Australian Government
Department of Health
Therapeutic Goods Administration

Provisional determination eligibility criteria

Including supporting documentation

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TGA Health Safety Regulation

Contents

This guidance helps sponsors to understand the eligibility criteria and supporting documentation required for a medicine to be eligible for provisional determination.

To assist with the process of applying for provisional determination, please see Provisional determination: A step-by-step guide for prescription medicines.

Eligibility for provisional determination

If you have not had a pre-submission meeting with TGA to discuss your prospective application for provisional determination, or if your pre-submission meeting was more than six months ago, you should notify TGA of your intent to lodge a provisional determination application at least one month prior to lodgement. Consider all of the eligibility criteria and supporting documentation before notifying us.

Provisional determination may be granted for the following medicines only:

- a new prescription medicine which contains:
    a. a chemical, biological or radiopharmaceutical active ingredient that has not previously been included in the Australian Register of Therapeutic Goods (ARTG)

    OR

    b. a fixed combination of chemical, biological or radiopharmaceutical active ingredients at least one of which has not previously been included in the ARTG
- an already registered prescription medicine with a new indication (a new indications medicine) that:
    a. has the same chemical, biological or radiopharmaceutical active ingredient (or fixed combination of such ingredients) as another prescription medicine included in the ARTG

    AND

    b. does not have the same indications as that other medicine

Provisional determination eligibility criteria

A medicine may be eligible for provisional determination if **all** eligibility criteria in the table below are satisfied.

Eligibility criteria for provisional determination*	
1. Medicine	a new indications medicine **OR** a new prescription medicine
2. Serious condition	an indication of the medicine is the treatment, prevention or diagnosis of a life threatening or seriously debilitating condition **AND**
3. Comparison against existing therapeutic goods	either: i. no therapeutic goods that are intended to treat, prevent or diagnose the condition are included in the Register (except in the part of the Register for provisionally registered goods) **OR** ii. if one or more therapeutic goods that are intended to treat, prevent or diagnose the condition are included in the Register (except in the part of the Register for goods known as provisionally registered goods)—there is preliminary clinical data demonstrating that the medicine is likely to provide a significant improvement in the efficacy or safety of the treatment, prevention or diagnosis of the condition compared to those goods **AND**
4. Major therapeutic advance	there is preliminary clinical data demonstrating that the medicine is likely to provide a major therapeutic advance **AND**
Clinical study plan	the person who made the application under subsection 22C(1) of the Act has provided sufficient evidence of the plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years (starting on the day that provisional registration of the medicine would commence if the Secretary were to provisionally register the medicine).

*regulation 10L Therapeutic Goods Regulations 1990

Provisional determination

The provisional determination for a medicine is specific to the following (section 22D(3) of the Act):

- the person who is the provisional applicant
- the medicine
- each active ingredient of the medicine to which the determination relates
- the provisional indication

The provisional determination therefore applies to a specific medicine for a specific indication.

The indication proposed at determination may be different to that approved at the time of registration as a result of the assessment of the quality, safety and efficacy data submitted with the registration submission for provisional registration, but must be a related indication.

Provisional determination for one indication and one medicine

You can apply for only one indication and one medicine per determination application. If you are seeking determination for multiple indications or medicines, you must submit one application for each indication and/or medicine. A separate fee applies to each application.

Only one determination can apply to each registration application. A registration application that is a combination of provisional designated and any non-provisional indications will not be eligible for review under the Provisional pathway. You may lodge a separate submission where the scope of the submission is not covered by a provisional determination.

The determination will apply to the corresponding registration application for a new prescription medicine or new indications medicine.

You must apply for more than one determination if your product is for a combination treatment, but not a fixed dose combination.

In vitro diagnostic device use

If your provisional determination application is supported by clinical trials where an in vitro diagnostic (IVD) medical device was used to select patients who should or should not be treated, or to monitor patients with the aim of improving the safety or efficacy of the medicine, it is important that you supply the following information:

- specify the name of the IVD medical device and the name of the manufacturer of the device; and
- indicate whether the IVD medical device is an in-house IVD medical device (this includes the use of products that are intended by the manufacturer as being for research use only); and
- if the IVD medical device is included in the ARTG, provide the ARTG entry number and name of the sponsor; or
- if aware, provide details on any current application for inclusion of the IVD medical device in the ARTG; or
- if the IVD medical device is not included on the ARTG, we would appreciate an update on what steps the manufacturer of the medical device might be making to include the product in the register in Australia

Supporting documentation requirements

The main body of your application should be no more than 10 pages. Include additional supporting documentation as attachments.

Your application should include a cover letter and be based on preliminary clinical data that is promising evidence of efficacy and safety of the medicine.

- The main body of the application should address:
  - justifications for addressing all eligibility criteria
  - justification of any early, or surrogate endpoint(s) used to demonstrate clinical benefit specific to the condition that is subject of the application
  - overseas regulatory status
- Attachments should include:
  - sufficient evidence of a plan to submit comprehensive clinical data on the safety and efficacy of the medicine within the provisional registration timeframes and whether recruitment is completed, commenced, or not started for each study.
  - summaries of pivotal studies or appropriate study summary
  - summaries of any available other important safety data obtained in the preclinical and clinical setting
  - where published papers are highly relevant for the medicine, surrogate or early endpoint, the full text of such literature (including supplementary appendices)
  - other forms of literature references or unpublished reports and expert statements may also be used in addition to the pivotal study summaries but would be considered low-level evidence
  - an abbreviations list

Preliminary clinical data

The determination stage comes before the prescription medicine registration application (for further information refer to Provisional determination: A step-by-step guide for prescription medicines.

The determination application is based on preliminary data and a plan for comprehensive data that confirms predicted benefit and safety as early as possible in the provisional registration period.

Assessment of preliminary data could be based on:

- a non-validated surrogate endpoint
- a single arm study
- a non-randomised comparison
- an interim analysis/duration of study
- a small database
- recruitment from a narrow group of patients

Clinical data supporting provisional determination

For a provisional determination and subsequent provisional registration application, the clinical data available may be limited. For example, data on final outcomes such as morbidity and mortality may not be available yet and results may be based on surrogate endpoints that are reasonably likely to predict clinical benefit. The scientific evidence may therefore be less comprehensive than would typically be required, but needs to be adequate and convincing evidence based on clinical trials (usually randomised controlled trials).

We recommend that you support your application with justifications and as an appendix the pivotal clinical study synopses that would be included as part of the body of the clinical study reports intended to support the registration application. Also include a clinical study plan, including study protocols and top-line recruitment status. Where study synopses are not available, provide a summary of the study with detail comparable to a study synopsis. We do not require a full module 2 summary. Do not submit full study reports.

Where a surrogate endpoint is used it should be recognised to be reasonably likely to predict an effect on clinical outcomes that establish direct clinical benefit (for example morbidity and mortality). A surrogate endpoint does not need to be validated (i.e. be an endpoint that is known to predict clinical benefit and could be used for standard approval), but needs empirical evidence to support that it is reasonably likely to predict direct clinical benefit.

Submit a justification of the suitability of the surrogate endpoint with the application that considers:

- the ability to predict benefit based on evidence
- the strength of the evidence
- the certainty of the prediction
- why remaining uncertainties are considered acceptable

The appropriateness of a surrogate endpoint for provisional registration will be assessed in the determination application. Consideration will be given to evidence linking the surrogate endpoints to important clinical endpoints, and the clinical study plan that outlines the data that will likely be provided within the period of provisional registration. Whether an endpoint is reasonably likely to predict clinical benefit (i.e. the suitability of the endpoint) will be determined on a case by case basis. Appropriateness of a surrogate endpoint in one condition may not necessarily be appropriate for a different condition.

Choosing the most appropriate registration pathway

The use of a surrogate endpoint as a primary endpoint in a pivotal study of clinical efficacy/safety will not automatically require a registration application to be submitted through the Provisional pathway.

We will determine the appropriateness of a surrogate endpoint or early endpoint for provisional registration versus standard registration on a case-by-case basis. In the case of medicines treating rare diseases where the collection of comprehensive confirmatory data for submission at a later time may not be possible, the standard registration pathway may be more appropriate than the provisional registration pathway. These medicines would not be eligible for the provisional registration pathway if you are unable to demonstrate that you have a plan to collect comprehensive clinical data on the safety and efficacy of the medicine before the end of the provisional registration period.

We strongly encourage you to arrange a pre-submission meeting with TGA prior to lodging your determination application and include this as part of the agenda.

Addressing the criteria

We will determine the validity of your justifications against the eligibility criteria on a case-by-case basis. As part of the routine determination process, the extent to which criteria are met will be assessed at the time a decision is made on the application.

Criterion 1: New indications medicine or new prescription medicine

Only certain types of medicines are eligible for provisional determination. The medicine must either be a new indications medicine or a new prescription medicine, as described in regulation 2 (Therapeutic Goods Regulations 1990).

Criterion 2: Provide a justification of the life-threatening or seriously debilitating nature of the condition

Justify the severity of the disease in Australia (i.e. its seriously debilitating or life-threatening nature), based on objective and quantifiable medical information.

Your determination application must justify the:

- **life-threatening** nature of the disease or condition based on figures of mortality and life expectancy in Australia
- **seriously debilitating** nature of the condition based on morbidity over the course of the disease and its consequences on patients' day-to-day functioning

The serious debilitation or fatal outcome should be a prominent feature of both the target disease or condition and therapeutic indication, i.e. affect an important portion of the target population. The therapeutic indication is the proposed indication for ARTG registration, based on the proposed indication at the time of the determination application.

Criterion 3: Comparison against therapeutic goods registered in Australia for diagnosis, prevention or treatment

You must establish that:

i. there are no registered therapeutic goods for diagnosis, prevention or treatment of the condition in question included on the ARTG

   OR

ii. if such therapeutic goods are on the ARTG that the medicine will provide a significant improvement in efficacy or safety

Any reference to a registered therapeutic good must be limited to the conditions of the relevant ARTG entry. Therefore, a product that is administered or applied outside the approved product information (off-label use) cannot be considered a registered therapeutic good for the purposes of regulation 10L of the Therapeutic Goods Regulations 1990.

Provisionally registered goods on the ARTG are excluded from this comparison.

Registered therapeutic goods

You must review therapeutic goods included in the ARTG for diagnosis, prevention or treatment for the proposed indication in Australia, and provide:

- details of any registered therapeutic goods for diagnosis, prevention or treatment (overview table of Tradename(s), ARTG number, holder of the ARTG entry, and the registered indication)

  AND

- either a declaration that there are no existing therapeutic goods in Australia in accordance with ARTG entries at the date of determination lodgement

  OR

  a justification demonstrating a likely significant improvement in safety or efficacy against existing therapeutic goods

If the medicine is already registered for a similar condition, a justification that the new indication should be considered on a provisional basis should be provided.

Justification of significant improvement in safety or efficacy

You must demonstrate, based on preliminary clinical evidence, that the medicine provides a clinical benefit over existing therapeutic goods for the indication that is the subject of the determination application (for either treatment, prevention or diagnosis of the condition) by addressing either of the following:

- improved efficacy for the entire population relevant to the therapeutic indication

  OR

- a better safety profile for the entire population relevant to the therapeutic indication

If new goods for the diagnosis, prevention or treatment of your proposed indication are included on the ARTG after you lodge your application, you will have the opportunity to submit a further justification of significant improvement in safety or efficacy in relation to those goods before a decision is made on your application.

Base the supporting evidence on clinical trial data. Surrogate endpoints require a justification, as explained in Clinical data supporting provisional determination.

Comparator studies against registered therapeutic goods are expected to be generated (for pivotal study reports). Scientific argument/justification may be appropriate for demonstrating significant improvement in safety or efficacy of the medicine relative to products not studied in available clinical trials (this may involve cross study comparisons).

For a claim of improved efficacy or safety (eligibility criterion 3(ii)), we will evaluate whether there is a high probability that patients will experience a clinically relevant benefit on the basis of preliminary clinical data. Therefore, this claim must be supported by evidence from summaries of the pivotal study reports that form the basis of the intended provisional registration application, and the justifications you are required to submit. You must consider the evidence/data in light of the particular characteristics of the condition (life expectancy, symptoms, pivotal study surrogate endpoints) and the existing medicines for the treatment, prevention or diagnosis of the proposed therapeutic indication.

TGA will not assess significant improvement in safety or efficacy against comparators that are a subject of concurrent determination or registration applications, those that are the subject of a provisional registration submission that is under review by TGA, or medicines that are currently provisionally registered.

Consider diagnostic performance (sensitivity and specificity), predictive values and likelihood ratios, among other endpoints, for diagnostic agents. Further information is available in the Guideline on Clinical Evaluation of Diagnostic Agents. Justify safety in the same way as for all medicines.

Criterion 4: Justification of major therapeutic advance

You must provide a justification that there is preliminary evidence that the medicine is a major therapeutic advance based on the following aspects:

- the magnitude of the demonstrated improvement in safety and/or efficacy
- the likelihood of the early data or surrogate endpoints to predict clinical benefit
- the impact on patient outcomes taking into account both safety and efficacy
- the magnitude of the advance in relation to other therapeutic goods registered for the indicated population. Where no product is registered on the ARTG, the comparison should occur against the accepted standard of care
- the strength of the preliminary evidence, characterising the uncertainty (general TGA adopted guidelines about appropriate trial design apply)

You must include an assessment of the **magnitude** of the demonstrated improvement in safety or efficacy based on preliminary data (including surrogate endpoints). The demonstration of a medicine's clinically significant benefit based on improved safety and/or efficacy is not sufficient. Rather, there should be demonstration of a major benefit, i.e. beyond the level that could be described as clinically significant. Due to the uncertainty around the benefits and risks that are demonstrated by the available preliminary data, the observed effects would be expected to translate into a major clinical benefit in order to meet this criterion (for example a major improvement in mortality endpoints). Even if the benefit appears in one aspect only, you must assess the overall impact on patient outcomes taking into account both safety and efficacy.

The medicine should provide a therapeutic advance, in comparison with other registered therapeutic goods, where possible, by addressing a major or urgent unmet need for Australian patients in a substantial way. You must describe how and to what extent the medicine is expected to fulfil a major or urgent unmet medical need with reference to the therapeutic goods registered for the indicated population, the importance of the effects of the proposed medicine, and the added value of the proposed medicine.

The description of the strength of the preliminary evidence should include a brief outline of the main available evidence (for example number and type of clinical interim or final trials with clear delineation of pivotal versus supporting studies, sample size, design and key results) on which the claim is based. In the context of preliminary data, weak data evidence would be weighted less than comprehensive data evidence. See Justification of significant improvement in safety or efficacy for further information on cross study comparisons.

A medicine that demonstrates significant improvement in safety or efficacy may constitute a major therapeutic advance if for example, the medicine that demonstrates cure rates that are considerably higher than those observed in previous treatment options, while also replacing a standard treatment which has poor tolerability and potential for serious side effects.

Criterion 5: Clinical study plan

The purpose of the clinical study plan is to set out how you will achieve submission of confirmatory efficacy and safety data required for full registration. What constitutes sufficient evidence of a plan may vary from condition to condition. In all cases, the plan should address any uncertainties or identified gaps in data that would be required to transition the medicine from provisional to full registration on the ARTG within the registration period.

Ensure that supporting trials are designed and conducted in accordance with established international standards. Plan the pivotal studies to ensure that safety and efficacy, based on comprehensive clinical data, will be established as early as possible in the provisional registration period. In general, confirmatory trials should be fully accrued or near fully accrued following the end of the second round of assessment of the future related registration application. Please supply the recruitment status of the confirmatory clinical studies, whether completed recruitment, in progress or the recruitment is yet to start. Depending on the medicine and indication the extent of the level of accrual will be a consideration for eligibility.

You may provide very early studies as supporting documentation but these cannot be considered pivotal confirmatory studies.

Clinical study plan for provisional determination

You are required to provide sufficient evidence of a clinical trials plan to submit comprehensive clinical data on the safety and efficacy of the medicine within the provisional registration period. This will be required to be updated at various milestones during the registration process and in the provisional registration period.

The clinical study plan for provisional determination application provides an example of the types of information that you could include in your clinical study plan.

Clinical study plan for provisional determination application

Study and *Status*	**Summary of objectives**	**Confirmatory nature** **(i.e. uncertainty addressed)**	**Key milestones**	**Recruitment status**	**Proposed submission date**
Clinical Trial Study ID ##### *Ongoing*			*e.g percentage of target number of patients meeting a primary endpoint;* *e.g. accrual status as percentage of planned enrolment:* - *not started;* - *started (ongoing or delayed-revised end date ;* - *complete*		
Patient registry Study ID #### *Planned*					

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Prescription Medicines Authorisation Branch	March 2018
V1.1	Minor edit Update to currency of data required for criteria assessment	Prescription Medicines Authorisation Branch	April 2021

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