Orphan Drugs Consultation
Regulatory Operation Unit
Market Authorisation Division
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

24 November 2016

Dear Sir/Madam,

2016 Consultation Paper of TGA Orphan Drugs Program

Please find attached the response from Novartis Pharmaceuticals Pty Ltd ['Novartis'] on the September 2016 orphan drug public consultation paper.

Novartis responded to the 2015 public consultation and our submission is available in full on the TGA website1. Before commenting on the latest consultation paper, Novartis wishes to reaffirm its support for the objectives of the TGA’s orphan drug program, which aims to help make medicines available to patients who suffer from rare diseases. Addressing significant unmet medical need remains a cornerstone of Novartis’ research and development strategy.

At the same time, we feel that the Australia’s orphan drug policy should also help support the Government’s innovation agenda and not be a disincentive, or an impediment to the development of new treatments for rare diseases by a company, or to increasing university (and other research organisation) engagement and collaboration with local businesses.

We welcome the opportunity to provide feedback on the proposals described in the 2016 consultation paper, ahead of the legislative changes needed to implement amendments to the TGA orphan drug program. In this submission, Novartis has responded to the six questions posed by the TGA in the 2016 consultation paper. For clarity and convenience, we have included each question ahead of our response.

Responses to TGA questions on new criteria

Question 1: Do you support criterion one? [Rare disease threshold or lack of financial viability and seriousness of the condition]

Novartis position: Agree

Novartis remains strongly in favour of a rare disease threshold based on prevalence rather than a fixed number of affected patients. This was the view we expressed in our 2015 submission. We support the proposed threshold of 5/10,000 as this is comparable to thresholds used in comparable jurisdictions. In addition, we accept the seriousness of the condition as a new criterion to ensure that only conditions that are life threatening or chronically debilitating will qualify.

We would however seek clarity on how financial viability will be determined at the point when an orphan designation is being sought and before the registration application is submitted to the TGA and any subsequent filing for PBS listing. The Australian sale estimates cited in the discussion paper are based on PBS (Government reimbursed) sales and we therefore assume this will be used to determine financial viability. If this is the case, then Novartis would respectfully ask how the TGA will administer this over the course of a product’s post-approval lifecycle.

**Question 2: Do you support criterion two? [Alternative methods of diagnosis, prevention or treatment]**

**Novartis position: Partially agree**

Novartis agrees that orphan designation should be reserved for conditions where there is no existing therapy, or where the product represents a significant benefit over existing therapies. However, we believe this should not preclude a sponsor from seeking orphan designation for new drugs in class that may offer clinically relevant benefits, even if a benefit has not been directly established in a head-to-head trial with the Australian standard of care. It is important to keep in mind that some patients may be unable to tolerate, or may develop resistance to the original orphan drug, so an alternative therapy would represent a potential benefit to them.

The availability of newer compounds which are able to overcome resistance represents a significant clinical advantage. By way of example, ceritinib (Zykadia®, AUST 235737) and crizotinib (Xalkori® AUSTs 190966 190965 & 190964) both received orphan designation from the TGA for the treatment of patients with ALK-positive non-small cell lung cancer (NSCLC). Crizotinib is approved as a first line agent, although resistance often occurs. Ceritinib was specifically developed and approved by the TGA for patients who relapse on crizotinib.

Novartis considers that establishing a significant benefit should not simply be based on a direct comparison with the Australian standard of care. Rather, the criteria should recognise the clinically relevant need for effective follow-on agents for patients who are unable to tolerate, or develop resistance to, or otherwise fail to respond to the original orphan drug and where there is evidence to support use in that setting.

**Question 3: Do you support criteria three and four? [Medical plausibility]**

**Novartis position: agree**
Novartis has no objection to the introduction of these criteria.

**Question 4: Do you support the proposed consideration of paediatric indications?**

**Novartis position: agree**

Novartis agrees paediatric indications should continue to be considered for orphan designation.

**Question 5: Do you support the proposed changes to the designation process and the timing of automatic lapsing?**

**Novartis position: partially agree**

Novartis has no objection to the TGA introducing a mechanism by which an orphan designation can lapse or be cancelled, as long as there is a fair and reasonable opportunity for the sponsor to offer a justification against such action being taken. We also agree that it is important that an orphan designation is based on information that is as up to date as possible. However, Novartis believes that automatic lapsing or cancellation of an orphan designation would not be in the interests of procedural fairness. Novartis is concerned that if the TGA apply an indiscriminate expiry period to all orphan designations, the unique difficulties sometimes encountered when preparing the regulatory application for orphan drugs may not be properly taken into account.

The risk of an orphan drug development program failing is arguably higher than that of a non-orphan drug due to the challenges of establishing treatment effects in very small populations (ref). According to the 2016 consultation paper, only 30% of orphan registration applications were lodged within 3 months of designation, while 57% were lodged within a year and 34% had not been lodged in 5 years. Although the paper does not specify how many of these applications were finally approved, it is concerning to think that many of these orphan designations would have lapsed if the 3 to 6 month period proposed by TGA had been imposed at the time. Moreover, it would seem peculiar for a sponsor to seek an orphan designation without the intention of subsequently submitting a regulatory application within a reasonable time period. We therefore suspect that the 34% of orphan designations that did not proceed to a registration application may reflect the significant challenges associated with the development of orphan drugs.

In addition, sponsors could be especially disadvantaged when a registration application for an orphan drug relies solely, or predominantly, on published literature to support the safety and efficacy claims (eg. ‘Literature Based Submissions’ or ‘Mixed Applications’). These special types of submissions would conceivably be more commonplace for orphan drugs compared to non-orphan drugs, due to the general paucity of data on rare diseases. Literature based submissions (LBS) represent a significant commitment and resource-intensive undertaking for the sponsor. It has been our experience that the pre-submission planning for LBS can generally take several months. This, together with the fact that there is no fixed, or statutory timeframe for the TGA to review an orphan application, leaves the sponsor without a procedural remedy or recourse if faced with an automatic cancellation of an orphan designation during the course of the LBS pre-
submission planning and preparation. For orphan drugs that are subsequently submitted for TGA approval as a LBS, we believe it would fair for a sponsor to have a reasonable degree of certainty of maintaining the orphan designation for a long enough period of time to effectively prepare and submit the LBS.

Novartis is particularly concerned with the proposal that the TGA can be withdraw or cancel an orphan designation at any time if there is evidence that the criteria are demonstrably no longer valid. Given that the only incentive offered by the TGA for orphan designation is the evaluation fee waiver, Novartis seeks clarity on how this proposal would be leveraged over the course of the evaluation and during the product’s post-approval life-cycle, and what the consequences might be if the TGA rescind an orphan designation. By way of comparison, in the EU, the criteria are reviewed at the end of the registration process to decide whether a product should keep its orphan designation and consequently benefit from the market exclusivity incentive.

**Question 6: Are there any other key issues that should be considered in developing the changes to the orphan drug program?**

In a subsequent email to respondents dated 7 November 2016, the TGA explained that other issues raised by a number of respondents, including additional incentives, have not been addressed as part of the 2016 proposal. Novartis has certain reservations with the explanation, specifically in relation to the decision to not consider the TGA’s current 5-year data exclusivity provision as part of the 2016 consultation.

We understand the objective of the 2016 public consultation is to frame an orphan drugs proposal, which is based on options presented in the 2015 consultation that received support from the majority of respondents. As the issues of “additional incentives” and “market exclusivity” and/or “data exclusivity” were out of scope of the original 2015 consolation, it seems understandable that they did not receive majority support. Indeed, the fact these issues were raised at all suggests that respondents felt there was a clear enough need to review the matter.

Novartis believes that market exclusivity is crucial to any system of incentives for research and development of orphan drugs and to finding innovative new pathways to treat rare diseases. The limitations of TGA’s current incentive for orphan drugs could make local research into developing effective treatments for rare diseases less attractive and viable compared to overseas. This could inadvertently diminish Australia’s competitiveness in industry relevant collaborations and research outcomes. Rewarding research based on its impact and relevance to industry and society is a key principle of the Government’s Medical Research and Innovation Strategy 2016-2021. A fee waiver for an orphan application represents only a small proportion of the drug development costs, while the real value is arguably in gaining additional market exclusivity. By not extending the data exclusivity period for orphan drugs, there seems no long-term incentive for local

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3 Australian Medical Research and Innovation Strategy 2016-2021.
companies and academic research institutions to pursue or invest in any research and development into rare diseases, particularly those that may be unique to Australia’s public health.

It is difficult to see why changes to Australia’s current data exclusivity laws would require any further analyses and could not be considered as part of the current consultation and round of legislative changes. Extending the data exclusivity for orphan drugs (from 5 to 7 years, for example) would have no economic or resource impact on TGA. Certainly the criteria proposed in the 2016 consultation objectively applied would make it unlikely that increasing data exclusivity for orphan drugs would somehow lead to a sudden increase in the number of orphan applications or designations. What an extension of the data exclusivity provisions would do is help offset the higher commercial risks associated with developing these orphan drugs in keeping with orphan programs of other comparable regulatory authorities.

**Concluding remarks**

Novartis continues to support for the objectives of the Australian orphan drug program to help make medicines available to patients who suffer from rare diseases. We welcome the proposed changes to the rare disease threshold which we agree will create a more equitable and sustainable framework. The other proposed consultation items also have merit, although Novartis recommends that further consideration be given the short and long-term implications described in this letter, so that they do not detract from the objectives of the Australian orphan drug program. Finally, we would urge the TGA to take this opportunity to reconsider extending the data exclusivity provisions of orphan drugs as part of the current consultation, in keeping with systems in place in comparable jurisdictions. We believe a key benefit of this would be to enable innovative treatments to be developed in rare disease.

Novartis thanks the TGA for considering its submission.

Yours sincerely,

George Lillis