Interventional Cardiology Advisory Group
Meeting held 17 February 2017

(minutes for web publishing)

In consideration of the upcoming request for proposals for permanent coronary drug eluting stents (DES) PHARMAC is publishing the relevant portions of the minutes of the Interventional Cardiology Advisory Group meetings that relate to DES and to the development of a market share procurement process for these devices.

The role of the Interventional Cardiology Advisory Group is to:

- provide objective advice to PHARMAC on the possible approaches for standardisation and rationalisation of interventional cardiology devices nationally,
- assist with defining requirements and specifications that require consideration in relation to each interventional cardiology subcategory,
- review clinical evidence and appropriateness of new interventional cardiology devices and/or new technology offered by interventional cardiology suppliers,
- help ensure that products are fit for purpose, clinically appropriate and meet the needs of patients at a sustainable cost, and
- consider, make recommendations or report to PHARMAC and/ or PTAC on matters that may be referred to it by PHARMAC.

Record of the Interventional Cardiology Advisory Group meeting held at PHARMAC on 17 February 2017

Present from the Interventional Cardiology Advisory Group:

Scott Harding (Chair)
Rajesh Nair (Deputy Chair)
Seif El-Jack
Sandi Graham
Marius Rademaker (PTAC member)
David Smyth
Mark Weatherall (PTAC member)
Mark Webster

1 Clinical Review – Intracoronary Drug Eluting Stents

1.1 The Advisory Group noted a paper by PHARMAC staff, titled Clinical Review – Intracoronary Drug Eluting Stents, seeking advice from the Interventional Cardiology Advisory Group (ICAG) to determine strategies going forward in regards to managing future assessment, standardisation, prioritisation, and procurement of interventional cardiology devices that best meet patient care requirements.

Classification of Bioresorbable Stents

1.2 The Group recommended that drug eluting stents (DES) with bioresorbable platforms should not be classified in the same category as DES with durable platforms for the purpose of market share discussions.

1.3 Members considered that the evidence currently available showed bioresorbable DES to be inferior to durable DES.

1.4 Members considered that for bioresorbable DES to be considered clinically acceptable for use in a significant proportion of patients, well designed clinical trials would need to show benefit or non-inferiority over current generation durable DES and show good safety data.

Comparison of Drug Eluting Stents (DES)

1.5 The Group considered that the following physical characteristics are considered by specialists when deciding on the preferred brand(s) of DES for use in hospitals and for determining which brand of DES would be most appropriate for each patient:

a) Deliverability,

b) Size matrix -size of actual stent, and size that a stent expands to (expandability),

c) Radial strength,

d) Longitudinal strength,

e) Visibility,

f) Conformability,

g) Side-branch access,

h) Strut thickness,

i) Lesion coverage,

j) Drug used,

k) Polymer used,

l) Material used

m) Balloon used.

1.6 The Group reiterated that different brands of stents are useful in different clinical situations and characteristics that were advantageous in one area could be disadvantageous in other areas depending on the particular clinical situation. The overall performance of DES is the result of a combination of the above characteristics (item 3.5). Members considered that it was important to match the most appropriate DES to the specific coronary artery lesion as, for example, some lesions might do better with a high-visibility stent at the expense of conformability. Members also suggested that it would be possible for a complementary set of features from more than one supplier could cover the spectrum of features required.

1.7 The Group felt it was not appropriate to define in general terms which of the above listed characteristics were the most important when selecting a DES and considered that both individual clinicians and individual patient requirements meant that a diverse range of characteristics may be appropriate. However, most members agreed that deliverability (getting the stent to the right place) was likely to be considered one of the most important features but noted that clinician skills may be a determinant of this. Many physical features combine to affect deliverability. Some Members considered that side-branch access could be considered the next most important DES feature.

1.8 The Group noted that difficult to deliver DES could incur additional costs if ancillary products and additional time were necessary to complete a procedure.

1.9 The Group noted that for some of the physical characteristics listed above, it is not the individual feature e.g. strut material, that is of importance to the clinician, but the outcome provided by that feature such as visibility. For example, it does not matter that a DES contains platinum, but rather that the platinum provided better visibility during intervention.

1.10 The Group noted that physical characteristics are not the only characteristic considered when clinicians are deciding if a DES is fit for clinical purpose. The Group considered that the following are also important factors that are reviewed by clinicians in the decision-making process:

a) Clinical trials with effectiveness and/or safety data,

b) Manufacturer and independent bench tests,

c) Laboratory pathology results from animal and human clinical studies.

1.11 The Group considered that bench testing was a valuable way of evaluating the physical characteristics of DES, particularly as part of assessing a new stent. Members noted that while manufacturer bench test reports were useful, they tended to focus on positive data that supports the marketing strategy for that DES. Members noted that independent bench tests were preferred as they can present a wider range of data. Members noted that there was no international standard for how bench tests were conducted; however, there were published guidelines.

1.12 The Group considered that a national procurement activity on DES would provide a valuable opportunity to implement a standardised data collection registry in order to compare DES and recommended that this service be included in any contracts with suppliers to ensure that the costs of setting up and maintaining a registry were covered by suppliers. Members considered that a registry would also prove useful to suppliers as they could use the data from the New Zealand market to add to the international knowledge base about these devices. Members indicated that device type data was not collected as part of the New Zealand Acute Coronary Syndrome Quality Improvement (ANZACS QI) Data Registry.

1.13 The Group considered that it was difficult to determine what level of clinical data would be necessary before implementing a new DES and noted that a balance was needed between having enough data and allowing innovative technology to enter the marketplace. Members considered that if the bar was set too high, it could significantly delay the entry of innovative DES to New Zealand. Members considered that it would be appropriate to accept three different levels of clinical evidence based on the level of innovation, for majority use:

a) Level 1 – for brand new, first-in-line technology e.g. a new stent platform;

b) Level 2 – for an actual feature and/or characteristic change on an existing, proven device e.g. a new stent from an existing company with a good track record or a similar stent platform.

c) Level 3 – an iteration of an existing, proven device e.g. a new delivery system for an existing stent.

1.14 The Group considered that non-inferiority data would be acceptable for Level 3, while Level 1 would require a large, randomised, multi-centre, multi-national cohort, head-to-head clinical study with good end points, powered to find a clinically and statistically significant difference, with a minimum follow-up duration of one year and preferably registry data showing effectiveness in a wider range of patients.

1.15 The Group considered that DES registered and approved by either the Food and Drug Administration (FDA) or CE Marked, in general, were of appropriate standard to be registered with Medsafe in New Zealand. Members considered that the FDA approval process was designed to protect the public while the European Union focussed more on

doctor and specialist discretion but that there was no reason for New Zealand regulatory authorities to reinvent the wheel in terms of investigating new technologies which pass both the FDA and EU standards. The Group considered that non-FDA approved or CE marked devices, would need a higher level of scrutiny prior to being approved for use in NZ.

1.16 The Group reviewed a list of DES currently available in the New Zealand market and considered that the stents fell into three groups (DES listed in no order):

a) Fit for purpose and clinically appropriate for the majority of patients:
   i. Promus Premier
   ii. Xience Alpine and Xience Xpedition (same stent with different delivery systems)
   iii. Resolute Integrity
   iv. Resolute ONYX
   v. Synergy

b) Niche characteristics, all different, suitable for specific lesions/patients but not sufficient evidence to be considered fit for purpose and clinically appropriate for the majority of patients:
   i. Ultimaster
   ii. Orsiro
   iii. Biomatrix Neoflex

c) Currently lacks sufficient evidence to be considered over other available DES:
   i. BioFreedom
   ii. CRE8
   iii. Magmaris
   iv. Absorb

1.17 The Group considered that the BioFreedom and CRE8 stents in group c) had potential although the level of data for each was immature at the time of the meeting (small numbers, narrow set of patients, follow up too short, outcomes not yet there). **[withheld]** Members considered that the Magmaris was a niche product, currently had very limited clinical outcomes, and had very little data. Members considered that Absorb had relatively long-term data; however, the outcomes were shown to be no better than other commercially available DES and could be inferior to some. The Group noted it would be happy to review new evidence for any of the DES once it became available.

1.18 The Group considered that the clinical evidence for Biomatrix Neoflex in group b) was good when the stent came to market (comparable to the 'gold standard' stent at the time); however, the data would no longer be up to today's standards (the Xience level of data would be considered the acceptable standard at present). Members considered its older design with fixed struts had not been improved, had weak physical features overall, usability was less than others on the market, and accordingly had not been used in the past couple of years. Members noted that the newer iteration of the Neoflex, BioFreedom, was more visible, more usable and more deliverable and was a significant change from the Biomatrix NeoFlex.

1.19 The Group noted that Orsiro was used primarily in Waikato, but only for a specific patient sub-set. Orsiro stent was particularly deliverable and was useful for patients who had

tortuous coronary arteries. **[withheld].** Members considered that the published clinical evidence for Orsiro was not as strong as other stents on the market.

1.20 The Group noted that the primary trial for the Ultimaster, Century II, would likely not be considered a large enough equivalence study by New Zealand standards, although noted that 1100 patients in that trial provided some confidence to support its use. Members considered that the Ultimaster was not used as much as other stents due to less trial evidence than the other stents already widely used **[withheld].** The stent does not have many features that make it superior to the stents listed above in a). Members considered that of the stents listed in group b), it was the closest to being considered for widespread use.

1.21 The Group noted that based on clinical evidence, the different drugs used in DES were unlikely to lead to a clinically significant difference in clinically important end points. Members considered that the industry was learning more about latency problems with longer term data becoming available; however, at this stage benefits related to latency were yet to be supported by robust clinical evidence. Members considered that if there was restenosis with a DES, clinicians would likely switch to a stent with a different drug; although no evidence for the change. Members considered that with event rates now less than 5%, that studies designed to support different strategies for the treatment of restenosis, and in particular randomised controlled trials, would have to be very large, and were unlikely to be performed.

1.22 The Group considered that allergy to the stent components causing late-stent thrombosis was more of an issue with older generation stents; this was uncommon with the new generation stents, which contained more hypoallergenic polymers, metals and drugs.

1.23 The Group considered that lesion subsets e.g. bifurcation lesions, large or small vessel size, or difficult to deliver lesions such as heavily calcified lesions; were a more important consideration than patient subsets and that most lesions could be covered by group a) stents above and considered that with the group a) stents available in a DHB, there would not be a need for a unique stent to also be available. Members considered that if all possible lesions were to be covered by a range of available stents, two suppliers would cover 90% of all lesions. Members noted some DHBs held three or more brands of DES, to ensure coverage of all possible cases. The members noted the importance of holding stock of the required stents as most of the procedures were ‘cath and proceed’, and approximately 70% of cases would be considered acute, where time was critically important.

1.24 Members considered that interventional cardiologists would select a specific stent for any given lesion based on several factors; contract obligations with percentage agreements, lesion characteristics, and the price of an individual DES. Members agreed that all other factors being equal, the cheapest stent was selected.