Therapeutic Goods Administration consultation

Provisional Approval pathway for prescription medicines: proposed process and post-market requirements

Submission from the Clinical Oncology Society of Australia and Cancer Council Australia

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

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.

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Thank you for extending an invitation to Cancer Council and the Clinical Oncology Society of Australia to the stakeholder workshop held in Canberra on 20th April 2017. This workshop provided good insight into the development of the Therapeutic Goods Administration (TGA) Provisional Approval pathway. The workshop provided clarity to the issues raised in our joint response to the Expedited Review process consultation. Concluding remarks on the Provisional Approval pathway are provided below.

Pre-market registration process

Data requirements for the registration application:

The introduction of this formal pathway addresses the need for earlier access to promising therapeutic products, and reflects the necessary flexibility required of an expedited review process. The data requirements for applications considered via the provisional pathway, appropriately and critically continue to reflect the fundamental principles of safety, quality and efficacy.

Therapeutic product development for many cancer indications typically targets specific patients. Clinical trial methodology, recruitment and retention of trial participants required to generate comprehensive data has been a barrier to satisfying regulatory data requirements which has delayed registered access to promising treatment options. Previous challenges

associated with satisfying traditional regulatory data requirements will be reduced with the ability to submit evidence of efficacy based on validated surrogate endpoints, patient reported outcome measures, and/or data relevant to demonstrate the specific medicines' safety and efficacy.

Timeframe for the pre-market registration process:

Advice from the TGA indicates that the review of an application for provisional approval will meet the legislated timelines. However, increased administrative requirements and deliberation of uncertain or incomplete data, with the possibility of additional review by external experts or TGA sub committees, may impact on this goal. Timelines for review must be specifically documented, and the TGA must commit to ongoing and open communication with sponsors throughout the application and designation periods to manage the expectations of sponsors, health care professionals and consumers.

It is appropriate that provisional approval applications will receive priority review. However, applications considered under the full registration process should be informed of any potential impact to their scheduled review. The introduction of expedited review pathways should not delay any other products' introduction to market given that patient access is dependent on their approval also.

We recommend that a plan for the evaluation of the provisional approval pathway is developed. An initial evaluation should take place 12 months after the introduction of the pathway to identify whether applications are being reviewed in a 'timely' manner as per legislative timeframes and whether the program, and the timeframe, are meeting stakeholder expectations.

Factors influencing our decision-making:

The factors considered for the approval of a designation reflect the pathway's objective.

In addition, consideration of the following points would assist reviewers to determine the level of benefit against the potential risks:

- Link the severity, from a patient perspective, of the unmet need to the level of uncertainty in the clinical evidence;
- Identify the availability of alternative treatment options and the extent to which this product meets the needs of the patient, and/or the new medicines' capacity to enhance current treatment available;
- Patient perspective and considerations such as quality of life, reduction of toxicity, reduced side effect profile, and improved formulation.

Currently, unregistered therapeutic products can be prescribed on a case by case basis through existing schemes; however, this is complicated by conditions of the Pharmaceutical Benefits Advisory Committee (PBAC) and health insurance coverage. The PBAC will only consider applications for reimbursement from sponsors of products registered on the Australian Register of Therapeutic Goods (ARTG) as they has proved safety and efficacy. Therefore, in addition to ensuring the product's safety, this process contributes significantly to ensuring affordable access to products for patients. Although existing schemes, through the Special Access Scheme and Compassionate Access Scheme, have provided patients with early access to unapproved or off label products, ongoing access to products through these programs is at the discretion of the sponsor.

A product listed on the ARTG has a known safety profile. An application to extend the indication/s of a registered therapy could be streamlined by only requiring the review of

efficacy data of the product for the proposed new use. This would further reduce time to provisional approval. The TGA could request additional data where there are substantially different indications or the safety profile is questioned.

Post market requirements in the provisional registration period

Without the option to extend the designation, the two year lapse would be a barrier to comprehensive data collection. The efficiency of conducting clinical research to produce efficacy data could be subject to variables including, commencement of recruitment or retention of patients, ethics and governance process requirements, and establishment of agreements or arrangements with other jurisdictions.

Conditions of provisional registration:

The conditions of provisional approval must be specific to the product and its intended use, clearly stated, and jointly agreed between the TGA and the sponsor. The development of milestones, such as recruitment targets or progression free survival, provides clarity to the expectation and conditions of the provisional approval registration.

Essential conditions for post-market requirements must include:

- Commitment to the production of significant evidence of the product's effect on the intended population;
- Monitoring and reporting of adverse events;
- Risk reduction and minimisation activities including a duty of care to the patients within and beyond the data collection period.

The de-registration or narrowing of the product's indication is a significant concern. This will impact patients who have demonstrated a benefit or are concerned about the removal of access to the product. There should be a plan for continued access without disruption to the course of treatment, such as commitment by the sponsor to continue working with the TGA to provide access to the product for patients who have demonstrated benefit through Compassionate and Special Access Schemes.

The TGA must determine whether the sponsor's proposal for collecting confirmatory data is sufficient by:

- Assessing the feasibility of the proposed methodology to test the hypothesis, and that the factors to be measured are consistent with the understanding of the issue;
- Review of proposed milestones and end points indicating clinical efficacy;
- Use of patient reported outcome measures and appropriately weight this contribution to the assessment;
- Australian specific context activities may be required where the population or situation is unique to the Australian context, or where an application to the PBAC is intended;
- Detailed risk management plan.

Enhanced risk communication

Communication from sponsors:

The patient will be required to provide their consent to be involved in the collection of data to support a full registration application to be listed on the ARTG. The use of provisionally approved products, and recruitment to clinical trials requires the referring specialist to be aware of the product and its purpose. The decision to use a provisionally approved medicine in a treatment plan must be made with the specialist based on appropriate information.

The following must be discussed with the patient when considering the use of a provisionally registered product:

- The role of provisionally approved medicines, and how a medicine becomes provisionally approved, including that the:
  - earlier introduction of promising therapies to market access to fulfil an unmet clinical need is the primary benefit;
  - product is safe and that the primary purpose of ongoing research is to confirm efficacy;
- The collection of clinical information and its use to support full registration;
- The limitations and risks of a provisionally approved product, including that the product may become de-registered and discontinued, and communicate any assurances from the sponsor of ongoing access.

Communication from TGA:

The TGA must invest in a campaign to raise the awareness of the expedited review pathways, including provisional approval, to effectively engage with consumers and health care professionals, including pharmacists.

In addition to an awareness campaign, communication and public reporting of applications for new chemical entities or extension of indication through the provisional approval pathway should be consistent with current Australian Public Assessment Reports (AusPARs) for prescription medicines. It also may be appropriate to provide a rapid or consumer focused report.

Tracking and enforcement of registration conditions:

Reporting of adverse events, periodic risk evaluation documentation, and progress of confirmatory studies must be published on the website for transparency and to aid decision making by health care professionals and consumers in the use of provisionally approved product. The TGA is required to have the authority to raise concerns where issues of safety or efficacy emerge or where a patient is negatively impacted. The TGA must engage in activities which will identify adverse events or other variations related to the product's registration in overseas markets, and assess the influence these changes make on the products ongoing availability in Australia.

Lapsing or transition for full registration

Lapsing or extending provisional registration, and transitioning to full registration:

The TGA must encourage sponsors to recognise the benefits of registering the product, and to collect and submit the appropriate clinical data. Although current schemes enable access to unregistered products, these programs do not ensure sustainable and ongoing access to patients and they are not always provided at an affordable price.

The guidance document must detail the criteria and requirements needed to satisfy an application for the extension of provisional approval, and the scenarios for which a product may qualify for extension. Qualification should include evidence that continuation of the research will produce additional clinically meaningful data, and propose any revised timelines or milestones for the next period.

Legislative and regulatory amendment:

The consultation paper states that 'under Section 60 of the Therapeutic Goods Act 1989, a person whose interests are affected by certain TGA decisions may make an appeal to the

Minister for review of the decision.' The consultation paper acknowledged that appeal rights will be limited to the applicant, typically the sponsor, however, a patient accessing the product would also be considered a 'person whose interests are affected.' The TGA should consider any scenarios in which an individual or group may appeal the decision, although we acknowledge this may be uncommon.

Other feedback

The pathway must focus on reducing the impact of de-registration, or narrowing of indications on patients who have demonstrated clinical benefit. This should be in the form of clear communication about the possibility that the product will not receive full application, identify and communicate alternative access options, commitment from sponsors to exploring and assisting these patients with access, and to consider that access must encompass affordability of the product.

The impact of de-registration of the product or narrowing of indications will affect the continuation or ability to gain reimbursement through listing on the Pharmaceutical Benefits Scheme. The PBAC's Managed Access Scheme only applies to products that have sufficient efficacy and safety as reviewed by the TGA.