2019 REPORT
FUNDING MEDICINES FOR RARE DISORDERS

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Contents

Executive Summary 3
Part 1: The international context 5
Defining rare: the rare disorders paradox 5
Health system barriers 5
The 'Diagnostic Odyssey' 5
Difficulties in access to care, support and coordination of care 6
Lack of medical expertise in rare disorders 6
Lack of effective medicines and issues of cost 6
The New Zealand context 7
Medicines access: International policy settings 7
Australia 7
International comparisons 8
Part 2: Access to rare disorders medicines in New Zealand 10
Funding mechanisms 10
Pharmaceutical Schedule listing process 10
Exceptional Circumstances Framework 11
Funding pilot for rare disorders medicines 11
How the rare disorders funding pilot worked 12
Evaluation and analysis of the rare disorders funding pilot 14
Successes from the funding pilot 14
Limitations of the funding pilot 15
Analysis of rare disorders medicines funded by PHARMAC 16
Part 3: PHARMAC's ongoing commitment to funding medicines for rare disorders 18
Adjusted policy settings 18
Establishment of specialist clinical advisory committee 20
Regular call for funding applications 20
Dedicated pre-engagement with suppliers 22
Regular portfolio review and horizon scan of rare disorders medicine 22
Appendix 1: The New Zealand Context 23
Appendix 2: Limitations of analysis for figures shown in Table 2 27
Reference List 28

Executive Summary

Meeting the health needs of people with rare disorders is a challenge faced by jurisdictions around the world. There are several well-documented and common health system barriers that disproportionately impact people with rare disorders, with many of these barriers being collectively unique to this population. These include challenges in getting a diagnosis, access to support and coordinated care, scarcity of medical expertise and a lack of effective and affordable medicines.

Different jurisdictions have attempted to overcome these barriers through changing policy settings. The United States and European Union have lowered the bar for market access for medicines for rare disorders. This has incentivised more suppliers to develop medicines for rare disorders, but with the unintended consequence that these medicines are becoming increasingly exorbitantly priced due to a lack of competition in the market and the small size of the potential market. Perhaps influenced by increasing medicines prices within this small market, most countries of particular relevance to New Zealand, notably Australia, Scotland and England, have updated their funding mechanisms and methods of evaluating medicines for rare disorders since 2017.

New Zealand's pharmaceutical management agency, PHARMAC, has been grappling with the same challenges. The broader health system challenges are somewhat exacerbated by New Zealand's small population size and geographical isolation. PHARMAC's role in the New Zealand health system is to decide what medicines to publicly fund, and access to medicines for rare disorders has been a contentious issue in the public and political realm for many years.

PHARMAC currently funds medicines for rare disorders through three mechanisms:

- The Pharmaceutical Schedule listing process – the standard process for deciding which medicines to fund at the population level, within its fixed budget, that will achieve the best health outcomes for New Zealanders.
- The Exceptional Circumstances Framework – a pathway for considering medicines funding applications for individual patients that fall outside of the Pharmaceutical Schedule listing process due to the individual's unique clinical circumstances.
- The rare disorders medicines contestable funding pilot – a pilot process that PHARMAC initiated to stimulate competition amongst suppliers of rare disorders medicines, with the outcome being the funding of 10 new medicines listed on the Pharmaceutical Schedule.

The successes and insights garnered from the pilot process have resulted in some permanent changes to PHARMAC's policies and processes to try to address the system barriers relating to access to medicines for rare disorders. This includes:

- Adjusted policy settings for rare disorders medicines that are considered through PHARMAC's usual processes. Most significantly, this includes the

removal of the requirement for Medsafe[1] approval prior to PHARMAC consideration and clarifying the definition of 'rare' in relation to the patient group and the medicine.

- Establishment of a rare disorders expert clinical subcommittee of the Pharmacology and Therapeutics Advisory Committee (PTAC), specifically to consider funding applications that meet PHARMAC's definition of 'rare'.
- A regular call for rare disorders medicines funding applications, to encourage suppliers to enter the market and to continue to stimulate competition amongst suppliers.
- Dedicated pre-engagement with new, as well as existing, suppliers prior to each call for rare disorder medicine funding applications.
- Regular horizon scanning for rare disorder medicines coming down the development pipeline.

PHARMAC considers the introduction of these permanent changes to its policies and processes to be a significant step forward in enabling people with rare disorders to have access to medicines. However, there remain issues to be addressed at the broader health system level, and medicines suppliers also need to be more responsive to the needs of these patient groups through making their medicines more affordable.

[1] Medsafe is New Zealand's medicines and medical devices safety authority, the medical regulatory body run by the Ministry of Health.

Part 1: The international context

Defining rare: the rare disorders paradox

Jurisdictions around the world are grappling with the challenge of meeting the often-high health needs of people with rare disorders. Complicating the landscape of rare disorders is that the term 'rare' is not consistently described. Various definitions of 'rare' are used across different jurisdictions, from one person affected in 1,600, to one person in 50,000 (1), (2), (3). Collectively it is estimated there are between 5,000 and 8,000 specific rare disorders (4).

Differences in the definition for rarity have a significant impact on which disorders are considered rare, as well as the total population impacted by the collective group of rare disorders. For example, using an expansive definition of rare, Rare Disorders New Zealand (previously known as the New Zealand Organisation for Rare Disorders (NZORD)) estimates that almost 8 percent of the NZ population could be living with a rare disorder.[2] This raises a challenging paradox for rare disorders, in that though by definition each disorder is rare, the collective group of disorders affect a significant number of individuals and whānau (5).

Health system barriers

There are several well documented and common health system barriers that disproportionately impact people with rare disorders. Many of these barriers are unique to this collective population. Access to medicines that are clinically effective and affordable is only one of the many health system barriers.

The 'Diagnostic Odyssey'

International literature from Europe, the United States, the United Kingdom, Ireland, Canada and Australia report that people with a rare disorder commonly experience long delays, often years, in obtaining a diagnosis. They can receive many misdiagnoses and undergo inappropriate and sometimes harmful medical interventions before obtaining a correct diagnosis, often consulting multiple specialists and in turn experiencing delays in treatment (6), (7), (8), (9), (10). For people with a rare disorder, having a lack of diagnosis is often a major barrier to accessing care, resulting in the 'diagnostic odyssey' (the process of time and effort to obtain a diagnosis and treatment plan) (8), (11), (12).

The Royal College of Physicians of Ireland notes that many rare disorders have a serious incapacitating and chronic nature, often associated with multiple disabilities including physical, sensory and intellectual disabilities. Moreover, due to the rarity of these conditions and often a lack of national expertise, a diagnosis is often delayed for many years. This is associated with significant hardship for individuals and whānau. The report notes that accurate and timely diagnosis and access to treatment for individuals with rare disorders is severely hampered by their lack of recognition and visibility in healthcare systems.

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[2]New Zealand Organisation for Rare Disorders estimate

Difficulties in access to care, support and coordination of care

The international literature from many comparable jurisdictions reports that challenges for patients with a rare disorder often include: difficulties in finding and accessing the right specialists; a lack of appropriate health services, skilled health professionals and treatment options; a lack of clear communication between different service providers and poor coordination of care; and limited availability of peer and community support services (8), (13), (7).

It should also be noted that there are costs in relation to administering medicines, such as those that require the person to undergo regular infusions. These costs, although important to highlight, are not the focus of this paper.

Lack of medical expertise in rare disorders

The World Health Organization (WHO) notes that as people with rare disorders are scattered across countries, medical expertise for each of these disorders is a scarce resource (14). With a relatively small number of people with each rare disorder, understanding of potential diagnosis and possible therapeutic options are beyond the scope of many health professionals who treat these individuals (8).

Lack of effective medicines and issues of cost

In January 2018, EURODIS Rare Diseases Europe published a position paper 'Breaking the access deadlock to leave no one behind' highlighting their experience from "countless examples" where the price of a new medicine had been the major barrier to agreement between manufacturers and funders. This has had potentially dramatic consequences for people in need of access to these medicines (15).

The prices of rare disorder medicines was also highlighted in a paper in the Lancet in 2018 (16), where concerned professionals in Europe called for new legislation and provided recommendations to redress the balance between the profit the pharmaceuticals industry expects and the costs that health services can bear.

Alongside the high cost, many of these medicines do not perform well following health economic analysis when compared with other medicines (17). In many instances the evidence supporting rare disorder medicines is poor quality and low strength (18). Further, the research supporting the medicine may have small study populations or use interim or short-term results to infer the long-term health benefit of a medicine. This makes it difficult for funders to determine the value of rare disorder medicines.

The WHO notes one of the challenges with medicines for rare disorders is ongoing research into the disease process to discover more targets for drug development for a specific rare disorder. This, combined with making a disorder easy to diagnose at an early stage, will allow the development of prevention strategies that even in the absence of an underlying treatment can have a positive impact on a person's life (14). The WHO also advises that clinical trial funding programmes remain essential for rare disorder medicines development, especially for rare disorders that appear less attractive for the pharmaceutical industry (14).

The New Zealand context

New Zealand's relatively small population, and its geographical dispersion and isolation, exacerbates the challenges being faced by many other countries. For example, New Zealand has only a handful of specialists able to manage specific conditions, which means that diagnosis and subsequent support and treatment can be more time consuming and challenging.

In terms of access to medicines, the very small patient population provides little incentive for pharmaceutical suppliers to enter into the market in New Zealand, taking into account regulatory costs. Further, limited competition between suppliers reduces the commercial levers available to influence pricing. These two elements have been core to the changes PHARMAC has made to enhance the accessibility of medicines for people with rare disorders. This is discussed in more detail in Parts 2 and 3.

Medicines access: International policy settings

Access to medicines for rare disorders can be problematic for various reasons, as discussed above. From a medicines funding perspective, the biggest issue is that medicines are often very highly priced relative to their efficacy. High launch prices of 'new' medicines have become a matter of global debate (19), (20), (21). With no competition for branded products that are on patent, or for which there are no alternative medicines available, suppliers can command premium prices.

This has been exacerbated by changes to policy settings in the United States where the orphan drug legislation and Food and Drug Administration (FDA) has lowered the bar for entry into this market and provided significant incentives for suppliers to develop treatments for rare disorders, but which have not corresponded to improvements in orphan drug pricing (22), (16). Similarly, in the European Union orphan medicines regulation, which was introduced to encourage the development of medicines for rare disorders, has also had the perverse outcome of driving up prices as medicines gain monopoly of the market (16), (23).

Perhaps influenced by the ripple effect of increasing medicines prices within these influential markets, most jurisdictions of particular relevance to New Zealand have updated their funding mechanisms and methods of evaluating medicines for rare disorders since 2017. A more detailed summary of changes in Australia is explained below. The table in the subsequent section provides a breakdown of changes in several countries.

Australia

Australia recently reviewed its Life Saving Drugs Programme (LSDP), which provided access to essential and very expensive medicines for eligible people with rare and life-threatening disorders. Medicines funded through the LSDP included high cost medicines that did not meet the comparative cost-effectiveness criteria for funding through the Pharmaceutical Benefits Scheme (PBS). Sustainability was identified as a risk to the LSDP, with an average annual growth rate of the LSDP from 2009/10 to 2013/14 of 12.68 percent, compared with the average expenditure for all medicines growing at a rate of 2.18 percent

for the same period (24). In 2014/15 the LSDP treated 289 patients at a cost of approximately $85.9 million (25).

The outcomes of the review included 10 recommendations, of which seven have been adopted, including (26):

- adopting a definition of 'rare disease' that is a disease prevalence of 1:50,000 people or less in the Australian population (around 500 people);
- the development of explanatory materials to support the criteria, specifying that lifesaving medicines are those that extend lifespan;
- the implementation of more transparent and rigorous clinical efficacy and cost effectiveness assessment of medicines through the establishment of an Expert Panel, to provide advice and assistance to the Commonwealth's Chief Medical Officer;
- the introduction of a mechanism where medicines listed on the LSDP will be subject to a review of usage and financial costs after 24 months, to ensure a medicine's usage and performance is in line with the recommendations and expectations at listing and in line with recommendations of the Chief Medical Officer and the Expert Panel. Over the first two years from the commencement of the new programme (1 July 2018), similar reviews will be undertaken on all existing LSDP medicines;
- negotiated application of pricing policies to new and existing medicines on the LSDP, as per those applying to PBS listed medicines; and
- streamlining administration of the LSDP and implementing cost recovery arrangements from sponsors for listing considerations and management of their agreements (27).

There are similarities between Australia and New Zealand in terms of the recent policy changes. Both countries have adopted the same definition of 'rare', as well as Australia increasing the rigour around assessment of clinical efficacy and cost effectiveness of proposed medicines, and the introduction of a specialist committee to provide advice to the decision maker (in this case the Commonwealth's Chief Medical Officer).

Of the 16 medicines currently funded on the LSDP for the treatment of 10 conditions, PHARMAC has considered applications for all but one of these medicines. Six of the medicines are currently funded on the New Zealand Pharmaceutical Schedule with funding criteria targeting treatment to some patients with a rare disorder. Five medicines have been recommended for decline by PHARMAC's expert clinical advisors. One medicine has been recommended for funding and is currently ranked as a future funding option. Individual patient funding applications have also been considered under PHARMAC's exceptional circumstances framework.

International comparisons

The table below provides a summary of some of the similarities and differences in policy settings of different countries

Table 1 : International definitions and funding processes for rare disorders medicines

Country	Definition of 'rare'	Separate process for rare treatments	Separate fund for rare treatments	Altered decision criteria	Decision maker
Australia	A disease prevalence of 1:50,000 people or less in the Australian population	Life Saving Drugs Program (LSDP)	LSDP is separate to the Pharmaceutical Benefits Scheme. There is no fixed budget	Expert Panel assessment of medicines for rare diseases	Department of Health
England	Affecting 5 people or fewer in 10,000	NICE Highly Specialised Technologies (HST) program	There is no separate fund	Drugs for very rare diseases will be evaluated against a sliding scale	NHS England
Scotland	Affecting 5 people or fewer in 10,000	Scottish Medicines Consortium Patient and Clinician Engagement Process (PACE)	New Medicine Fund established 2014 replacing the Rare Conditions Medicine Fund	A new definition of 'ultra-orphan' medicines that can treat rare conditions affecting fewer than 1 in 50,000 people to take effect 1 October 2018	NHS Scotland
Canada	No definition adopted. Health Canada refers to the definitions used by the European Union and the United States	Orphan medicine applications reviewed by Health Canada	In 2019 Government pledged $1 billion over the next two years (starting in 2022) towards medicines for rare disorders	Regulatory Review of Drugs and Devices Initiative (August 2018)	Currently decisions made by Canadian territories[3]
United States	A condition that affects fewer than 200,000 people	Orphan Drug Act (1983) Orphan Drug Modernization Plan (est. June 2017) Orphan Products Council (est. November 2017)	Orphan Products Grants Program Rare disorders medicines may be accessed via private healthcare insurance	No altered decision criteria	U.S. Food & Drug Administration
New Zealand	Population of less than 1:50,000 in New Zealand	Call for applications Rare Disorders Subcommittee of PTAC	There is no separate fund. Funding for medicines comes from fixed Combined Pharmaceutical Budget	Adjusted policy settings	PHARMAC

[3] In March 2019 the Government proposed to create a Canada Drug Agency, that will work with territories and take a co-ordinated approach to both assessing effectiveness and negotiating prescription drug prices on behalf of Canadians.

Part 2: Access to rare disorders medicines in New Zealand

Funding mechanisms

The topic of access to high-cost and highly-specialised medicines has been a contentious debate in the public and political realm in New Zealand for many years. New Zealand's relatively small population, and its geographical dispersion and isolation, exacerbates the challenges being faced by many other jurisdictions around the world.

PHARMAC currently funds medicines for rare disorders through three mechanisms:

- the Pharmaceutical Schedule listing process;
- the Exceptional Circumstances framework; and
- the rare disorders medicines contestable funding pilot.

Pharmaceutical Schedule listing process

The New Zealand Pharmaceutical Schedule is a list of the prescription medicines and some medical devices that are subsidised by the New Zealand Government for community or hospital use. The Pharmaceutical Schedule is managed by PHARMAC, as per its statutory function. The decision to add new medicines, or widen access to existing funded medicines, is made by PHARMAC.

Importantly, this pathway requires comparing and ranking funding options against each other using the Factors for Consideration[4], to determine which option is the next best investment for PHARMAC to make. Decisions made through the Pharmaceutical Schedule process are considered at the national population level; i.e. a medicine is considered for listing or widening access in the context of all who are expected to benefit based on the defined condition, disorder or illness. This pathway is the mechanism through which the majority of rare disorder medicines are funded.

The Factors for Consideration require PHARMAC to take into account a broad spread of issues, which can be particularly relevant for people with rare disorders. This includes:

- Health need of the person – rare disorders can often be debilitating and severe, so individuals with a rare disorder are often considered to have a high health need.
- The availability and suitability of existing medicines, medical devices and treatments – people with rare disorders often have limited alternative treatment options available that would treat the disorder itself (as opposed to the symptoms or side effects of their illness).

[4] PHARMAC's Factors for Consideration are described in Appendix 1

- Health need of others – caring for a person with a rare disorder can affect the health of those with this responsibility.

In 2017/18, at least 150 people were receiving 16 different medicines that are only used for the treatment of a definable rare disorder and were funded through the Pharmaceutical Schedule listing process. This figure is an under-estimate as it is likely that individuals will be using other medicines that have multiple indications. This demonstrates that PHARMAC's process for considering medicines for funding at a population level can account for very small patient populations.

Exceptional Circumstances Framework

The Exceptional Circumstances Framework provides a pathway for considering medicines funding decisions for individuals whose clinical circumstances cannot be met through the Pharmaceutical Schedule at a given point in time. This pathway is complementary to the Pharmaceutical Schedule funding process. The Named Patient Pharmaceutical Assessment (NPPA) policy is the main part of the Framework and is used when a prescriber wants to use a medicine that is not on the Pharmaceutical Schedule (either at all or for their patient's clinical circumstances). An application for medicines funding will be considered under the NPPA policy if it meets NPPA's core principles (28). Following this the application is then assessed for a funding decision against the Factors for Consideration.

As discussed above, there are several Factors that can be particularly relevant to people with rare disorders. In 2017/18, 160 people received funding for 76 different medicines specifically for their rare disorder through the NPPA process.

Funding pilot for rare disorders medicines

In 2014 PHARMAC released the discussion document *High cost medicines for rare disorders* (29). This sought input from the public about developing an alternative commercial approach to funding rare disorder medicines. The document laid out the New Zealand-specific context for rare disorder medicines:

- *High Costs:* Treatments for rare disorders are often priced very highly; pharmaceutical suppliers claim this is due to the high research and development costs across a lower volume of patient numbers. However, a BMJ journal in 2012 noted that more than four fifths of all funds for basic research to discover new medicines and vaccines comes from public sources (30). This is further enhanced by the policy settings in jurisdictions such as the US and EU which incentivise development of medicines through public funding, lowered regulatory costs and extensions to market exclusivity.
- *Developing Evidence:* Suppliers claim that it is difficult to build clinical evidence because of the natural limitations on the size of randomised controlled trials, due to the rarity of the condition. However, this also means that rare disorder medicines potentially offer some financial advantages to pharmaceutical companies over conventional medicines, including faster development timelines, lower research and development

expenses, a higher likelihood of clinical and regulatory success, premium pricing, lower marketing costs and a lower risk of generic competition (31).

- *Fixed Budget:* PHARMAC must consider the best health outcomes that can be reasonably achieved within its fixed pharmaceutical budget, and these medicines "often do not compare favourably to other medicines that benefit larger populations and achieve greater overall health gains for less money."(29) Rare disorder medicines may compare favourably on other measures, such as health need, but affordability and budgetary impact need to be taken into account due to PHARMAC's fixed budget.
- *Small market:* Suppliers in the past have been dis-incentivised to make competitive offers in the New Zealand market because New Zealand is only 0.1% of the global pharmaceutical market. Suppliers are also aware that PHARMAC's current funding model (in the year 2014) meant that high cost medicines were less likely to be funded, as outlined in the points above.

With these issues framing the problem definition for access to rare disorders medicines, PHARMAC decided to trial a new commercial approach with the intention to encourage competition in a market where no competition currently exists. In its 2014 discussion document PHARMAC proposed a pilot Request for Proposals (RFP) process that was intended to test whether competition could be stimulated in this market (29).

Following two rounds of public consultation on the proposed process, PHARMAC released the RFP, seeking funding applications for treatments for rare disorders medicines. Though a pilot RFP process is a common commercial strategy that PHARMAC uses to stimulate competition amongst suppliers for medicines, this strategy is generally used for products in the same therapeutic area. Releasing an RFP for treatments to address a range of conditions for a broad potential patient population was a new approach for PHARMAC.

As part of the RFP, PHARMAC also allowed suppliers to provide bids on medicines that were not Medsafe approved in New Zealand, in order to further stimulate competition and supplier interest in the New Zealand market. Although PHARMAC did not require suppliers to have Medsafe (or other international regulatory authority) approval to bid on medicines funding, the expectation was that suppliers receive this regulatory approval prior to the medicine being listed on the Pharmaceutical Schedule (29).

How the rare disorders funding pilot worked

PHARMAC committed to spending up to $5 million per year (ongoing) for medicines funded through the RFP, from within its fixed budget. Importantly, this was not a ring-fenced fund, but rather signalled the maximum amount of money available.

This was intended to guide suppliers as to the competitive nature of the bids that they would submit to PHARMAC. It was noted that suppliers may need to propose a form of risk sharing or to cap expenditure. Suppliers were also required to define the patient population and propose eligibility criteria for patients to access their treatment, should it be funded.

The following were the pre-requisites for PHARMAC's rare disorders medicines contestable funding pilot, which began in 2014.

Pre-requisites for PHARMAC's rare disorders medicines contestable funding pilot

Disorder related

1. There is a rare[5] but clinically defined long-term disorder that is identifiable with reasonable diagnostic precision.
2. Epidemiological and other studies provide evidence acceptable to PHARMAC[6] that the disorder causes a significant reduction in either absolute or relative age-specific life expectancy or quality of life, for those suffering from the disorder[7].

Treatment related

3. The medicine is regarded as a proven therapeutic modality for an identifiable patient population[8] ie the medicine has been approved by Medsafe or an international regulatory authority[9] for the identified indication.
4. There is evidence acceptable to PHARMAC[6] that the medicine is likely to be clinically effective for the identified patient population[8].
5. The patient's absolute or relative age-specific life expectancy and/or quality of life could be substantially improved as a direct consequence of the treatment[10].

Alternatives related

6. The medicine is not registered for the treatment of another, non-rare disorder, or if it is, the cumulative prevalence across all the indications still falls within the definition of rare[11].
7. There is no suitable comparable[12] alternative treatment on the Pharmaceutical Schedule.
8. There is no suitable[12] funded alternative non-drug therapeutic modality for the rare disorder.

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[5] PHARMAC defined 'rare' as an identifiable and measurable patient population with a prevalence of 1:50,000 or less. This definition would mean there are currently up to 90 people across the whole of New Zealand that have each rare disorder.
[6] On the basis of advice from PTAC and / or the Rare Disorders Subcommittee of PTAC.
[7] As measured by absolute or proportional Quality Adjusted Life Years (QALY) loss.
[8] The definition of the patient population must be clinically meaningful (not arbitrary) and must treat patients with the same clinical circumstances equally.
[9] Regulators that are recognised by Medsafe for the purposes of an abbreviated approval process, as listed on page 38 of New Zealand regulatory guidelines for medicines.
[10] As measured by absolute or proportional QALY gain.
[11] Bidders would be required to reveal their overseas approved indications and their phase three development programme.
[12] Suitable is defined as a treatment that provides a comparable health outcome to the medicine under consideration, for the patient population under consideration.

Those applications that met the prerequisites were then assessed against PHARMAC's decision-making criteria, and a priority list was established.[13]

PHARMAC received 28 bids from eight suppliers of medicines for rare disorders. It should be noted that some of these bids were different commercial proposals for the same medicines. Many of these medicines had not been considered in New Zealand before and were from suppliers PHARMAC has not previously done business with. PHARMAC received clinical advice and assessed each medicine using the decision-making criteria ranking these bids in order of priority. Once PHARMAC had established its priority list each proposal was progressed individually, and contracts and listing agreements with suppliers were secured throughout 2015 and 2016.

At the conclusion of the pilot PHARMAC had approved funding for 10 new medicines for rare disorders. Nine of these medicines were listed on the Pharmaceutical Schedule for ongoing funding. The remaining medicine is not formally listed on the Schedule, as it is unlikely to receive Medsafe approval (32), but is available for eligible patients through a separate process.

Evaluation and analysis of the rare disorders funding pilot

PHARMAC commissioned an external evaluator to formally evaluate the rare disorders contestable funding pilot.[14] This evaluation and PHARMAC's own assessment identified a number of successes and insights to take away from this process. These are outlined below. Note that some of the relative comparisons made below are comparing the treatments funded through the rare disorders pilot (10 medicines) to what would have been the next best spend with the same amount of money through the Pharmaceutical Schedule listing process (11 medicines based on the top ranked funding options in June 2017).[15]

Successes from the funding pilot

- 10 new medicines were funded to treat rare disorders. The people accessing these new medicines had, on average, a higher health need (ie severity of their illness was greater) than the people who would have benefited from the medicines that would otherwise have been funded through the Schedule listing process.
- This process attracted new pharmaceutical suppliers to the New Zealand market that otherwise would not have been incentivised to enter the market.
- PHARMAC received better commercial proposals for some medicines that had already been considered for national funding or were being funded through the NPPA policy. This demonstrated that introduction of competition through the RFP resulted in more competitive prices.

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[13] The nine decision criteria were replaced by the Factors for Consideration in July 2016.
[14] The full report from the external evaluator is available on the PHARMAC website at https://www.pharmac.govt.nz/assets/2017-06-final-Grant-Thornton-evaluation.pdf
[15] The 11 medicines used as a comparator were subsequently funded following additional savings and increases in the CPB over the next 12-month period.

- PHARMAC's relationship with suppliers of rare disorders medicines and patient advocacy groups improved through having more involvement and a more hands-on process. PHARMAC consulted with consumers at various stages of the funding process via phone calls and meetings. PHARMAC also worked closely with suppliers, particularly those new to the New Zealand system, providing detailed guidance on the funding process, standard commercial terms, and the New Zealand health system.

Limitations of the funding pilot

- The medicines funded through the rare disorders RFP had significantly poorer cost-effectiveness, measured through Quality Adjusted Life Years (QALYs), than what would have been otherwise funded through the Pharmaceutical Schedule listing process. A QALY is a measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to also reflect the quality of life (33). The 10 treatments approved for funding through the RFP had an average of 4.5 QALYs per $million, that could have otherwise been funded with the money spent on the 10 rare disorders medicines, which had an average of 236 QALYs per $million.
- The criteria to consider rare disorders medicines was not restrictive enough to exclude a treatment for an extremely resistant form of tuberculosis (TB). Feedback highlighted TB was not viewed as a 'rare disorder' by stakeholders, as it is a common infection and resistance is growing internationally.
- PHARMAC's commitment to fund up to $5 million annually created a public expectation that was not aligned with the intent. The intent in specifying an amount was to signal the competitive nature of the bids that suppliers needed to submit; however, there became a public expectation that all of this money would be spent on rare disorders medicines. In order to ensure that the entire $5 million allocation would be fully spent, PHARMAC would have needed to fund one more medicine, however, funding additional medicines would have resulted in the $5 million cap being greatly exceeded.
- There was difficulty in predicting the uptake of new medicines, including determining how many people would begin or continue treatment and the impact of this on a fixed budget. One of the medicines selected for funding has not had any uptake.
- The process undertaken for the pilot was resource-intensive for PHARMAC staff and added to the time taken for extended commercial negotiations.

The successes and insights gained from running the pilot process has been extremely beneficial in considering permanent changes to PHARMAC's processes and policy settings. This is discussed in more detail in Part 3.

Analysis of rare disorders medicines funded by PHARMAC

In 2018, PHARMAC staff undertook an analysis of all rare disorders medicines funded through the Pharmaceutical Schedule, Rare Disorders Pilot and Exceptional Circumstances pathways over the previous three financial years. This analysis used the PHARMAC Rare Disorders Pilot and adjusted Rare Disorders Policy Principle 2 (see page 18) definition of 'rare' (population of less than 1:50,000 in New Zealand) and only included medicines that were used specifically to treat a rare disorder. The analysis could not include the range of other more widely used funded medicines that many people with rare disorders access to manage the symptoms of their disorder (e.g. pain relief, muscular or seizure-related treatments). Accordingly, the analysis is a conservative estimate of patient numbers, funding and medicines used to manage rare disorders in New Zealand. A fuller discussion of the limitations of the data can be found in Appendix 2.

The results of the analysis are shown in Table 2 below. This summary demonstrates that the largest proportion of the medicines used to manage rare disorders were funded through the Pharmaceutical Schedule and Exceptional Circumstances Framework pathways. These mechanisms also have the greatest number of individuals receiving funded medicines. This summary also shows that the number of people, and amount of expenditure, on rare disorders medicines funded through the pilot has increased over the past three financial years. These figures indicate that all three mechanisms have contributed to meeting some of the diverse health needs of patients with rare disorders in New Zealand.

Table 2: Medicines for rare disorders funded through PHARMAC's three funding mechanisms[16]

	Mechanism	Gross spend	Patients	Medicines
2015/2016	Pharmaceutical Schedule	$2,648,269	138	17
	Exceptional Circumstances Framework	$1,678,968	125	69
	Rare Disorders Pilot	$184,979	15	10
	TOTAL	$4,512,216	278	96
2016/2017	Pharmaceutical Schedule	$2,974,172	149	17
	Exceptional Circumstances Framework	$2,258,167	156	78
	Rare Disorders Pilot	$1,029,017	35	10
	TOTAL	$6,261,356	340	105
2017/2018	Pharmaceutical Schedule	$3,013,567	150	16
	Exceptional Circumstances Framework	$2,090,573	160	76
	Rare Disorders Pilot	$1,694,107	38	10
	TOTAL	$6,798,247	348	102

[16] For a full discussion of the limitations of the data, please refer to Appendix 2.

Part 3: PHARMAC's ongoing commitment to funding medicines for rare disorders

Following the evaluation of PHARMAC's rare disorders medicines contestable funding pilot, PHARMAC committed to implementing a series of dedicated features through operational policy change to its existing processes. This sought to optimise patient access to rare disorders medicines. Over the course of 2018, the following changes were introduced:

- adjusted policy settings for rare disorders medicines for when they are considered through PHARMAC's processes;
- establishment of a standing expert clinical subcommittee of the Pharmacology and Therapeutics Advisory Committee for rare disorders;
- a regular call for rare disorders funding applications;
- dedicated pre-engagement with new, as well as existing, suppliers prior to each call for applications; and
- regular horizon scanning for pharmaceuticals coming down the pipeline.

Adjusted policy settings

PHARMAC has introduced new permanent policy settings that apply to funding applications for medicines for rare disorders. These are represented by three principles, outlined in the table below. When a treatment meets all three principles, this enables an earlier entry into PHARMAC's usual Pharmaceutical Schedule funding process.

The notable feature of the adjusted policy settings is that suppliers are not required to have gained Medsafe approval for the medicine before it can be considered for funding, unlike PHARMAC's usual processes. Medsafe approval can cost suppliers a significant amount of money and time. For suppliers of medicines for rare disorders the process of gaining Medsafe approval is often not considered to be commercially viable, particularly where there is only a very small potential patient population (therefore low total usage/revenue) and uncertainty of public funding. This separate entry into the Pharmaceutical Schedule funding process therefore helps reduce the current market challenges for these medicines in New Zealand. Note that, although it is not a requirement for suppliers of medicines to receive Medsafe approval before submitting a funding application, it is a requirement to have Medsafe approval before funding is provided.

These principles apply at any time for medicines for rare disorders, and do not require PHARMAC to make a call for funding applications or run a specific competitive funding process. This gives suppliers of these medicines the flexibility to submit an application when it suits them and enables PHARMAC to consider which process would be best to elicit the best health outcomes from within its current budget.

PHARMAC's processes also allow for clinicians and patient groups to submit funding applications. Additionally, PHARMAC can generate applications itself where it considers evidence or information to be sufficient for an application.

Principle	Explanation
1. The medicine has been approved by Medsafe, or an approved international regulatory authority, for the identified indication.	PHARMAC generally requires Medsafe approval before a medicine is considered for funding on the Pharmaceutical Schedule. This principle recognises that getting Medsafe approval can be a significant barrier for suppliers of medicines for very small population groups in New Zealand. By loosening PHARMAC's standard requirement, PHARMAC can consider funding applications for medicines that have approval granted by an approved international regulatory authority. Medsafe approval is still required prior to listing on the Pharmaceutical Schedule.
2. The disorder is a clinically defined disorder affecting an identifiable and measurable patient population with a prevalence of less than 1:50,000 in New Zealand.	This principle defines the patient population who may be living with a rare disorder in New Zealand. This definition equates to approximately 90 people in the New Zealand population. PHARMAC has retained this definition from the 2014 pilot, which was consulted on during the development of that process. This definition of 'rare' aligns with Australia, and England and Scotland's definition of 'ultra-rare.'
3. The medicine is only registered for the treatment of the rare disorder, or if it is registered for other disorders (or is part of phase three clinical trials for other disorders), the cumulative prevalence across all indications still meets principle 2.	This principle defines the treatment as 'rare', and therefore ensures that only those suppliers of treatments that are disadvantaged, as a result of their very small patient population, are given consideration through this alternative entry. Where the treatment may be appropriate for multiple indications, it is likely the patient population potentially benefiting from the treatment will not meet principle 2. In these circumstances, the standard entry into the Pharmaceutical Schedule is more appropriate.

If the above principles have been met, PHARMAC will assess funding applications as per its standard pharmaceutical funding process. This includes assessment against the Factors for Consideration, and comparative ranking against all other possible funding options.

PHARMAC faces the continuing challenge of managing expectations around what can realistically be funded. PHARMAC needs to make difficult choices about the best use of available funding from a fixed budget, as there are always many different medicines that could potentially be funded under the right circumstances.

Establishment of specialist clinical advisory committee

PHARMAC has established a Rare Disorders Subcommittee of the Pharmacology and Therapeutics Advisory Committee (PTAC). PHARMAC has several PTAC Subcommittees, but until now there has not been one for rare disorders.

Membership applications were sought through colleges and clinical networks (both New Zealand and Australian based), from people with a special interest in managing patients with rare disorders.

The nine appointed members include some of New Zealand's leading experts in treating rare disorders, from specialties such as paediatric nephrology, metabolic disorders, blood disorders and neurology. One member is an Australian specialist in genetics and metabolic disorders who has been involved in Australia's Life Saving Drugs Programme (LSDP). The Subcommittee also includes two PTAC members (one of whom is the Chair of the Subcommittee), to maintain links between this new Subcommittee and PHARMAC's primary clinical advisory committee. Membership is reviewed regularly, and additional members added if required to support the needs of the Subcommittee.

The Subcommittee is brought together on an as-needed basis depending on when funding applications require its specialist clinical assessment.

Regular call for funding applications

PHARMAC initiated the first regular call for supplier applications in June 2018. The intent of the regular call is to demonstrate PHARMAC's commitment to evaluating rare disorders medicines in a timely manner and to encourage more medicines suppliers to enter the New Zealand market.

Through this first call, PHARMAC received 13 applications from eight different suppliers, for 10 different medicines for rare disorders. Multiple applications for two medicines were received from different suppliers and these were considered together. Nine of the 13 applications received were for medicines that were not Medsafe approved when applications closed (three had already been submitted to Medsafe and were under evaluation); and four were Medsafe approved.

In their first meeting held in November 2018, the Rare Disorders subcommittee's advice was to recommend to PHARMAC to fund five treatments, decline six, and defer one on the basis of further analysis of two trials. Clinical advice that is provided to PHARMAC is also made publicly available on the PHARMAC website (34).

These recommendations were considered and reviewed by PTAC in February 2019 (35) (see Table 3 below).

Table 3: Rare disorders medicines funding recommendations by PTAC, on 21-22 February 2019

Pharmaceutical	Indication	Rare Disorders Recommendation (Nov 2018)	PTAC Recommendation/ comment (Feb 2019)
Agalsidase alfa	Fabry disease	Recommended for funding with a medium priority	Recommended for decline
Alglucosidase alfa	Late-onset Pompe disease	Recommended for decline	Accepted Rare Disorders Subcommittee Recommendation
Carglumic Acid	Treatment of hyperammonaemia due to urea cycle disorders	Recommended funding with a high priority	Accepted Rare Disorders Subcommittee Recommendation
	Treatment of hyperammonaemia due to organic acidaemias	Recommended funding with a medium priority	Accepted Rare Disorders Subcommittee Recommendation
Elosulfase	Mucopolysaccharidosis type IVA	Recommended for decline	Accepted Rare Disorders Subcommittee Recommendation
Ivacaftor	Cystic Fibrosis – with G551D mutation	Recommended for funding with a medium priority	Recommended funding with a low priority
Migalastat	Fabry disease	Recommended for decline	Accepted Rare Disorders Subcommittee Recommendation
Miglustat	Neimann-Pick disease Type C	Recommended for decline	Accepted Rare Disorders Subcommittee Recommendation
Miglustat	Type 1 Gaucher disease	Recommended for decline	Accepted Rare Disorders Subcommittee Recommendation
Nitisinone	Hereditary tyrosinaemia type 1	Recommended for funding with a high priority	Accepted Rare Disorders Subcommittee Recommendation
Nusinersin	Spinal muscular atrophy	Deferred until longer-term follow-up data available	Recommended that the funding application be deferred, pending longer-term follow-up analyses of two trials. We expect to receive more evidence by the end of 2019
Teduglutide	Short bowel syndrome – Type 3	Recommended for decline	Accepted Rare Disorders Subcommittee Recommendation

Another call for funding applications was issued in April 2019. The Rare Disorder Subcommittee will meet again in September 2019 and will review any new applications received, as well as providing advice on the rare disorders therapeutic group and horizon scanning of rare disorder medicines.

Dedicated pre-engagement with suppliers

Following on from the rare disorders medicines contestable funding pilot, PHARMAC has continued pre-engagement with suppliers in New Zealand and Australia of medicines for rare disorders prior to and during the call for applications. This acknowledges that the New Zealand market is so small that suppliers are not necessarily incentivised to pursue regulatory approval, let alone submit funding applications for their products.

Feedback from suppliers involved in pre-engagement with PHARMAC has been very positive. Suppliers have been particularly supportive of the removal of the requirement for Medsafe approval prior to being considered for funding (principle 1). Prior to this change, the need to have Medsafe approval prior to applying for funding was seen as a significant barrier to entering the New Zealand market. PHARMAC continues to develop good working relationships with suppliers that are new to New Zealand and to PHARMAC processes.

Regular portfolio review and horizon scan of rare disorders medicines

PHARMAC is continuously undertaking horizon scans to identify new rare disorders medicines. As new information and evidence becomes available, PHARMAC can approach suppliers or even initiate funding applications if opportunities arise.

PHARMAC's clinical advisors also stay abreast of clinical advancements in their therapeutic areas, and discussions on future funding opportunities take place regularly at PTAC and Subcommittee meetings. The establishment of the Rare Disorders Subcommittee provides further opportunity for horizon scanning for rare disorders medicines and this will be incorporated into future meetings with this group. PHARMAC continues to regularly discuss the development pipeline for rare disorders medicines with suppliers.

Through relationships with suppliers, rare disorder consumer groups, and its clinical advice network, PHARMAC stays aware of the current rare disorders medicines on the market in New Zealand and internationally. There are many treatments in clinical trials that will potentially enter the market in the near future. With the new policy settings, and PHARMAC's flexible approach to running commercial processes, the PHARMAC model can adapt to the changing pharmaceutical market accordingly.

Appendix 1

Explaining the New Zealand health system

New Zealand has mainly a publicly-funded healthcare system. Primary healthcare is subsidised and secondary care in public District Health Board (DHB) hospitals is free. New Zealand has the Accident Compensation Corporation (ACC) which covers the costs of injuries (including illnesses) caused by accidents. Private health insurance companies also operate in New Zealand and offer access to private health care for non-emergency and non-funded medical care.

Health and disability services in New Zealand are delivered through a complex network of organisations. Most of the day-to-day business of the system is administered by the 20 DHBs. DHBs plan, manage, provide and purchase health services for the population of their district. This includes funding for primary care (including pharmacy services), hospital services, aged-care services and services provided by other non-government health providers including Māori and Pacific providers (36).

The Ministry of Health is the principal policy advisor to the Minister of Health who, with Cabinet and Government, provides leadership to the health system. The Ministry of Health also funds a range of national services, including disability support and public health services, and has a number of regulatory functions including the role of regulating medicines for use in New Zealand. This is undertaken by Medsafe, a business unit within the Ministry of Health.

The role of PHARMAC

PHARMAC's role within the health system is to make decisions on which medicines and medical devices are publicly funded. PHARMAC's statutory objective is to:

> 'secure for eligible people in need of pharmaceuticals, the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the amount of funding provided'
>
> *New Zealand Public Health and Disability Act 2000*

PHARMAC is a crown entity and reports directly to the Minister of Health. Each year the level of the Combined Pharmaceutical Budget (CPB) is set by the Minister of Health following joint advice from PHARMAC and DHBs. The CPB provides for publicly funded medicines in the community and hospital settings, along with some medical devices. Although the Minister of Health sets the amount of health funding spent on medicines, PHARMAC independently decides how to use the CPB, including deciding what new pharmaceuticals to invest in. The DHBs are then responsible for CPB spending via hospitals and community pharmacies, and PHARMAC (as well as deciding which medicines and medical devices to fund) monitors this expenditure to ensure it does not exceed the allocated budget.

PHARMAC's work

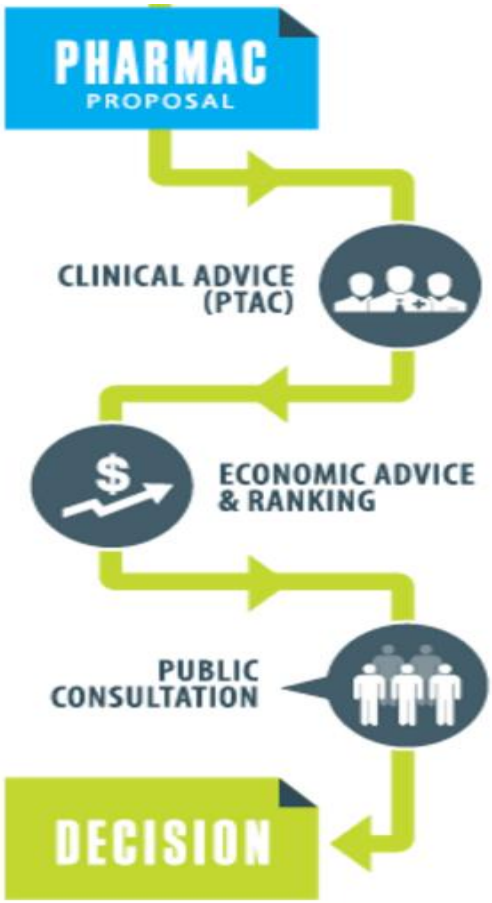
PHARMAC has four main functions:

1. *Managing the Pharmaceutical Schedule:* The Pharmaceutical Schedule contains the list of government subsidised medicines and medical devices.
2. *Promoting the responsible use of medicines:* The responsible use of medicines is important to ensure the medicines that PHARMAC are providing funded access to, are being used optimally.
3. *Managing the assessment of exceptional individual clinical circumstances for medicines not funded through the Pharmaceutical Schedule:* PHARMAC's Exceptional Circumstances Framework considers funding decisions in exceptional circumstances that fall outside of the Pharmaceutical Schedule funding process. This Framework includes the Named Patient Pharmaceutical Assessment (NPPA), special authority waivers and hospital medicine restriction waivers. The NPPA policy provides a pathway to consider funding medicines for patients whose clinical circumstances cannot be met through the Pharmaceutical Schedule.
4. *Engaging in research as required.*

The PHARMAC model is unique in a couple of ways. Firstly, the CPB is a fixed budget that, as noted above, is annually determined by the Minister of Health. PHARMAC forecasts the level and cost of growth in demand for products and then decides what additional medicines to fund within the fixed budget that has been allocated for that financial year. Having a fixed budget means that PHARMAC needs to free up funding through reducing the cost of medicines that are currently funded in order to be able to fund the maximum possible amount of new medicines. To do this PHARMAC employs a number of commercial strategies to get the best value from medicines spending.

Secondly, PHARMAC has a comprehensive assessment process to help the organisation achieve 'best health outcomes' as per its statutory objective. This includes undertaking economic assessment, seeking expert advice, and utilising commercial strategies as appropriate. Each potential investment option is ranked against all other funding options based on the results of this assessment. This process is outlined in Figure 1 below.

Figure 1: Process of assessing medicines for funding consideration



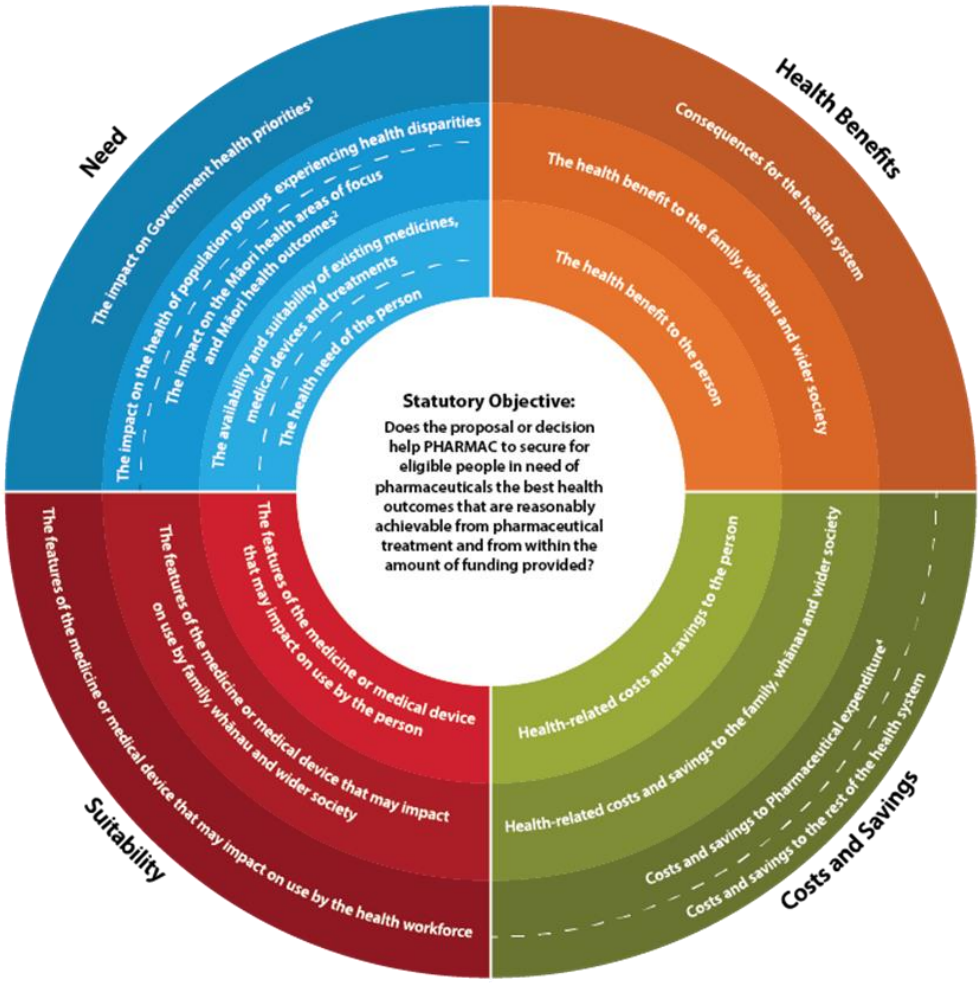
Factors for Consideration

PHARMAC applies a decision-making framework throughout the assessment (and decision making) process called the Factors for Consideration (see Figure 2 below). The Factors set out what PHARMAC takes into account when making medicines funding assessments and decisions.

The Factors cover four dimensions: need, health benefits, costs and savings, and suitability. Within each of the dimensions we consider impacts on the person; their family, whānau and wider society, and the health system (including the health workforce). Not every Factor is relevant to every decision that is made, and some Factors will be more relevant to some medicines than others; hence no prescribed weightings are applied to the individual Factors.

PHARMAC compares potential medicines investments against one another using the Factors for Consideration, to determine which investments will ultimately result in best health outcomes. Each potential investment option is then ranked against all other funding options based on the results of this assessment. This helps PHARMAC decide which investments to progress, depending on the amount of funding available within the fixed annual budget (CPB).

Figure 2: Factors for Consideration



Footnotes to the diagram

1 The person receiving the medicine or medical device must be an eligible person, as set out in the Health and Disability Services Eligibility Direction 2011 under Section 32 of the New Zealand Public Health and Disability Services Act 2000.

2 The current Māori health areas of focus are set out in PHARMAC's Te Whaioranga Strategy.

3 Government health priorities are currently communicated to PHARMAC by the Minister of Health's Letter of Expectations.

4 Pharmaceutical expenditure includes the impact on the Combined Pharmaceutical Budget (CPB) and/or DHB hospital budgets (as appropriate).

5 Note that the Factor 'The health needs of the family, whānau, and wider society' does not appear in the diagram of the wheel. Nonetheless it is considered to be a Factor for Consideration as another element of the Need quadrant and the 'Family, whānau, and wider society' band.

Appendix 2

Limitations of analysis for figures shown in Table 2

Analysis such as that provided in Table 2 always has limitations. The intent of the table is to provide as accurate a picture as possible of the mechanisms through which PHARMAC funds medicines for rare disorders. Given the data available these figures are an underrepresentation of the actual medicines PHARMAC funds for rare disorders. Below is further explanation of the limitations:

- The Pharmaceutical Schedule and Exceptional Circumstances Framework figures use PHARMAC's definition of 'rare' (prevalence less than 1:50,000). Disorders that may be widely held as 'rare' but do not meet this threshold have been excluded from these figures e.g. phenylketonuria has been excluded.
- The figures presented are different to that which was provided in May 2018. Data has been updated to reflect PHARMAC's definition of 'rare'. The Pharmaceutical Schedule and Exceptional Circumstances Framework mechanism figures do not include medicines for rare cancers and infections. The rare disorders medicines contestable funding pilot includes one medicine used for the treatment of highly resistant tuberculosis (bedaquiline). The pilot data reflects the medicines approved for funding through the pilot and now listed on the Schedule, or via the Exceptional Circumstances Framework pending Medsafe approval.
- The Pharmaceutical Schedule and Exceptional Circumstances Framework analysis is limited to those medicines where a distinct rare disorder could be identified. This was derived from the accompanying clinical information for patients applying under the Exceptional Circumstances Framework or by using the medical indications specified in Special Authority criteria in the Pharmaceutical Schedule. The analysis excludes expenditure on some medicines used to manage rare disorders where the indication data is not available (i.e. open listed) or is not available at a sufficiently detailed level. In cases where treatments are open listed, they may be used for a variety of purposes.
- The analysis excludes hospital purchases of medicines under either the normal Pharmaceutical Schedule (Hospital Medicines List) or the Exceptional Circumstances Framework mechanism, due to the limitations of the datasets from the hospital setting. Many of the medicines approved for hospital use under these mechanisms are high cost medicines (e.g. biologic medicines used for rare autoimmune diseases such as rituximab).

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