MSD
Merck Sharp & Dohme (Australia) Pty Limited
ABN: 14 000 173 508
Level 1 - Building A, 26 Talavera Road
Macquarie Park NSW 2113
North Ryde Post Business Centre
Locked Bag 2234 North Ryde, NSW, 1670
T 02 8988 8000
F 02 8988 8001
msd-australia.com.au

October 17th, 2013

To whom it may concern:

MSD supports the conclusions of the report from Deloitte Access Economic on Access to Cancer Medicines in Australia, namely that stakeholders should engage in an open, informed dialogue, on how to ensure that Australian patients continue to benefit from equitable and affordable access to cancer medicines. Inaction will inevitably result in Australian patients being denied major therapeutic advances, with the risk that Australia will fall behind other developed countries with respect to the delivery of innovative cancer medicines to patients.

The purpose of this submission is to make suggestions on how the re-imbursement of oncology medicines could be reviewed to ensure timely and appropriate access to these medicines, commensurate with access in other countries.

Specifically MSD would like to propose that:

1. The PBAC and MSAC should take a more pragmatic approach towards trial evidence in oncology. Other fit-for-purpose data should be considered acceptable.
2. The value of surrogate endpoints from clinical trials should be recognised and used to make re-imbursement decisions.
3. PBAC should acknowledge the unique challenges in establishing cost-effectiveness of oncology medicines, and adapt the current decision-making criteria accordingly.
4. PBAC should review the process for pricing new oncology agents to ensure commercial viability of launching new agents in Australia.
5. PBAC should make ICER thresholds transparent so that companies have a reasonable expectation of the comparator price and the willingness-to-pay.
6. Risk sharing arrangements need to ensure that companies are fairly compensated for innovation, and that risk is more equitably shared.
7. The framework for managed entry schemes should be re-assessed.
8. MSD would like to see a more streamlined process for reviewing co-dependant technology to speed up access to oncology medicines.

Further details are provided in the following pages.

The PBAC and MSAC should take a more pragmatic approach towards trial evidence in oncology. Other fit-for-purpose data should be considered acceptable.

- With the introduction of targeted cancer therapies, as well as in rare forms of cancer, the small patient population means there might be insufficient recruitment to undertake an RCT; alternatively, recruitment could be slow, thereby increasing exponentially the cost of undertaking research.

- In certain situations, there are ethical considerations regarding the inclusion of placebo arms in randomised trials. Similarly, testing a targeted therapy in a biomarker unselected population unnecessarily exposes a proportion of patients to an investigative treatment.

- The impact of crossover, which occurs where patients randomised to the comparator arm cross to the intervention arm following progression, is another major issue in oncology research. The impact of this on reimbursement was recently illustrated by Lewis and colleagues (2013)[1] using the example of epidermal growth factor receptor (EGFR) tyrosine kinases for first line treatment of non-small cell lung cancer. Crossover confounds the interpretation of survival benefits, the outcome that drives cost effectiveness of cancer therapies. However, preventing crossover in the design of trials is not a solution – it raises significant ethical challenges. Moreover, there is a high likelihood that these patients would be enrolled in other trials or receive compassionate access to other investigative drugs which would likewise confound the survival analysis. In an attempt to mitigate the impact of crossover statistical approaches have been proposed, but they have limited ability to robustly quantify survival gains.

- MSD therefore proposes that payers should consider alternative approaches, such as the use of observational cohorts, or information derived from real-world clinical settings, to determine the comparative effectiveness of a new intervention.

The value of surrogate endpoints from clinical trials should be recognised and used to make re-imbursement decisions.

- At present overall survival is considered to be the most clinically relevant and meaningful endpoint. However, collection of this endpoint takes time, and can unnecessarily delay access to an effective treatment. As discussed previously, interpretation of overall survival in oncology research is often confounded by differences in post-progression treatment amongst trial participants. In addition, trials can sometimes be terminated early if the data for the surrogate endpoint was compelling.

[1] Lewis JRR, Lipworth WL, Kerridge IH, O Day R. The economic evaluation of personalised oncology medicines: ethical challenges. MJA 199(7):471-473.

- Surrogate endpoints are substitutes for definitive endpoints predictive of clinical efficacy. Whilst on one hand, they are by definition associated with higher levels of uncertainty, on the other hand surrogate endpoints may be considered more reliable as they are measured much closer to the time that the intervention is delivered and are less likely to be confounded by other therapies.

- Surrogate endpoints have been considered acceptable by regulatory bodies such as the FDA and TGA and thus reasonable harmonisation with re-imbursement bodies should occur.

- The clinical benefits to end stage patients of surrogate endpoints should also be acknowledged. An extended "time to progression" may represent a large benefit to a patient with advanced disease; yet, in isolation, it would struggle to meet the "value" criteria set by re-imbursement authorities.

PBAC should acknowledge the unique challenges in establishing cost-effectiveness of oncology medicines, and adapt the current decision-making criteria accordingly.

- The PBAC assesses cost-effectiveness of a medication relative to a comparator (drug replaced most often by the new therapy). As Australia typically has less influence in trial design, comparators used in oncology clinical trials are frequently not available here or are not the standard of care. This means that indirect comparisons, which are methodologically less rigorous, are required for the PBAC submission. The PBAC has demonstrated a low acceptance rate of submissions based on indirect comparisons to prove superiority and this creates challenges with establishing cost effectiveness of an intervention.

- The level of acceptance of indirect comparisons when assessing cost effectiveness submissions should be increased, and a more pragmatic approach should be adopted when assessing the presented evidence.

- Whilst Australia has traditionally been at the forefront of Health Technology Assessment, PBAC guidelines have not evolved sufficiently to reflect the challenges posed by the development of new oncology medicines. A concerted effort to address this is urgently needed.

PBAC should review the process for pricing new oncology agents to ensure commercial viability of launching new agents in Australia.

- The price of new drugs needs to be referenced to that of the comparator, often cytotoxic chemotherapies. These agents have invariably seen their price eroded by price disclosure. A recent example is that for docetaxel, which in the interim supplementary cycle of price disclosure was reduced by 76.2%. This means that as of December 2012 it has become significantly more challenging to prove cost effectiveness of a new therapy relative to

docetaxel, notwithstanding that the new interventions might provide clinically important benefits to patients. In addition, this molecule may experience further price disclosure reductions in April 2014.

- The erosion of the price of the comparator makes it difficult to establish cost effectiveness at a price that is considered reasonable by the Sponsor. This results in innovative cancer medicines not being launched in Australia or launches being restricted to the private market, resulting in accessibility and affordability constraints.

- MSD therefore proposes that, where a price-disclosed F2 product is the appropriate comparator, a shadow price should be used that reflects either the price of the comparator before the listing of a second brand or a constructed price that reflects fair value for an innovative product.

PBAC should make ICER thresholds transparent so that companies have a reasonable expectation of the comparator price and the willingness-to-pay.

- Cost effectiveness submissions for anticancer agents have a low probability of approval for the first submission. The most common reason for rejection is "high and uncertain cost effectiveness", as the ICER is too high. A re-submission adds another minimum of 9 months on to the listing timeline. Greater transparency in the thresholds against which incremental cost effectiveness ratios (ICERs) are being assessed would afford companies greater certainty about acceptable price ranges and reduce re-submissions. This is particularly important since a significant number of oncology medicines are being listed on the basis of undisclosed pricing arrangements, making the effective price paid by the Commonwealth significantly different from that disclosed on the PBS website.

Risk sharing arrangements need to ensure that companies are fairly compensated for innovation, and that risk is more equitably shared.

- Once launched, pharmaceutical companies are being asked to accept greater risk to revenue. In recent times, the government has instigated risk sharing arrangements where the rebate paid by the company for expenditure over a defined cap is 100%. Often these caps are applied together with restrictive criteria for use, in order to manage perceived risk to the Commonwealth. However, there is no due process, other than by a re-submission instigated by the Sponsor, to review the need for these additional impositions.

- MSD proposes that the Government should commit to a due process, where the need for risk sharing arrangements and restrictions imposed on new listings are reviewed periodically, and listings amended accordingly, for example, if a product fails to achieve the volumes anticipated in a risk sharing arrangement.

- The Government should also commit to the intent of risk sharing arrangements, namely to share risk, rather than have companies bear all risk.

- Their integration into the current process of reimbursement submissions and decisions should also be reviewed, in order to accommodate the use of risk sharing arrangements within the submission process to accelerate PBAC consideration and to limit the need for subsequent re-submissions. This would help ensure timely access to innovative cancer medicines.

The framework for managed entry schemes should be re-assessed.

- Managed entry schemes were introduced in 2011 to create a framework whereby the PBAC would recommend listing at a price justified by the existing evidence, pending the availability of more conclusive evidence to support its continued listing at a higher price.

- Soon after it was established, Wonder and colleagues (2012)[2] produced a commentary examining the scheme, its limitations and issues that are likely to arise from its implementation. The authors highlighted the lack of an explicit endorsement of the scheme by the PBAC, notwithstanding that decisions for funding are made by this Committee. In addition, the explicit requirement for high level (RCT) evidence makes this scheme relevant for a small subset of products, e.g. those used for chronic treatment where it would be unlikely that the Sponsor would have outcomes data at the time of submission, and rather would have relied on the use of surrogate outcomes to establish cost effectiveness.

- More recently, a report in PharmainFocus noted that few companies, if any, have taken up the Managed Entry Scheme as a means to get reimbursement.

- This is perhaps not surprising, given the stated requirements for a low initial price with minimal confidence for a potential price increase on the basis of submission of additional data, and an explicit requirement for submission of high-level (RCT) clinical evidence.

- MSD therefore proposes that the framework of the scheme should be re-assessed. In particular, MSD would support broader support for the scheme from representative stakeholders including the PBAC and MSAC, allowance for submission of fit-for-purpose data instead of a requirement for RCT evidence, and a more equitable sharing of risk.

[2] Wonder M, Backhouse ME, Sullivan SD. Australian managed entry scheme: a new manageable process for the reimbursement of new medicines? Value Health. 2012 May;15(3):586-90.

MSD would like to see a more streamlined process for reviewing co-dependant technology to speed up access to oncology medicines.

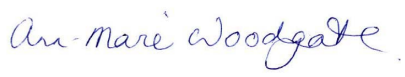
- Biomarkers are increasingly being used to predict patient response rates to therapies. The use of biomarkers is a positive step in terms of improving patient outcomes and cost effectiveness of treatment

- However, at present PBAC approval of a biomarker-dependent cancer drug is contingent upon the technology being available on the MBS through the MSAC process. This MSAC process is at least 1 year in length, whilst the PBAC process is a minimum of 9 months. As both committees only meet once every four month, delays in meeting a milestone can trigger a 4 month delay in the PBAC consideration of a drug. In addition, subsequent to PBAC approval, the current requirement is for a co-dependent technology to go back to MSAC.

- Greater co-ordination between MSAC and PBAC would reduce delays and uncertainty in medicine availability

MSD looks forward to the opportunity to engage in a comprehensive, meaningful dialogue with relevant stakeholders and the broader community, in order to develop a long term sustainable solution that ensures Australian patients have access to innovative cancer drugs.

Yours sincerely



Ann-Marie Woodgate
Health Outcomes Associate
MSD (Australia)

Yours sincerely

Carmel Spiteri
Health Outcomes Manager
MSD (Australia)