Busting myths about the assessment pathway for new treatments for rare diseases

It might be easier than you think!

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What I will cover today:

- What's changed?
- The fast track pathways
  - Priority
  - Provisional
  - COR A and B
  - International work sharing
  - Orphan drug program
- Uptake of the new pathways

What's changed for prescription medicines?

What we used to have:

- Prescription medicines registration pathway – 'standard pathway'
- Category 2 pathway – 175 day statutory timeframe if reports from 2 overseas regulators could be provided and other eligibility criteria met
- TGA worked with sponsors to facilitate early access (via informal process) – in exceptional circumstances e.g. significant therapeutic advance or emergency situations

What we have now:

- Multiple pathways for faster approval ranging from 120-220 target working days – formalised processes

Fast track approval pathways

An overview

Faster evaluation ***months earlier***	• **PRIORITY REVIEW** • **COR A and B** • **Work - sharing (e.g. Project Orbis with US FDA)**
Approval on basis of earlier data ***years earlier***	• **PROVISIONAL APPROVAL** • benefit of availability outweighs risk, time limited registration. • Sponsor obligation to provide confirmatory data
Mechanism for sponsor's to receive early advice	• Pre-submission meetings available

Australian perspective

- Aim to increase options for Australian patients
- Limit regulatory burden on sponsors and the regulator

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Priority and Provisional

- To facilitate earlier access to medicines that address unmet clinical needs for Australians, without compromising standards for safety, efficacy and quality.
- Two new ‘expedited’ pathways for prescription medicines based on the government response to the recommendations of the MMDR review:
  - **Priority Review** of a complete data dossier within a reduced timeframe in certain circumstances

    Implemented July 2017
  - **Provisional Approval** on the basis of early data on safety and efficacy, where the immediate availability of the medicine outweighs the risk that more data is required

    Implemented March 2018

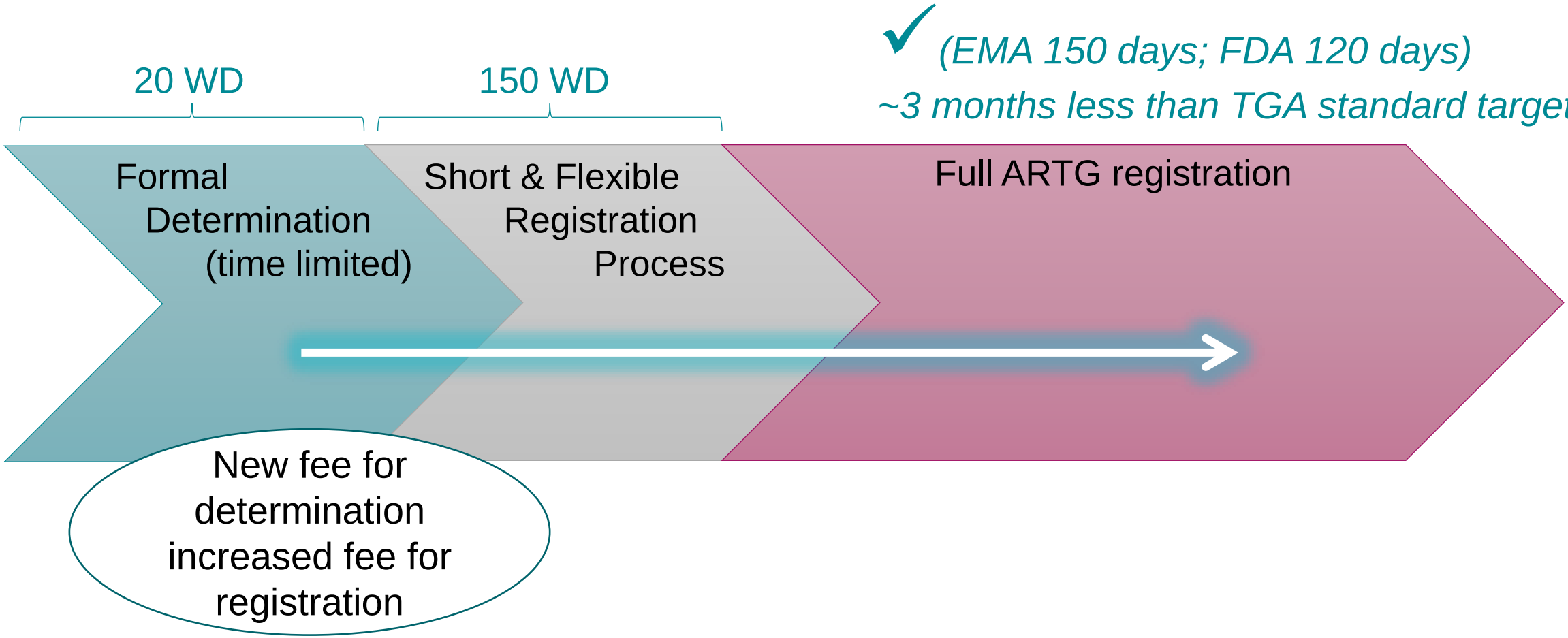
Determination process

- A determination must be approved by the TGA before the sponsor can lodge a submission for registration via the priority or provisional pathway
- Determination is a formal process to assess against the eligibility criteria
- Determinations lapse after 6 months
    - 1 extension possible for provisional; priority determinations cannot be extended
    - Positive determination decisions are published on the TGA website: https://www.tga.gov.au/designation-notices
- Negative determination decisions can only be appealed by the sponsor of the prescription medicine

Priority review pathway

✓ *(EMA 150 days; FDA 120 days)*

~3 months less than TGA standard target



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Provisional pathway

1. Determination process

3-6 months pre-dossier

2. Pre-market registration process

As quickly as possible (max. 255 working days)

3. Provisional registration period

2 years initially (with the possibility of 2 extensions of 1-2 years each)

4. Transition to fully registered

As quickly as possible (max. 255 working days)

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International collaboration and work sharing

- COR-A and COR-B: Use of assessments from comparable overseas regulators (CORs) to support TGA regulation decisions. Two processes (COR-A = 120 working days; COR-B = 175 working days)

- ACSS: Consortium of 'like-minded' regulatory authorities (Australia, Canada, Singapore, Switzerland). Involves collaboration between regulators for information and work-sharing initiatives. Sponsor initiated. Open to NCEs and NBEs submitted to TGA, with most evaluation pathways available.

- Project Orbis: Innovative evaluation process to collaboratively review applications with the US and Canada. This is used for new oncology medicines and is facilitated by the US Food and Drug Administration Oncology Centre of Excellence and Health Canada. Jurisdictions identify candidate products and approach the sponsor. Singapore and Switzerland are now also engaged in Orbis.

COR report based process

Aim:

- reduce duplication of evaluation effort
- maintain Australian jurisdictional autonomy.

Two approaches:

- COR-A 120 working days
- COR-B 175 working days

depending on extent of TGA evaluation required.

COR report-based process – prescription medicines

COR-A and COR-B application checklist

You must complete and submit this checklist as part of your Module 1.2.1 application form. This will enable the TGA to assess whether the application is eligible for the COR-A or COR-B process. If certain criteria are not met, the application can then only be submitted as a Category 1.

See guidance on the COR report-based process for further information.

Criteria	Checklist
General	
The assessment package is from a comparable overseas regulator (COR), as published on the TGA website. **Note**: Overseas approval older than 1 year is only eligible for COR-B.	Yes ☐ Name of COR: Choose an item. Date of approval:
The application meets the following general application criteria: • The COR assessment package relates to a *de novo* evaluation for full marketing approval of the medicine (i.e. not provisionally approved). • The COR assessment package is complete, in English and unredacted.	Yes ☐ eligible for COR-A or COR-B No ☐ not eligible for the COR report-based process.

COR Country	Regulatory authority
Canada	Health Canada
Japan	Pharmaceuticals and Medical Devices Agency (PMDA)
Singapore	Health Science Authority Singapore (HSA)
Switzerland	SwissMedic
United Kingdom	Medicines and Healthcare products Regulatory Agency (MHRA)
USA	Food and Drug Administration (FDA)
COR Jurisdiction	**Regulatory authority**
European Union	European Medicines Agency

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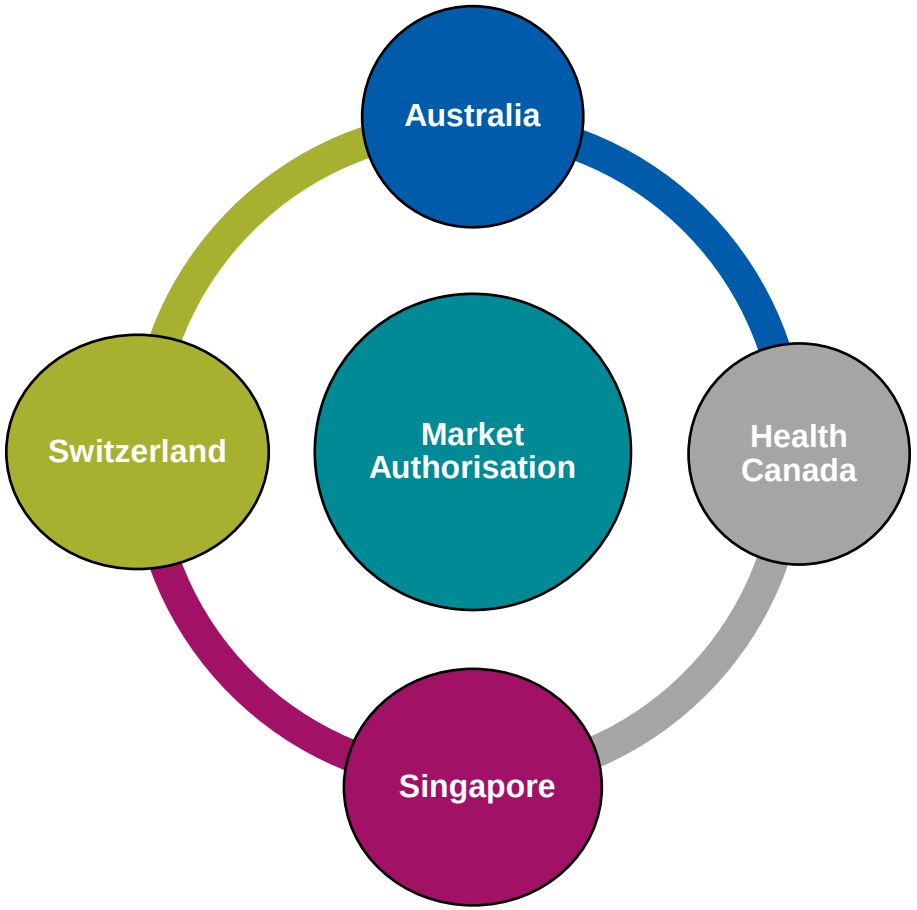
International work sharing



- An alternative to COR A/B submission pathways
- Promotes greater regulatory collaboration between international regulators
- ACSS explores opportunities for work-sharing through various working groups.
- Supported by confidentiality agreements & existing MOUs
- Work-sharing of evaluation phase only with sovereign decision relating to market authorisation

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ACSS CONSORTIUM
AUSTRALIA
CANADA
SINGAPORE
SWITZERLAND

Orphan Drug Program

Objective

- To provide an incentive to sponsors to bring medicines for a small population to market and make medicines available to patients who would not otherwise be able to access them.

Rationale for reforms (implemented 1 July 2017)

- Better reflection of population growth
- Potentially allows more diseases to be classified as rare
- Focuses consideration on the greatest unmet need
- Maintains a viable orphan drug program into the future

Information/guidance

- *Orphan drug program reforms: https://www.tga.gov.au/orphan-drug-program-reforms*
- *New Orphan Drug designation eligibility criteria (guidance) https://www.tga.gov.au/publication/orphan-drug-designation-eligibility-criteria*
- *Orphan drug designation: A step-by-step guide for prescription medicines https://www.tga.gov.au/publication/orphan-drug-designation*

What has the uptake been like?

With the new pathways having been in place for a while now, we are starting the see the results

- Increasing application numbers
- Reduced evaluation times
- Greater connection with overseas regulators
- Better patient outcomes
- 20 Orphan registrations in 2019 (1 in 2020)

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Priority Review Registrations

Implemented 1 July 2017

Calendar Year	Number of Priority registrations	Average days to approval
2018	12	112
2019	8	125

* As of February 2020: 3 Priority review designation approvals

Provisional Registrations

Implemented March 2018

Calendar Year	Number of Provisional registrations	Average days to approval
2019	6	110

*As of February 2020: 1 Provisional review designation approval

COR A and COR B approvals

Implemented January 2018

COR A

Calendar Year	Number of registrations COR-A	Average days to approval
2018	1	40
2019	2	55

COR B

Calendar Year	Number of registrations COR-B	Average days to approval
2018	0	-
2019	8	146

International Work Sharing 2019

ACSS AND PROJECT ORBIS Approvals 1/1/2019-31/12/2019

Product Name	Active Ingredient	Registration Date	Working Days	International Work Sharing Type
Verzenio	Abemaciclib	08/04/2019	141	ACSS
Zejula	Niraparib (as tosilate monohydrate)	28/06/2019	180	ACSS
Lenvima	Lenvatinib (as mesilate)	17/09/2019	54	Orbis
Keytruda	Pembrolizumab	17/09/2019	54	Orbis
Calquence	Acalabrutinib	21/11/2019	73	Orbis

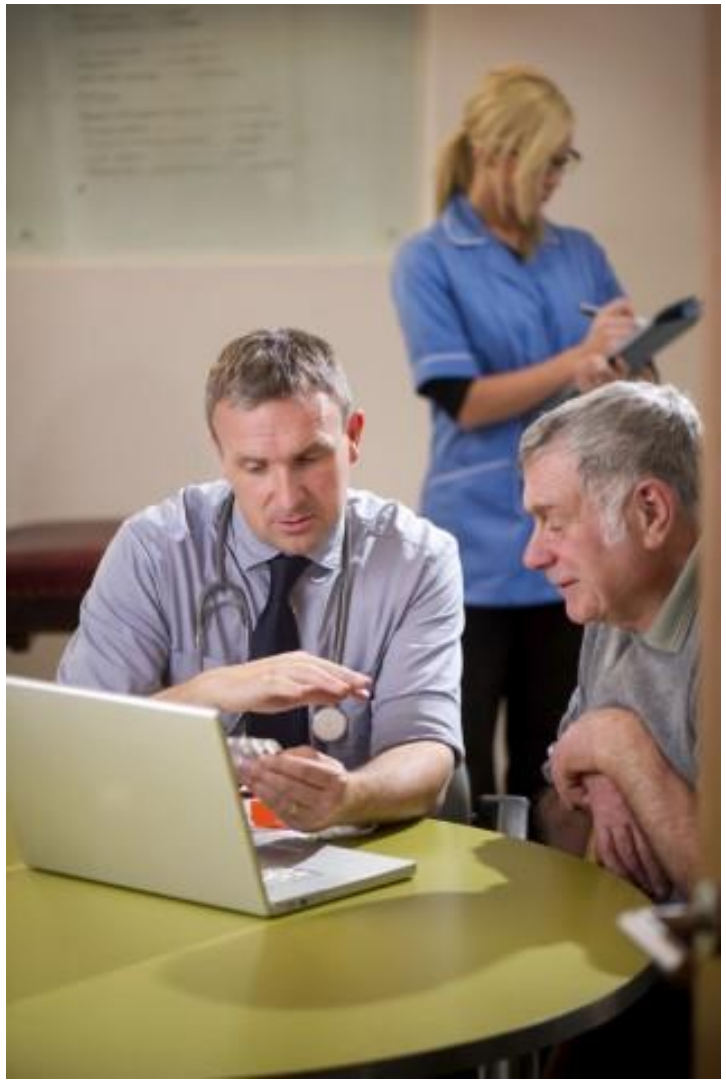
International Work Sharing 2020

ACSS AND PROJECT ORBIS applications with approvals in 2020

Product Name	Active Ingredient	Registration Date	Working Days	International Work Sharing Type
Xofluza	Baloxavir marboxil	21/02/2020	161	ACSS
Nubeqa	Darolutamide	26/02/2020	220	ACSS

Access to unapproved goods

- Why are some products not on the ARTG?
  - Not profitable in Australia
  - Australian version not available
  - Withdrawn from market due to safety concerns
  - Unproven therapy or new therapy
  - Individualised medicine/device i.e. Extemporaneous compounding, custom made devices
- There are several options for access to non-ARTG products:
  - Clinical Trial
  - Special Access Scheme (SAS)
  - Authorised Prescriber Scheme (AP)
  - Personal Importation



Clinical trials in Australia

Clinical trials conducted in Australia are subject to various regulatory controls to ensure the safety of participants. We regulate the use of unapproved therapeutic goods supplied in clinical trials in Australia under the therapeutic goods legislation.

Clinical trial sponsors must be aware of the requirements to import, export, manufacture and supply therapeutic goods in Australia.

The following avenues provide for the importation into and/or supply in Australia of 'unapproved' therapeutic goods for use in a clinical trial:

- Clinical Trial Notification (CTN) scheme (usually for low risk trials)
- Clinical Trial Exemption (CTX) scheme (usually for high-risk trials e.g. gene therapy)

Clinical Trial Notification Scheme (CTN)

- The Australian clinical trial sponsor must notify us of the intent to sponsor a clinical trial involving an 'unapproved' therapeutic good.
- We may give the sponsor of the trial written notice to provide specified information relating to goods.
- We do not evaluate any data relating to the clinical trial at the time of submission. The Human Research Ethics Committee (HREC) reviews the scientific validity of the trial design, the balance of risk versus harm and the ethical acceptability of the trial process.
- The institution or organisation at which the trial will be conducted gives the final approval for the conduct of the trial at the site, having due regard to advice from the HREC.
- Under **Schedule 5A item 3(e) of the Regulations**, we can direct the trial to not be conducted if we become aware that the trial is contrary to the public interest (e.g. a trial that carries an unacceptable risk of death, serious illness or serious injury)

Clinical Trial Exemption Scheme (CTX)

- We evaluate summary information about the product including relevant, but limited, scientific data (which may be preclinical and early clinical data) prior to the start of a trial.
- The HREC is responsible for considering the scientific and ethical issues of the proposed trial protocol.
- The sponsor must notify us of each trial conducted using the unapproved therapeutic good(s) approved in the CTX application.
- We can revoke an approval of a clinical trial where the conditions of approval are not met.
- Offence provisions may also apply where goods which are the subject of a CTX approval are not used in accordance with that approval or a statutory condition made under subsection 19(4A) of the Therapeutic Goods Act 1989.

Clinical trials and Australia

Australia ranked as country with third most clinical trials planned for 2020 (Global Data; 2173 trials planned):

1. USA (20% of trials)
2. China
3. Australia (4.6%)

Duchenne muscular dystrophy
Clinical trials recruiting in Australia

ANZCTR clinical trial registry Australia and New Zealand (accessed 27/2/2020)

A non-randomised Phase III study to evaluate the effectiveness of Deflazacort in boys with Duchenne muscular dystrophy in improving muscle strength and function and minimising side effects.

Recruiting | Ethics status: Approved | Retrospectively registered | Not up to date (Last updated: 22/8/2007)

The Duchenne Registry Australia - a patient registry to collect information about Australians with Duchenne or Becker muscular dystrophy and female carriers of these conditions

Recruiting | Ethics status: Approved | Prospectively registered | Not up to date (Last updated: 3/5/2018)

A randomized phase III study to evaluate the effectiveness of two different dosing regimens (high dose vs daily) of Prednisone for boys with Duchenne muscular dystrophy in improving muscle strength and function and minimising side effects.

Recruiting | Ethics status: Approved | Retrospectively registered | Not up to date (Last updated: 22/8/2007)

Duchenne muscular dystrophy
Clinical trials recruiting in Australia

From ClinicalTrials.gov- a database of clinical trials conducted across the world (accessed 27/2/2020)

A Study to Assess the Efficacy and Safety of Vamorolone in Boys With Duchenne Muscular Dystrophy (DMD)

Recruiting — Up to date (Last updated: 13/2/2020)

Long-Term Outcomes of Ataluren in Duchenne Muscular Dystrophy

Recruiting — Up to date (Last updated: 5/2/2020)

Study of SRP-4045 and SRP-4053 in DMD Patients

Recruiting — Up to date (Last updated: 11/2/2020)

Special Access Scheme summary

Category A

- Medical Practitioner
- Single Patient
- Patient Meets Category A Definition

Category C

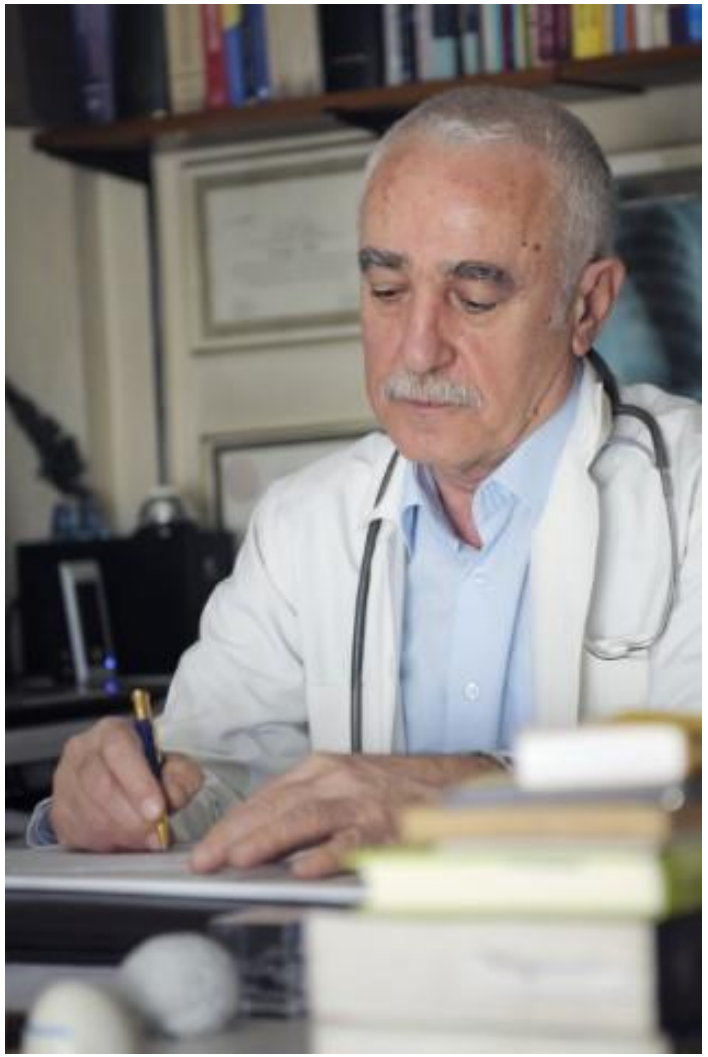
- Health professional type, product and indication included on SAS C legislative instrument list
- Established history of safe use
- Single patient

Category B

- Health Professional
- Single Patient
- Product not on SAS C list
- Patient does not meet SAS A definition

Authorised Prescriber Scheme

- The Authorised Prescriber Scheme allows doctors to be granted special authorisation by the TGA to order and legally prescribe a non ARTG product to appropriate patients
- Application form requires ethics committee/specialist college support for the doctor
- Patient being treated must be under immediate care of authorised doctor
- The doctor must provide supply report to the TGA every 6 months



Questions?