Submission from Myeloproliferative Neoplasms Alliance Australia (MPNAA)

Parliamentary inquiry: Approval processes for new drugs and novel medical technologies with particular focus on treatment of rare diseases and conditions where there is a high and unmet need

This submission is from Myeloproliferative Neoplasms Alliance Australia[1] (MPNAA). We are a patient-led advocacy group collaborating with the Leukaemia Foundation of Australia with the common goal of achieving better outcomes for Australian patients with a myeloproliferative neoplasm (MPN). This paper has been developed taking account of Rare Voices Australia's 'National strategic action plan for rare diseases'.

This paper addresses all the Inquiry's terms of reference with particular focus on 2, 3 and 4. MPNAA proposes several recommendations and the most pressing is to seek Parliament's/Government's support for the rapid approval in Australia of the new drug BESREMi® (ropeginterferon) for MPN patients. Ideally this would also be considered a priority by the Pharmaceutical Benefits Advisory Committee (PBAC) for inclusion on the Pharmaceutical Benefits Scheme (PBS).

Background

MPNs are a rare and chronic form of blood cancer usually caused by one of three acquired mutations, JAK2v617F, Calreticulin or MPL. They affect the bone marrow which proliferates in an uncontrolled manner, causing an overproduction of red cells, platelets and/or white cells. There are three main types of MPNs: essential thrombocythemia (ET), polycythemia vera (PV) and myelofibrosis (MF). Immediate risks to MPN patients are stroke, heart attack or blood clot (both venous and arterial) as well as the risk of transformation to myelofibrosis or acute myeloid leukaemia where prognosis is very poor. Symptom burden varies but in many cases significantly affects quality of life: severe spleen and bone pain, extreme fatigue, pruritis, headaches, burning of the hands and feet, night sweats being some of the more debilitating symptoms. MF patients suffer the worst symptoms and many are unable to continue working. The only cure is a stem cell transplant which is of course risky and not possible for every patient due to age and suitability.

Treatment options

Treatment options remain limited and patients are in great need of new therapy options. Most MPN patients are treated with antiplatelet medications (usually low dose aspirin). 'High risk' patients – that is, anyone over 60; and/or with a prior thrombosis – are also generally treated with oral chemotherapy (hydroxycarbamide) or interferon, an immune-modulator. For patients with advanced myelofibrosis, the most severe form of MPN, the Jak2 inhibitor Ruxolitinib is likely to be prescribed.

Interferon has re-emerged as an important option in MPN patients over the last decade. It is now recognised as a cytoreductive alternative to hydroxycarbamide in ET and PV and is consistently used as first-line therapy in younger patients and pregnant women. Patients are increasingly seeking to use the pegylated interferon treatment option, rather than oral chemotherapy, due to the possibility of normalising the bone marrow and achieving molecular remission. The reimbursement of pegylated-interferon therapy for MPNs in Australia arose from a patient-led initiative. The recent

[1] https://www.mpnallianceaustralia.org.au/

encouraging data surrounding ropeginterferon (BESREMi®) has precipitated clinician and patient-led efforts to facilitate approval and funding of this drug in Australia.

MPN Alliance Australia has concerns regarding continued access to interferon treatment into the future. Since the discontinuation of Roferon-A® in 2019, Pegasys® (Roche Australia's peginterferon alfa-2a) is the only interferon therapy available for MPN patients, which puts increasing demand on Pegasys® and pressure on ongoing supply. Since Pegasys® became available on the PBS for MPN patients in August 2018, there have already been 9,426 prescriptions and each month the number is increasing. In July 2020 there were 685 scripts written for Pegasys®[2] and it is believed that these were all for MPN patients. To ensure a reliable, sustainable and safe treatment option, access to BESREMi® for Australian patients with MPNs is essential.

Comments against the Terms of Reference

MPNAA has identified some possible systemic gaps that we believe hinder timely access to drugs or new technologies:

1. **a) Unclear line of responsibility for ensuring timely access for Australian patients to new drugs**
   When there is little incentive for a drug company to initiate a drug approval process due to small numbers of patients in Australia, it is unclear who has the major responsibility for commencing such a process, especially for rare diseases such as MPNs. Is it the relevant medical speciality, medical representative body, patients, patient advocacy groups where they exist, or the federal government health department or federal regulatory bodies?

   b) Future unavailability of existing drug – unclear line of responsibility to find replacement
   Similarly, it is unclear who is responsible for determining alternative options for patients when a drug company no longer manufactures a drug and so continued supply is precarious. Again the system for ensuring ongoing supply seems uncertain but the ramifications for patients are huge.

Case study for points 1a and 1b.

A case in point is the new orphan drug ropeginterferon (known as BESREMi®), which was approved for use with polycythemia vera patients by the European authorities in 2018 and recently passed the first approval step in the USA[3]. It is the first drug in the world developed and specifically trialled for safety and efficacy in polycythemia vera. Like the currently available long-acting interferon, Pegasys®, BESREMi® is injectable. Pegasys® is injected once per week by patients. BESREMi® is designed to be injected fortnightly, and trial results show an equivalent side effect profile with superior effectiveness to oral chemotherapy (hydroxycarbamide) over time. [4]

Pegasys® was originally developed and largely used for patients suffering from Hepatitis C. Hepatitis C patients now have alternative and more effective drug treatments and therefore the market for Pegasys® has greatly diminished, such that Roche may well cease production in the near future. This means an important drug treatment would no longer be available to Australian MPN patients.

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[2] Analysis based on Pharmaceutical Benefits Scheme and Repatriation Pharmaceutical Benefits Scheme Section 85 Supply Data, Australian Government Department of Health, www.pbs.gov.au

[3] The FDA has accepted Pharmaessentia's application

[4] https://www.sciencedirect.com/science/article/abs/pii/S2352302619302364?dgcid=coauthor

MPN patients typically use pegylated interferon long-term, and disruption in supply can cause blood counts to rise to a level which puts them at serious risk of thrombosis and disease progression[5].

Discussion

Is there a system in place to promptly alert Australian authorities to new drugs and new overseas approvals to expedite approvals in Australia? If not, we believe a system is needed where our government is promptly aware of overseas approvals. We understand the Therapeutic Goods Administration already takes into account decisions by reputable overseas regulatory authorities, thus minimising duplication and a lengthy process. However we are unsure of whose responsibility it is to initiate this process and so facilitate a rapid pathway to approval for Australian patients.

In addition to such a system, perhaps there could be a 'check and balance' role for patients and/or patient advocacy groups via a government patient portal or similar? Informed patients are well aware of overseas developments and significant drug approvals via reputable internet sites which are advised by leading MPN haematologists such as MPN-Hub and VJHem Onc. Such a role could perhaps ensure that approval processes in Australia are not inadvertently missed. If such a process already exists, then perhaps some form of awareness-raising would be useful, such as via the Leukaemia Foundation and other well-known organisations.

Recommendation: That urgent consideration be given by government to the approval of the new drug Ropeginterferon in Australia due to the uncertainty around continued availability of the only other available form of pegylated interferon, Pegasys. (ToRs 2 and 4)

Recommendation: That a system be put in place to facilitate prompt approval from Australian regulators when new drugs are approved by reputable overseas authorities and there is a clear need in Australia. (ToR 4)

2. Process for obtaining PBS approval

Similar uncertainty exists for obtaining timely approval of any new drugs for listing under the Pharmaceutical Benefits Scheme once they are approved for use in Australia by the TGA. If the drug company does not initiate prompt action for PBS approval, is it the role of patients to seek urgent approval in the case of a rare disease such as an MPN? Ultimately it was an MPNAA member who played a significant role in having the currently used pegylated interferon, Pegasys® listed on the PBS. Timing of any application to the PBS is critical because, even if approved for use in Australia, this drug may still be out of reach of patients should it not be available on the PBS.

Case study –The journal article *'Recommendations for the use of pegylated interferon-α in the treatment of classical myeloproliferative neoplasms'* outlines the role of MPN AA member Nathalie Cook in seeking inclusion of Pegasys® on the PBS [6]. While this is a wonderful outcome, it highlights a systemic gap in our Australian processes and places a serious burden on patients who are already struggling with managing their disease and paid employment etc.

[5] https://ashpublications.org/blood/article/134/Supplement_1/2942/423552/Interferon-in-Polycythemia-Vera-PV-Yields-Improved?searchresult=1
[6] https://pubmed.ncbi.nlm.nih.gov/30411442/

Recommendation: That a system be put in place to facilitate prompt PBS approval once new drugs are approved by the TGA. (ToR 4)

All the issues raised above fall under recommendation 2.4.3 of the Rare Voices action plan. 'Ensure people living with a rare disease have equitable access to medicines with demonstrated clinical benefit for a rare disease, including those that are already funded for another condition.'

3. Access for Australian patients to more clinical trials

We are aware that Australia has a strong international reputation for being a leader in clinical trials.[7] Despite this reputation however, for myelofibrosis patients in particular, there are few clinical trial options available and this is catastrophic if ruxolitinib treatment has failed them.

Hospitals – building capacity for clinical trials
As a systemic issue, we are not convinced that the process of drug companies choosing sites for clinical trials is especially robust or transparent. We are concerned that it is instead based on outdated knowledge and assumptions about hospitals' reputations, or sometimes choices even appear to be random and based on past history or personal connections. We believe there may be more clinical trial options for patients if a relatively simple issue such as hospital information and capability could be clear, consistent and readily identified for drug companies, ie providing an up to date database with transparent and consistent information about hospitals, hospitals' areas of particular expertise, size of the particular specialist unit and disease patient populations serviced by hospitals research capacity of the hospital etc.
As patients, ensuring as many hospitals as possible are offered the opportunity to run a trial and facilitating trial sites in each Australian state and territory would be a valuable outcome, broaden expertise in clinical trials and contribute to Australia being a more attractive place for clinical trials.

Recommendation: Establishment of a database for Australian hospitals to publicise their credentials to participate in clinical trials, areas of strengths etc. (ToR 3)

Importantly, sufficient funding for research and trials is also an issue. Patients are aware that medical specialists currently face very competitive grants processes with very limited pools of funds to facilitate further research. **(ToR 3)**

The issues of facilitating clinical trials, facilitating access to trials as well as funding for research fall under recommendations 3.2.4 and 3.2.5 of the Rare Voices action plan:

'Building on existing initiatives, continue to foster an environment conducive to clinical trials for rare diseases taking place in Australia.'
'Investigate and promote options that enable Australians living with a rare disease to participate in clinical trials and other research activity, both in Australia and internationally (without needing to leave Australia).'

4. Incidence of MPNs not fully transparent

MPN patient data is not yet consistently recorded across Australia – yet accuracy of disease numbers drives not only research, epidemiology, drug companies' interest, cost to government for health care, pharmaceuticals, clinical trial interest, etc. The MPN AA believes improved data acquisition

[7] https://www.abc.net.au/news/2020-06-14/coronavirus-opportunity-australia-medical-research-global-leader/12353754

systems would assist collection of accurate data on MPNs and other rare diseases and thus facilitate interest in and capacity for clinical trials. For example, based on a population study in Denmark identifying MPNs, if results are applied to Australia, MPN incidence is likely higher than currently recognised and lack of diagnosis is putting lives at risk of stroke, thrombosis and heart attacks. [8]

Recommendation: That all MPN diagnoses be recorded consistently across Australia. (ToR 3)

5. Tracking treatment outcomes

Patient outcomes, and which treatments have best impact on outcomes, are not systematically collected in relation to MPNs in Australia – yet via citizen science, patients may be able to help harness data collection if a system/researcher was able to facilitate and guide appropriate items for collection. The simple but valuable approach of collecting robust data could potentially highlight causes, symptoms, symptom related side effects or superior treatment outcomes, something still largely lacking for MPN patients world-wide. Such detailed personal perspectives could enrich data collected through clinical settings and thus boost Australia's potential as a valuable site for comprehensive clinical trials with potential for long term measurement and follow up capability.

Recommendation: That patient citizen science be harnessed to record and track patient data. If a secure app or website was established for patients to input data (or enable MyHealth record to collect this data?), this could inform research and provide an inexpensive means of tracking rare diseases, treatments, symptoms etc that could be used more broadly in health area. (ToR 3)

Issues 4 and 5 fall under recommendation 3.2.2 of the Rare Voices action plan 'Proactively address evidence gaps in areas that are important to people living with a rare disease.'

6. Access to Genetic (Next Generation Sequencing) testing

Genetic testing to identify risk factors and prognosis has dramatically changed the landscape for MPN patients. Most patients are now offered MPN driver-mutation testing (JAK2V17F, CALR, MPL). For those fortunate enough to have a full myeloid gene panel completed, identification of certain additional gene mutations are strong determinants of outcomes. This has amplified the necessity of stem cell transplants being offered earlier to those harbouring harmful additional mutations.

As outlined earlier in relation to drug approvals, MPN AA believes there could be more clarity around who should take responsibility for advocating access to new technologies, especially for genomic testing. Genomic testing is costly, yet can be a vital factor in determining prognosis and survival, particularly for patients resistant to current treatments or showing other signs of escalation in their disease path. Genomic testing can inform further treatment steps.

This is consistent with recommendation 2.4.1.2 in the Rare Voices action plan stressing the importance of systematic, equitable and timely delivery of genomic services, such as genetic testing (diagnostics). For patients accessing testing in centres where payment is required, we recommend that the federal health department offer financial assistance to patients who qualify.

[8] https://pubmed.ncbi.nlm.nih.gov/31217187/
Prevalence and phenotypes of JAK2 V617F and calreticulin mutations in a Danish general population

Case study. As a PV patient's blood counts were not being controlled even with the full dose of interferon, the haematologist explored genetic testing to identify any additional mutations other than the Jak2 v617F mutation. Genomic testing revealed an additional and particularly harmful mutation, meaning a high risk of developing acute myeloid leukaemia. The five years earlier bone marrow biopsy was then revisited and that same mutation was present but not tested for at that time probably due to cost constraints. This patient is in their late 50s. Their haematologist's advice is to take the route of a stem cell transplant. Had the patient not travelled to a major city hospital with access to genetic testing, the mutation may never have been found/or not early enough to have the chance for a life-saving transplant. Genomic testing identifies high risk mutations (and therefore high-risk patients) earlier, when survival chances from a transplant are substantially greater.

Recommendation – that all at risk patients around Australia are able to access genomic testing. While funding is a separate issue due to cost, ideally government could meet the cost of genetic (next generation sequencing) testing for patients who qualify. (ToRs 1 and 2)

Recommendation 2.4.1 of Rare Voices action plan refers. 'Develop policy that supports people living with a rare disease to have timely and equitable access to new and emerging health technologies'

7. Ensuring supply of medication due to geopolitical considerations – developing a stockpile, ensuring alternative supply lines or considering an Australian manufacturing capacity?

Of further concern to us is the issue of the supply chain of medications in an unstable world. For example, ropeginterferon is manufactured in Taiwan. If Australian patients are able to access this new drug, geopolitical tensions in the South China Sea heighten our fears about ongoing access. Is our government considering acquiring a stockpile of medications in such circumstances? Or if this is not an option, is considering alternative supply lines such as from India being considered. For example we believe that pegylated interferon (Pegasys®) is off patent in India and so perhaps could be imported for Australian patients should BESREMi® not be available?

Or, as COVID 19 has recalibrated Australian policy makers thinking on our capacity to produce vaccines, is the ability to manufacture pegylated interferon something Australian companies could do? The newly developed ropeginterferon may not be able to be manufactured here due to its orphan status but perhaps the current pegylated interferon Pegasys® could be produced here? An Australian manufacturer may have the added benefit of lowering drug costs.

Recommendation – that Government have a back-up planto ensure supply of medications that could be compromised due to geopolitical problems. (ToR 2)

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