participation.

20. Are there other practical options to overcome the socialised benefits in order to secure at least one application?

Beyond the remit of Cancer Council, COSA and MOGA.

21. What time period would be considered sufficient for sponsors to consider their interests and apply?

Beyond the remit of Cancer Council, COSA and MOGA.

Please feel free to provide any other information or suggestions that you may have.

Although touched on in this submission it is worth being specific about the recommendations by clinicians regarding the prioritisation of repurposing medicines to support equitable access to optimal cancer care for people affected by cancer. Consideration of some obvious candidates could be made with an immediate beneficial impact on patient outcomes. A summary of impact versus effort is listed below.

Medicine	Use	Issues/Impacts	Efforts for approval/ recommendations
Dacarbazine	Used commonly for curative cancer treatment.	At risk of becoming too expensive for patients despite being an in-hospital medicine	Requires a lot of effort to get TGA and PBAC approval under the current processes and has generic medicine available.
Mitomycin C	Used relatively infrequently for curative treatment for anal squamous cell carcinoma and bladder cancer.	Getting expensive despite being prescribed for in-hospital use and only needing one dose per cycle.	Requires a lot of effort to get TGA and PBAC approval under the current processes and has generic medicine available.
Valaciclovir	Widely used in cancer for varicella zoster virus prophylaxis	Is not too expensive ($26 for 30 tablets) and is accessible as an out of hospital medication.	Requires a lot of effort to get TGA and PBAC approval for repurpose. Suggest PBAC derestrict, with the existing sponsor continuing in the role.
Goserelin	Used in prevention of early menopause for cancer patients	Has a large impact and treats very common cancers. Driven by clinicians who had designed and implemented the practice changing clinical trial.	Suggest PBAC derestrict, with the existing sponsor continuing in the role
Zoledronic acid	Used as adjuvant treatment to prevent bone metastases in women with early breast cancer.	Has a large impact, is used in large volumes as it treats a very common cancer? It has been supported by BCNA and one of the generic companies, with clinician support, and is in the Early Breast Cancer Guidelines of Cancer Australia along with international guidelines.	Would take moderate effort to get through TGA. PBAC is still relevant although price is now $84 for a 4mg dose. Suggest PBAC derestrict, with the existing sponsor continuing in the role
Olanzapine	Used for the treatment of nausea and vomiting.	Moderate impact. Has multiple generics and is now only $23 for a pack of 28 of the 10mg dose. It is already on the PBS for psychosis.	Suggest PBAC derestrict, with the existing sponsor continuing in the role
Infliximab	Used for immunotherapy induced colitis.	Has a major impact, is an expensive medicine at around $1000/dose. It has a small volume use, often only requiring one dose as an in-hospital medicine	Clinicians understand it is unlikely to be derestricted yet. Requires a lot of effort to get TGA and PBAC approval under the current processes and has 3 generic medicines available.
Lenalidomide	Useful in more types of cancers than myeloma	Will be one of the next medicines to expand its indication when it reduces in price.	Is coming off patent soon.