Life Saving Drugs Programme Post-market Review
Pharmaceutical Evaluation Branch
Pharmaceutical Benefits Division
Department of Health
GPO Box 9848
Canberra ACT 2601

7 November 2014

Dear Life Saving Drugs Programme Post-market Review

Re: Public consultation on the Post-market Review of the Life Saving Drugs Programme (LSDP)

BioMarin welcomes a review of the Life Saving Drugs Program and the opportunity to make a submission for consideration as part of the Review. The most important outcome of such a review is to ensure timely and sustainable access to treatments that have a positive impact on the quality of life and life expectancy of Australians living with rare diseases.

Whether funding for rare disease treatments is administered as a separate program such as the LSDP, or as part of the Pharmaceutical Benefits Schedule (PBS), the evaluation and administration process must have the capacity to clearly distinguish treatments for rare (orphan) and ultra-rare (ultra-orphan) diseases from those for conventional diseases because of their unique considerations. In this regard, there are several important principles regarding rare disease treatments that must be taken into account:

1) <u>Cost-effectiveness</u>
   Orphan drugs for rare diseases often do not meet the cost per Quality-Adjusted Life Year (QALY) threshold because of relatively high cost per patient despite their sometimes dramatic clinical benefit. This is due to the high fixed cost of Research and Development, and the need to recoup this investment from a small number of patients within limited periods of market exclusivity. The QALY approach assumes that all conditions and treatments are equal, no matter how many other treatment options are available, and no matter what the burden of illness may be for patients and their carers. Alternative measures of value such as social willingness to pay[1] and Multi-Criteria Decision Analysis (MCDA) [2, 3] may be more useful when considering rare disease treatments.

2) <u>Level of evidence</u>
   Rarity means the volume and type of evidence may not be the same as in the case of conventional diseases. Patient populations are small and heterogeneous, and there is often limited natural history data of the disease. There may be limited scientific understanding and consensus on clinical endpoints. There may be a lack of comparators and often limited hard clinical outcomes such as survival. Clear patient-relevant endpoints should be defined by considering the medical need and relevant criteria derived from literature review, past reimbursement decisions and consultation

with patient groups. These need to mirror the impact of disease for patients, families, society and payers.

3) Equity of access

Unlike a number of the major healthcare concerns facing Australia today, rare diseases are not lifestyle illnesses that patients have some control over. Australians living with rare diseases, many of whom are children, did not choose to be inflicted with a rare condition or the disability that often accompanies it. Australian human rights [4] and disability discrimination legislation [5] promotes the right to enjoy a life as normal and full as possible, the right to medical treatment, the right to measures that will enable individuals to become as self-reliant as possible, and the right to have their special needs taken into consideration at all stages of economic planning. These rights make it necessary to provide equity of access to treatments for rare diseases as with common illnesses.

4) Social preferences for healthcare in Australia

Social preferences of the Australian community[1] must be taken into account:

- a preference to prioritise health care for the worse off;
- a strong dislike for "all-or-nothing" resource allocation decisions;
- concern for the urgency of the initial health problem, especially if life-threatening;
- a preference for equitable outcomes over aggregate health benefits

It is therefore a matter of importance to the Australian community that patients with rare diseases are provided timely access to effective treatments. Please find specific comments on the terms of reference below.

Yours Sincerely

Kathryn Evans
Country Manager, Australia

Life Saving Drugs Program Review
Response to Terms of Reference

1) **Review the clinical effectiveness and safety of medicines currently subsidised through the LSDP.**
Current clinical effectiveness and safety data for galsulfase (Naglazyme®) was provided to the LSDP on 23 September 2014. This highlights the continued research on galsulfase conducted over a number of years since registration.

2) **Review emerging clinical treatments and diseases, including those that identify sub-groups by molecular target, which could potentially seek subsidisation through the LSDP in the future.**
Information on BioMarin's clinical development pipeline is available at www.bmrn.com

3) **Conduct an international comparison of subsidisation of drugs for rare diseases and the definitions for a rare/ultra-rare disease**
Subsidisation of BioMarin's commercial products is shown below.

Product/disease	**Countries where funded**		
galsulfase (Naglazyme®) for Maroteaux-Lamy (MPS-VI)	51 countries:	Austria	Russia
	Australia	Belarus	Slovakia
		Belgium	Slovenia
	Hong Kong	Bulgaria	Spain
	Japan	Croatia	Sweden
	Malaysia	Cyprus	Switzerland
	South Korea	Czech Republic	UK
	Taiwan	Denmark	Ukraine
		France	
	USA	Germany	Algeria
	Canada	Greece	Egypt
		Ireland	Iran
	Argentina	Italy	Israel
	Brazil	Kazakhstan	Kuwait
	Chile	Netherlands	Libya
	Colombia	Turkey	Qatar
	Guatemala	Norway	Saudi Arabia
	Mexico	Poland	UAE
	Peru	Portugal	
elosulfase alfa (VIMIZIM™) for Morquio A (MPS-IVA) NB: Vimizim was approved by FDA on 14 February 2014 and is currently being assessed by the TGA and PBAC	16 countries:		
	USA	Austria	Bahrain
	Canada	Czech Republic	Israel
		Denmark	Qatar
	Brazil	France	Saudi Arabia
	Argentina	Germany	UAE
	Colombia	Italy	

The definition of rare (orphan) diseases varies by country as shown in the table below, however rare diseases under consideration should be [2, 6]:

- Severe (i.e. life-threatening or chronically debilitating)
- Chronic
- represent clearly defined biological entities (i.e. are not created by artificial "slicing" of a biologically much broader and more prevalent indication)
- associated with a broadly accepted high unmet medical need

Country	Rare (orphan)	Ultra-rare (ultra-orphan)
Australia	prevalence <2,000 (<1:10,000) [7]	
USA	prevalence <200,000 (< 7.5:10,000) [8]	
Japan	prevalence <50,000 (<4:10,000) [9]	
European Union	prevalence <5:10,000 [10]	prevalence <1:50,000 [11]
UK		prevalence <1:50,000 [12]

4) Compare the subsidisation and equity principles of the Pharmaceutical Benefits Scheme and the LSDP.

The European charter of patients' rights explicitly states that an individual suffering from a rare disease has the same right to the necessary treatments and medication as someone with a more common disease [13]. In Australia, the Disability Discrimination Act 1992 promotes recognition and acceptance within the community of the principle that persons with disabilities have the same fundamental rights as the rest of the community [5]. Additionally the Australian Human Rights Commission Act 1986 promotes the principle that every person is equal in dignity and rights [4]. It emphasises the necessity of preventing physical and mental disabilities and of assuring the welfare and rehabilitation of the physically and mentally disadvantaged. Disabled persons, whatever the origin, nature and seriousness of their handicaps and disabilities, have the same fundamental rights as their fellow citizens of the same age, which implies first and foremost the right to enjoy a decent life, as normal and full as possible. The Act also states that disabled persons are entitled to the measures designed to enable them to become as self-reliant as possible, and they have the right to medical treatment which will enable them to develop their capabilities and skills to the maximum. Additionally the Act states that disabled persons are entitled to have their special needs taken into consideration at all stages of economic and social planning.

Rare disease treatments may be necessary to prevent deterioration in the health and quality of life of Australians with rare diseases, to develop their capabilities to the full and to enable them to be self-reliant. However it would be unjustifiable hardship for an individual suffering from a rare disease not to receive subsidisation for such treatments, particularly in light of the high cost often associated with orphan drugs. Therefore, access to funding for such treatments for rare diseases is a fundamental right for patients with rare diseases.

Additionally, the purpose of orphan legislation introduced in jurisdictions such as USA, Europe, Japan and Australia was to incentivise research in these patients where treatment is challenging and expensive [14]. However, such policies will have limited relevance if subsequent reimbursement of

treatments for rare diseases is denied on grounds of their high incremental cost–effectiveness ratios [2] and research for these vulnerable patients will be jeopardised.

The principles of the PBS are evaluation on the basis of safety, clinical and cost effectiveness, affordability and equity whereas the principles of the LSDP are safety, clinical effectiveness, affordability and equity. The removal of cost-effectiveness as a criteria for the LSDP is intended to provide equity of access. However, additional strict and sometimes subjective criteria for entry onto the LSDP means that equity of access is not always achieved for rare diseases, therefore other methods that are specifically designed for evaluating rare diseases may be needed [2, 3, 6].

5) **Assess the value for money of the medicines subsidised on the LSDP by evaluating the benefit of each drug's treatment outcomes, including in terms of quality of life achieved through the programme, and their cost.**

Assessing value for treatments of rare diseases has long been a challenge. New products for rare diseases are expensive due to the high fixed cost of Research and Development and the need to recoup this investment from a very small number of patients. Orphan drugs are priced so as to achieve a return on investment and even with a favourable clinical profile, are mostly not considered cost-effective relative to the standard thresholds. Rarity also means the weight of evidence is not the same as conventional diseases, risks in development are often greater, and there may be limited hard clinical outcomes such as survival or Quality of Life. This poses a challenge for decision makers, and other ethical, political and social factors come into play when considering reimbursement of orphan drugs.

"This raises a question of equity: is it fair to discriminate against those who are unlucky in having an illness where science has not found a cost-effective intervention?" [1] Results of a 2012 NHRMC funded study indicate that Australians consider sharing health resources to be important and would trade-off aggregate health benefits to mitigate the personal consequences of an illness with a high-cost effectiveness ratio [1]. Since the PBS was originally established to ensure equity of access to necessary drugs, it is perhaps unsurprising that Australians judge the importance of equity over aggregate health benefits and that researchers therefore suggest that the primary focus of evaluation of rare disease treatments should be upon equitable outcomes [1].

Using Incremental Cost-per-QALY-Gained Benchmarks would have the potential to necessarily and inevitably deprive many patients with ultra-rare diseases from any chance to ever get access to innovative, effective interventions. In most cases, criteria other than cost-effectiveness are used to inform reimbursement of orphan drugs, including severity of the disease, availability of other therapies to treat the disease and cost to the patient of the therapy if not reimbursed.

Researchers have suggested that medicines for rare disease may be more effectively valued using multi-criteria decision analysis that includes all relevant stakeholders, including patient groups [3]. Overall budgetary impact should be more relevant than incremental cost effectiveness ratios. Current expenditure on rare diseases in Australia is a very small proportion of the funded drug budget at approximately 0.79% [15, 16]. In Europe, it is anticipated that budget impact of rare disease treatments will plateau in 2016 at 4-5% of total drug spend [17].

6) **Review the administration of the LSDP, including the Guidelines with which the programme is administered for each condition, and assess alternative administration systems.**
Regardless of the administration system applied to the funding for rare disease treatments, it is necessary to clearly distinguish treatments for rare diseases from those for conventional diseases because of their unique considerations. In this regard, appropriate guidelines for approved treatments must be established in close consultation with experts in the disorder, and with regard to the specific patient groups affected.

Regarding the guidelines or criteria for access onto the LSDP itself, it is vital that these are reviewed so as to recognise the particular challenges associated with levels of evidence in the rare diseases field. As previously mentioned, rarity means the weight of evidence is not, and cannot be the same as many conventional diseases. The current guidelines requiring the provision of "evidence acceptable to the PBAC" that the treatment "substantially extends life expectancy" can be extremely challenging to meet for progressive rare diseases. Although it can be demonstrated that the disease substantially shortens patients' lives, it may be impossible to provide data on survival outcomes within the scope of phase III efficacy trials for orphan treatments. Once efficacy is established, it is unethical to continue patients on placebo for the time that may be necessary to demonstrate survival benefits. Nor is it ethical to deny effective treatment to patients for the time it may take to collect registry or other observational data to demonstrate a survival benefit. In the case of galsulfase for example, it is only with the publication of 10-year re-survey data that a clear survival benefit has been demonstrated between treated and untreated MPS VI patients in an observational study [18]. It would not be feasible, or indeed ethical to deny young children with MPS VI access to treatment or continue them on a placebo controlled study for that length of time, because of the severe and progressive nature of the disease.

Study endpoints should be defined by considering the medical need and relevant criteria derived from literature review and clinical experts in the disease state, past reimbursement decisions and consultation with patient groups, and need to mirror the impact of disease for patients, families, society and payers.

Given the need for specific considerations to be given to the evaluation of rare disease treatments, and indeed the necessity for guidelines on management of chronic patients on these long-term therapies, it may be an option to administer them under a special section of the PBS, not unlike Section 100, but with its own set of criteria and guidelines for evaluation and administration that recognise the unique set of challenges for these patients and for the clinicians, researchers and sponsors working in this field.

7) Establish a framework for data collection on rare diseases in Australia and assess how this could function internationally.
BioMarin maintains international registries on our products as part of our post-marketing commitments for Naglazyme and Vimizim. Annual reports are currently provided to the TGA and LSDP for approved products.

References:

1. Richardson, J., et al., *Maximising health versus sharing: Measuring preferences for the allocation of the health budget.* Social Science & Medicine, 2012. **75**(8): p. 1351-1361.
2. Schlander, M., et al., *Incremental cost per quality-adjusted life year gained? The need for alternative methods to evaluate medical interventions for ultra-rare disorders.* Journal of Comparative Effectiveness Research, 2014. **3**(4): p. 399-422.
3. Sussex, J., et al., *A Pilot Study of Multicriteria Decision Analysis for Valuing Orphan Medicines.* Value in Health, 2013. **16**(8): p. 1163-1169.
4. *Australian Human Rights Commission Act*. 1986: Australian Government.
5. *Disability Discrimination Act*. 1992: Australian Government.
6. Clarke, J.T.R., et al., *Toward a Functional Definition of a "Rare Disease" for Regulatory Authorities and Funding Agencies.* Value in Health, 2014.
7. *Therapeutic Goods Regulations*. 1990: Australian Government.
8. *Rare Diseases Act*. 2002: 107th United States Congress.
9. *Article 77-2 of the Pharmaceutical Affairs Law*, in *Japan*.
10. The Council of the European Union, *Council Recommendation of 8 June 2009 on an action in the field of rare diseases*. 2009.
11. Groote, M. and G. Willmott, *Proposal for a regulation on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.* 2014.
12. NICE, *Citizen Council Report on Ultra-Orphan Drugs*. 2004.
13. *European Charter of Patients' Rights*. 2002: Rome.
14. Rinaldi, A., *Adopting an orphan. Incentives to develop drugs for rare disorders raise hopes and controversy.* EMBO Reports, 2005. **6**(6): p. 507–510.
15. *Australian Government 2014-15 Budget Paper No.1 Statement 6: Expenses and Capital Expenditure, May 2014*.
16. *Communication to industry regarding LSDP post-market review*. Aug 2013.
17. Health Technology Assessment World Europe. *Top HTA considerations for orphan drugs*. 2013; Available from: http://www.terrapinn.com/template/Live/engage/6177/12364#sthash.fGLpsIJw.dpbs
18. Hendriksz, C.J., et al., *Efficacy and safety of enzyme replacement therapy with BMN 110 (elosulfase alfa) for Morquio A syndrome (mucopolysaccharidosis IVA): a phase 3 randomised placebo-controlled study.* Journal of Inherited Metabolic Diseases, 2014. (Published online 9 May).