EXTERNAL ASSESSMENT CENTRE REPORT

Title: SeQuent® Please coronary balloon catheter with paclitaxel release for coronary artery disease for the treatment of in-stent restenosis or stenoses of small calibre coronary arteries

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None

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The views expressed in this report are those of the authors and not necessarily those of the Centre for Health Technology Evaluation. Any errors are the responsibility of the authors.

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Abbreviations

AE	Adverse event
BCIS	British Cardiovascular Intervention Society
BMS	Bare metal stent
CABG	Coronary artery bypass graft
CHD	Coronary heart disease
DAPT	Dual anti-platelet therapy
DEB	Drug-eluting balloon
DES	Drug-eluting stent
EAC	External assessment centre
HRG	Health-related group
ISR	In-stent restenosis
LLL	Late lumen loss
MACE	Major adverse cardiac events
MI	Myocardial infarction
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
PCI	Percutaneous coronary intervention
PSS	Personal Social Services
PTCA	Percutaneous transluminal coronary angioplasty
RCT	Randomised controlled trial

TLR   Target lesion revascularisation

TVR   Target vessel revascularisation

Note on use of page numbers

In general, page numbers provided in parentheses in this assessment report refer to the manufacturer's submission document, unless otherwise stated. References to the assessment report are generally given in terms of section number (e.g. "see Section 3.1.2 for details").

1. SUMMARY

1.1 Scope of the submission

This report assesses the submission to NICE by the manufacturer (B.Braun) for the use of the SeQuent® Please coronary balloon catheter with paclitaxel release for coronary heart disease. Specifically the submission considers SeQuent® Please for the treatment of in-stent restenosis (ISR) or stenoses of small calibre coronary arteries, which is in line with the scope issued by NICE for the appraisal. The report includes an assessment of both the clinical effectiveness and the cost implications, based on evidence submitted by the manufacturer.

1.2 Summary of submitted clinical effectiveness evidence

The key sources of evidence on clinical effectiveness relating to ISR patients were the PACCOCATH® ISR (Treatment of In-Stent Restenosis by Paclitaxel-Coated Balloon Catheters) I and II trials and the PEPCAD (Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease) II trial. In addition, the PEPCAD I and PEPCAD V trials were identified by the literature searches, which relate to patients with small coronary arteries and bifurcations, respectively. The studies relating to ISR patients were randomised controlled trials (RCTs), with the remaining two studies of non-randomised design. All of the included studies were conducted in Germany, funded by either B. Braun or another manufacturer and included limited follow-up (12 months for the majority of the trials).

The trials compared the use of SeQuent® Please to treatment options such as the drug-eluting stent (DES), uncoated balloon catheter, and the additional use of bare metal stents (BMS). The studies demonstrated a reduction in restenosis, late lumen loss (LLL), target lesion revascularisation (TLR) and major adverse cardiac events (MACE) associated with the use of SeQuent® Please when compared to the various alternatives.

1.3 Summary of submitted economic evidence

The searches conducted by the manufacturer identified four relevant economic studies. However, these studies were not used to populate the cost model. The model instead relied on data derived from the PEPCAD II trial and a national costing source (i.e. NHS National Tariff). The PEPCAD II trial investigated the use of SeQuent® Please in comparison to DES for 131 patients with ISR.

Estimates of the cost associated with treatment of ISR patients are provided through the development of a cost model. The cost analysis took a simple 'within-trial' Markov approach, using TreeAge software, from the perspective of the NHS and Personal Social Services (PSS). The model compared the use of SeQuent® Please against DES in terms of the costs associated with treatment, device, medication and serious complications, along with the associated survival. Four health states were incorporated; 'alive pre-revascularisation', 'alive post-revascularisation', 'alive post-target vessel revascularisation (TVR)' and 'dead'. Events are then incorporated for each health state, such as revascularisation and various complications, including bleeding, myocardial infarction (MI) and stroke.

The time horizon of the model is one-year, using monthly Markov cycles. The base case analysis found that the average per-patient cost over the one-year time horizon was £4,134 for the SeQuent® Please treatment arm and £4,873 for the DES arm. Hence, a cost saving of £739 per patient was demonstrated through the use of SeQuent® Please compared to DES. The deterministic sensitivity analysis identified the key drivers of the analysis to be TVR rates, co-medication costs and initial revascularisation costs.

1.3.1 Strengths

The clinical effectiveness evidence was based on some RCT data and non-randomised trial data, where the RCTs were well conducted, and undertaken in a patient population relevant for the submission. The clinical events, such as LLL, restenosis, TLR and MACE reported in the analysis are considered to be clinically important and relevant.

The cost impact analysis, through the use of the TreeAge-based model, estimated cost savings from the use of SeQuent® Please. An appropriate comparator was included (i.e. the DES) and the choice of model parameters appears sensible. The analysis took a conservative approach in the percutaneous coronary intervention (PCI) costs that were used, and the application of bleeding complications, for example. Due to the model being based predominantly on one trial only, extrapolation or approximation of data was not required. In general, the cost impact analysis was adequate in addressing the decision problem.

1.3.2 Weaknesses

The search strategies used for the identification of data for the submission were not extensive and inadequately reported. The external assessment centre (EAC) cannot, therefore, be confident as to whether all relevant studies have been identified, and various inconsistencies have been noted. Information provided was not clear for some areas of the submission; for example, details of the model were not reported comprehensively for particular aspects.

The model only estimates the costs associated with SeQuent® Please over a period of one-year. Therefore the technology has not been assessed in the longer-term, as specified in the NICE scope. The submission document explains that this is due to the availability of only short-term follow-up data.

The main source of data for the cost model is the PEPCAD II trial. Although this trial focuses on the relevant patient population, it relates to the German setting. Hence there is the issue of generalisability for UK clinical practice (e.g. whether patient case-mix and routine clinical practice will vary). In addition, limitations of the study include the number and selection of patients in the study, and also that the majority of patients had simple patterns of ISR that are associated with a more favourable outcome.

The parameters used in the cost model have not been verified by clinical experts; hence expert clinical opinion has not been sought regarding whether the model accurately represents real clinical practice in the UK.

1.3.3 Areas of uncertainty

As described above, the EAC cannot be confident about the identification of studies from the literature searches that were conducted. The impact of SeQuent® Please in the long-term is a significant area of uncertainty. The current cost model has not extrapolated into the future; such medium- or long-term analyses would provide a valuable insight into the longer-term impact of SeQuent® Please.

There is some uncertainty around whether the appropriate durations for co-medication use have been applied in the model. The duration of co-medication was based on the PEPCAD II trial. However, further consideration around the durations is recommended. As previously stated, the generalisability of the PEPCAD II trial is an issue.

The cost analysis focuses on the comparison of SeQuent® Please with a DES. The cost impact of SeQuent® Please when compared to other treatment options has not been considered; hence it is not possible to determine the technology's value relative to further comparators.

Sensitivity analysis was undertaken as part of the submission. However, additional investigation into the price differential between SeQuent® Please and DES, and the duration of clopidogrel use for the DES arm would be valuable.

1.4 Key issues

The use of SeQuent® Please for the treatment of stenoses of small calibre coronary arteries has not been examined in detail in this submission. The focus is therefore on the treatment of ISR, with no sub-groups[1] considered in this submission. Only one comparator, the DES, has been included for the cost analysis.

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[1] Possible subgroups to be considered, as stated in the NICE scope, were patients with complex coronary disease (e.g. left main stem lesions, branch lesions, and vessel birfurcations) or in situations where standard stent use is undesirable (e.g. in calcified vessels or tortuous anatomy).

As previously discussed, the cost analysis is based on a one-year time horizon only, hence long-term costs associated with SeQuent® Please have not been estimated.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The submission provides details of coronary heart disease (CHD), which is characterised by a narrowing of arteries (i.e. stenosis) that supply blood to the heart. It focuses on CHD patients who present with ISR, and to a lesser extent on patients with small calibre coronary artery stenosis and bifurcations (these patient groups are addressed on an informational basis only).

Relevant information is provided in relation to the expected rate of restenosis and the number of patients assumed to be eligible for ISR in England and Wales, based on findings from the British Cardiovascular Intervention Society (BCIS). Data are not provided for the subsequent five years as specified by the submission, but it is assumed that the estimation of 10,000 ISR patients presenting for treatment each year would apply.

2.2 Critique of overview of current service provision

The scope describes several treatment options currently used for ISR and for small calibre coronary artery disease.

Drug-eluting stents, one of the current treatment options included in the scope, are described in the manufacturer submission as being the current clinical practice for ISR patients. Evidence about the use of comparators and the intervention is not featured in detail in the current service provision overview; this is covered in later sections, however.

The submission points out the use of other drug eluting balloons (DEBs) in the market, which "do not have any clinical evidence and were not properly evaluated as a combinational drug release product (device & drug) to obtain the CE mark" (page 15). Although this may be the case, the EAC has not seen evidence to support this claim.

The manufacturer states that use of SeQuent® Please is expected to involve similar NHS resources to those used under standard care. This is in terms of

staff cost, diagnosis equipment, administration and monitoring/test costs (page 16). Due to SeQuent® Please being used in the same manner as a regular uncoated balloon catheter during the intervention itself, the manufacturer expects there to be no difference in clinical practice. In addition, standard patient care/therapies (such as anti-platelet aggregation inhibitors, anticoagulatives *etc.*) is anticipated alongside use of SeQuent® Please. Such anticipated resource use appears sensible.

The potential constraint raised by the manufacturer in relation to the implementation of SeQuent® Please in the UK NHS involved the possibility of SeQuent® Please not being adequately reimbursed, due to it not being an implant.

3 Critique of definition of decision problem

3.1 Patient population

Patients with ISR or small calibre coronary stenosis were outlined as being relevant in the scope issued by NICE. The submission focuses on the ISR patient population, with some reference to small calibre coronary stenosis and bifurcation patients for information purposes.

The scope outlined that treatment using SeQuent® Please may be appropriate in patient subgroups. The subgroups include patients with complex coronary disease (e.g. left main stem lesions, branch lesions, and vessel birfurcations) or in situations where standard stent use is undesirable (e.g. in calcified vessels or tortuous anatomy). Subgroup analysis was not undertaken as part of the submission, as discussed on page 121 of the submission document.

3.2 Intervention

The intervention considered in the submission is the SeQuent® Please iopromide/paclitaxel eluting balloon catheter, based on Paccocath® technology, which is indicated for percutaneous transluminal coronary angioplasty (PTCA). The submission states that, "the balloon section of the distal end of the catheter is coated with paclitaxel at a dose of 3µg/mm^2. The balloon is expanded for approximately 30 seconds and paclitaxel is released into the vessel wall. The aim of targeted delivery is to ensure that the drug remains in the vessel wall. The balloon catheter is also coated in iopromide, an X-ray contrast medium which improves the solubility and transfer of paclitaxel to the vessel wall."

The manufacturer submission states that SeQuent® Please is CE marked for use within the coronary arteries for primary angioplasty within BMS and for restenosis.

3.3 Comparator

The possible comparators for ISR were identified in the NICE scope as repeat balloon angioplasty, repeat stenting, cutting balloon angioplasty, directional

coronary atherectomy, rotational coronary atherectomy, brachytherapy and drug eluting stents. The possible comparators for small calibre coronary stenosis were identified in the scope as PTCA and stent implantation.

For the purposes of the cost analysis, the comparator for ISR patients was the DES. This comparator choice is consistent with the scope, although it would be useful to consider further comparators in order to investigate additional options.

3.4 Outcomes

The outcomes included in the manufacturer submission are consistent with the scope. The clinical outcomes considered in the submission comprise angiographic LLL and clinical events such as major adverse cardiac events (MACE). Information relating to restenosis rates and TLR rates is also reported. Although additional outcomes were featured in the scope, the submission includes the outcomes that are considered clinically significant by the included studies. Safety outcomes were reported, including death and other adverse events. The cost model incorporates TVR events in addition to complications such as MI, stroke and bleeding events

3.5 Time frame

The analysis provided in the cost section of the manufacturer submission takes a short-term approach in the base case (i.e. 12 months). Although the scope states that long-term management of the disease should be taken into account, the submission does not extrapolate into the future. The reason provided in the submission is that due to 12-month data being reliably available (page 102), the long-term impact of SeQuent® Please was not evaluated.

Due to the uncertainty of the long-term effectiveness of SeQuent® Please, the short-term time frame considered is reasonable. However, it would be useful to explore the potential impact in the medium-term by incorporating the available evidence, whilst keeping in mind the reliability of this data.

3.6 Other relevant factors

None identified

3.7 Equality and diversity issues

No equality and diversity issues were identified to be addressed in the submission for the use of SeQuent® Please technology.

4 Clinical effectiveness

4.1 Critique of manufacturer's approach

4.1.1 Description and critique of the manufacturer's identification and selection of studies.

Assessment of literature searches

Sequent® Please is a paclitaxel-coated balloon catheter and the submission presents evidence around the product and the effectiveness of paclitaxel in intracoronary use. The reported searches focus on the product and not on the evidence for the effectiveness of paclitaxel. If there is uncertainty about the effects of paclitaxel a specific search for evidence would be merited.

There is a lack of detail in the description of the manufacturers' searches for studies. The following critique is based on the information provided in the submission in Appendix 2: Search strategy for section 5.1 (Identification of studies), page 128.

The submission does not include a search of the Cochrane Library, but does include a search of EMBASE and PubMed (which includes Medline and Medline In-process).

The search strategy presented in the submission is quite minimal and does not include any synonyms or indexing terms. Stringent limits have been applied to the search strategy in MEDLINE which means that the strategy may have missed relevant records. The impact of the search approach, including the impact of the limits, is described below. The submission includes two strategies for EMBASE and we have assumed that the strategy presented in appendix section 7.2.4 of the submission is the correct strategy.

The PubMed (MEDLINE) strategy is not sensitive. We note the use of the terms 'paclitaxel eluting' in various references and these do not appear in the strategy. We also note the absence of other synonyms and the use of subject indexing terms. The use of such a search runs the risk of missing relevant

studies. Possible additional search approaches are presented in Section 4.1.2 of this report.

In appendix section 7.2.1 the search is reported to have significant limits and in 7.2.4 there are 'no limits'. It is difficult to know which represents what happened during the search. If the limits listed in section 7.2.1 were applied then the consequences for the strategy are various:

Limiting the search to records with abstracts runs the risk of missing relevant records which do not have abstracts. Not all PubMed records have abstracts and conference abstracts, in particular, may not have abstracts.

The explicit limit to human studies might more safely be approached by excluding animal studies (a cautious search approach to remove animal studies can be achieved by NOTing the search results with the following search line: animals [mh] NOT humans [mh]). Many records in PubMed relating to humans do not have the Humans indexing tag, so limiting to records with that tag runs the risk of missing relevant records.

Limiting to records coded as 'Clinical Trial' is likely to find a large proportion of relevant records. However, MEDLINE in process records have not yet received Clinical Trial indexing terms and so will be excluded from the search results.

Restricting to English language records. This means that any relevant studies in languages other than English will not have been retrieved.

Restricting to 'Core clinical journals' means that the search results do not include results from other journals which may introduce publication bias.

The search is not limited by date – this is ideal.

If the searches were not limited then none of these issues apply.

The EMBASE strategy suffers similar limitations to the PubMed strategy. The strategy is again very focused, in particular the 'balloon' term is linked to 'dilatation' which seems very stringent and may explain the low number of

results. Again, additional synonyms and the use of truncation would improve the sensitivity of the search. It is unclear whether the same limits used for PubMed were applied to the EMBASE search as limits appear in 7.2.1 but not in 7.2.4. In addition two different search strategies are presented in the two tables. The search is not limited by date – this is ideal.

No additional searches are reported, although it seems that searches for trials were undertaken.

The searches for evidence on adverse events were reported in Appendix 4: Search strategy for section 5.9 (Adverse events). The submission does not include a search of the Cochrane Library, but does include a search of EMBASE and PubMed (which includes Medline and Medline In-process).

The search strategy is minimal and does not include any synonyms or indexing terms. Stringent limits may have been applied to the search strategy in MEDLINE which means that the strategy may have missed relevant records. Research into searching for adverse events indicates that it is complex and a variety of search approaches should be used (1). The approach described in the submission is minimal and runs a severe risk of not identifying relevant studies. For example, the search has not included known specific adverse events (as well as the general concept of adverse events), has not used MEDLINE options to capture adverse events such as floating subheadings, and has not used additional synonyms for adverse events such as side effects and adverse effects.

The subject search is also minimal with no synonyms for in-stent or restenosis.

It is unclear whether limits were applied to the searches as one table lists limits and another says there were no limits. The best approach would be to apply no limits.

The same comments apply to the EMBASE strategy, but in addition it is not clear whether DIMDI implements automatic truncation. If automatic truncation is not implemented by DIMDU then the search terms used have reduced sensitivity: without automatic truncation 'event' only retrieves 'event' and will miss records where the wording is actually 'adverse events'. There are inadequate synonyms for all the elements of the strategy.

It is helpful to know that www.clusty.com was searched, but the search terms are not presented so the adequacy of the search is unknown.

Details of the cost-effectiveness literature search are provided in Section 5.1.1 of this assessment report

There are some inconsistencies between the search strategies and the studies that were identified, and in the application of the inclusion/exclusion criteria. For instance, the search strategy appears to have excluded animal studies, yet one of the identified studies (Posa *et al*. 2008 (2)) is an animal study. Another example is that the search strategy restricts to English language records, yet the inclusion/exclusion criteria refer to including studies that are either in English, German, French and Spanish. The submission highlights that the studies considered to be relevant in relation to the DEB technology were those undertaken by B.Braun, which brings into question the use of search strategies and criteria.

Use of inclusion/exclusion criteria in the selection of studies

The inclusion criteria used for the selection of studies in the manufacturer submission (page 25) are consistent with the decision problem and therefore are considered to be, in the main, appropriate. Patients included were those with coronary artery disease, and the interventions eligible for inclusion were coronary revascularisations by catheter based interventions and cardiac surgery. The included outcomes were angiographic LLL and clinical events such as MACE. The remaining outcomes specified in the scope (recurrence of angina symptoms, quality of life, successful device placement and safety outcomes) were not featured in the criteria. Study designs comprising RCTs, single armed trials and clinical registries were included. However, it was not

stated whether published systematic reviews or meta-analysis of primary studies would be included in the review.

The exclusion criteria are not strict, in that the only studies excluded from the search were those published prior to 1995 (when stents were not standard practice) and those with language restrictions (all those apart from English, German, French, Spanish studies were excluded).

The submission refers to the literature review as being systematic. However, the review did not appear to follow systematic methodologies. For instance, information relating to data selection such as the number of reviewers who screened the studies and applied the inclusion/exclusion criteria was not provided. Hence it is unclear whether the review process was subject to reviewer error or bias.

In total, the clinical effectiveness search identified 130 references, 11 of which referred to coronary DEB with iopromide/paclitaxel matrix, as stated in the submission document (page 27). Of the 11 abstracts considered for the review, 5 were identified as being relevant, with 6 excluded. The included studies comprised:

- Scheller *et al.* 2006 (3) (PACCOCATH® ISR I trial: Treatment of In-Stent Restenosis by Paclitaxel-Coated Balloon Catheters);

- Scheller *et al.* 2008 (4) (PACCOCATH® ISR II trial: Treatment of In-Stent Restenosis by Paclitaxel-Coated Balloon Catheters);

- Unverdorben *et al.* 2009 (5) (PEPCAD II trial: Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease to treat In-Stent Restenoses);

- Unverdorben *et al.* 2010 (6) (PEPCAD I trial: Paclitaxel-Eluting PTCA-Balloon Catheter to treat Small Vessel);

- Mathey *et al.* 2009 (7) (presentation on PEPCAD V trial: Paclitaxel-Eluting Balloon Angioplasty and Coroflex Stents in the Treatment of Bifurcated Coronary Lesions).

4.1.2 Table of identified studies. What studies were included in the submission and what were excluded?

Five clinical effectiveness studies were identified as being relevant by the submission, comprising three RCTs (3-5) and two non-randomised trials (6, 7). Three of these studies (ISR I (3), ISR II (4) and PEPCAD II (5)) relate to patients with in-stent coronary artery stenosis. The PEPCAD I (6) trial involves patients with small vessel coronary artery disease and the PEPCAD V (7) trial focused on patients with bifurcation coronary lesions. Therefore, three of the five included studies (ISR I and II trials and the PEPCAD II trial) are relevant for the ISR patient population, which is the focus of the submission. Four of the five relevant studies have been published; the PEPCAD V trial results presented in the submission document are sourced from a slide presentation.

All of the included studies were funded by either B. Braun or another manufacturer and were conducted in Germany, which raises the issue of generalisability to clinical practice in the UK. All but one of the trials involved a clinical follow-up period of 12 months; the remaining trial (ISR II) followed patients for 24 months. The studies followed MACE for up to 3 years. The trials relating to ISR patients were of a reasonable size; the PEPCAD II trial included 131 patients and the ISR I and II trials included 108 patients in total. The PEPCAD I trial included 118 patients in the analysis whilst the PEPCAD V only considered 28 patients.

The included clinical trials evaluated the efficacy and safety of paclitaxel-coated balloon catheters; either the SeQuent® Please DEB was investigated or a DEB that uses identical Paccocath® technology. The ISR I and II trials investigated the use of Paccocath® technology DEB[2] compared to an uncoated coronary balloon catheter for coronary ISR. The PEPCAD II trial compared Paccocath® SeQuent® Please with the Taxus® DES. Both the PEPCAD I and PEPCAD V trials investigated SeQuent® Please use only, with no comparator group included, although the PEPCAD V trial considered the addition of a BMS for some patients.

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[2] The manufacturer states this is identical to SeQuent® Please.

Details of the studies that were excluded from the submission, or the reasons behind the exclusions, were not provided in the submission document; the only information regarding excluded studies was provided in the literature research chart on page 27. However, the excluded studies were supplied by the manufacturer when requested by the EAC; details of these can be seen below:

- Tepe *et al.* 2010 (8): review of the use of paclitaxel-coated balloons in peripheral arterial disease;

- Werk *et al.* 2008 (9): RCT pilot study investigating efficacy and safety of uncoated balloons versus paclitaxel-coated balloon catheters, for patients with hemodynamically relevant stenosis, restenosis, or ISR of femoropopliteal arteries;

- Posa *et al.* 2008 (2): animal study to investigate the local drug delivery of paclitaxel-coated balloons;

- Fanggiday *et al.* 2008 (10): evaluates the short-term efficacy and safety of DEB in patients with coronary artery bifurcation lesions;

- Tepe *et al.* 2008 (11): paclitaxel-coated angioplasty balloons and paclitaxel dissolved in the angiographic contrast medium during angioplasty of the leg were investigated;

- Agostoni *et al.* 2007 (12): investigates the treatment of restenosis with a paclitaxel-coated balloon catheter (further study details unavailable).

The manufacturer submission identified relevant ongoing studies. For the treatment of ISR, these include[3]:

- PEPCAD DES: Treatment of DES-In-Stent Restenosis with SeQuent® Please Paclitaxel Eluting PTCA Catheter;

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[3] Note: information regarding the ongoing trials is sourced from www.clinicaltrials.gov.

- ISAR DESIRE 3 trials: Randomized Trial of Paclitaxel-Eluting Balloon, Paclitaxel-Eluting Stent and Plain Balloon Angioplasty for Restenosis in "-Limus"-Eluting Coronary Stents;

- SEDUCE: Healing Responses after Treatment of Bare Metal Stent Restenosis with Implantation of an Everolimus-eluting Xience V Stent Versus Use of a Paclitaxel-eluting Balloon: Optical Coherence Tomography Study.

The ongoing studies in relation to de novo lesions comprise:

- PEPCAD IV: Paclitaxel-Eluting Balloon Angioplasty and Cobalt-Chromium Stents Versus Conventional Angioplasty and Paclitaxel-Eluting Stents in the Treatment of Native Coronary Artery Stenoses of Diabetic Patients;

- PEPCAD CTO: The Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease to Treat Chronic Total Occlusions;

- INDICOR: The Paclitaxel-Eluting PTCA-Balloon Catheter in Combination with a Cobalt-Chromium Stent to Treat Coronary Artery Disease in a Real World Scenario;

- PEPCAD DEB: The Paclitaxel-Eluting PTCA-Balloon Catheter in Combination with a Cobalt-Chromium Stent to Treat Coronary Artery Disease in a Real World Scenario.

The estimated completion dates of the studies can be seen in Table 1.

Table 1: Estimated completion dates of ongoing studies

Study	Estimated completion date
PEPCAD DES	May 2011
ISAR DESIRE 3	July 2014
SEDUCE	December 2015
PEPCAD IV	September 2011
PEPCAD CTO	September 2014
INDICOR	April 2012
PEPCAD DEB	March 2015

(Source: www.clinicaltrials.gov)

In addition, the manufacturer referred to an international registry being available in relation to the use of SeQuent® Please which is likely to provide valuable information.

Include details of any relevant studies that were not included in the submission

The approach taken for the search strategies is at risk of missing potentially relevant studies. Additional search strategies put forward by the EAC for identification of clinical studies (following on from the PubMed (MEDLINE) strategy critique in Section 4.1.1) could include:

Paclitaxel AND eluting AND balloon*
Paclitaxel AND coated AND stent*
Sequent*
Paclitaxel [mh] AND coronary angiography [mh]
Paclitaxel [mh] AND (coronary stenosis [mh] OR coronary restenosis [mh])
Coated Materials, Biocompatible [mh] AND (coronary stenosis [mh] OR coronary restenosis [mh])
Coated Materials, Biocompatible [mh] AND angioplasty,balloon [mh]

When we reran the submission search (paclitaxel AND eluting AND balloon) ("paclitaxel"[MeSH Terms] OR "paclitaxel"[All Fields]) AND coated[All Fields] AND ("balloon dilatation"[MeSH Terms] OR ("balloon"[All Fields] AND "dilatation"[All Fields]) OR "balloon dilatation"[All Fields] OR "balloon"[All Fields])) we identified 135 records (set #2 below). Expanding the search with additional term combinations (sets #3 to #9) retrieved additional records as follows:

#2 paclitaxel AND coated AND balloon 135
#3 paclitaxel AND eluting AND balloon* 166
#4 paclitaxel AND coated AND stent* 289
#6 paclitaxel [mh] AND coronary angiography [mh] 345
#5 paclitaxel AND coated AND balloon* 58

#7 paclitaxel [mh] AND (coronary stenosis [mh] OR coronary restenosis[mh]) 623

#8 Coated Materials, Biocompatible [mh] AND (coronary stenosis [mh] OR coronary restenosis [mh]) 380

#9 Coated Materials, Biocompatible [mh] AND angioplasty,balloon [mh] 343

#10 #3 OR#4 OR #5 OR #6 OR #7 OR #8 OR #9 1299

#11 #10 not #2 1164

The additional searches therefore indicate that there may have been relevant studies that were not included in the submission.

4.1.3 Description and critique of manufacturers approach to validity assessment and details of the quality assessment of studies.

The manufacturer assessed the quality of the clinical effectiveness studies using appropriate criteria. The checklist used was based on the criteria for assessment of risk of bias in RCTs, issued in guidance for undertaking reviews in health care, by the Centre for Reviews and Dissemination (University of York) (13). The checklist used to assess the quality of the studies does not cover certain aspects, such as whether follow-up was adequate, relevance to the UK, whether any confounding factors were present *etc*. However, the main characteristics of the study quality are captured.

It is not clear whether the studies were assessed by a single reviewer or multiple reviewers. The manufacturer's comments regarding the studies' approach to addressing the areas covered by the questions can be seen in Table 2, alongside comments by the EAC.

Table 2: Critical appraisal of relevant clinical effectiveness studies

ISR I and II [Scheller *et al*. 2006 & 2008] (3, 4)		
Study question	**How is the question addressed in the study?**	**Comments by EAC**
Was randomisation carried out appropriately?	randomized in 2 groups	The two studies randomised eligible patients to the DEB group (54 patients) or uncoated balloon catheter group (54 patients), by use of envelopes.
Was the concealment of treatment allocation adequate?	when randomized against an uncoated balloon, the actual treatments could be concealed	The trial was reported as being double-blinded (i.e. patient selection and core-lab data undertaken whilst investigators were perfectly blinded). However it is noted that the appearances of the devices could have resulted in unblinding in some patients.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	no significant differences in terms of lesion and patient risk factors	Baseline characteristics were similar
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	outcome assessors, participants and providers were blind to the actual treatment	Blinding did occur in theory, although unblinding could have occurred (as discussed above).
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	no unexpected imbalances between the two groups	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The NEJM and the Clin Res Cardiology publication offer a wealth of information of the ISR data, more outcomes are not likely	There is no evidence of additional outcomes being measured but not reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	An ITT approach was used for data-analysis.
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

PEPCAD I [Unverdorben _et al_. 2010] (6)

Study question	How is the question addressed in the study?	Comments by EAC
Was randomisation carried out appropriately?	single arm trial due to lack of gold standard in small vessel disease	The trial was not randomised.
Was the concealment of treatment allocation adequate?	was not part of the study design	
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	non randomized	One patient group was followed for DEB treatment, with some patients having an additional BMS implantation. Baseline characteristics were typical for patients with diffuse coronary artery disease (including 33% diabetic patients).
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	outcome assessors, participants and providers were not blind to the actual treatment	No blinding was described. Detection bias may be an issue.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	when analyzing the two subgroups in PEPCAD I, there were imbalances relative to the rate of dissections in the DEB vs. DEB+BMS treatment groups	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	all a priori defined outcomes were in agreement with the internal report which is available on request	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	An ITT analysis was undertaken, in addition to an as-treated analysis (for description comparison only).
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

PEPCAD II [Unverdorben *et al.* 2009] (5)

Study question	How is the question addressed in the study?	Comments by EAC
Was randomisation carried out appropriately?	randomized in 2 groups	65 patients were randomly assigned to DES and 66 patients were randomised to DEB group. Randomisation of eligible patients was by use of envelopes (further details not provided). The PEPCAD II trial report (14) states that block randomisation occurred by centre and by groups of 4.
Was the concealment of treatment allocation adequate?	when randomized against a DES, the actual treatments could not be concealed	
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	no significant differences in terms of lesion and patient risk factors	Similar baseline characteristics (higher proportion of patients with unstable angina in DEB group).
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	outcome assessors, were blind to the actual treatment, participants and care providers were aware whether a DES or a DEB was used	The trial was not blinded and details of any blinding to treatment allocation were not provided in the publication. Detection bias may be an issue.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	no unexpected imbalances between the two groups	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The Circulation publication offers a wealth of information of the ISR data, more outcomes are not likely	There is no evidence of additional outcomes being measured but not reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	An ITT approach was used for data-analysis, in addition to an as-treated analysis (for descriptive comparison only).
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

PEPCAD V [Mathey *et al.* 2009] available on TCT congress website (7)		
Study question	**How is the question addressed in the study?**	**Comments by EAC**
Was randomisation carried out appropriately?	non-randomized	
Was the concealment of treatment allocation adequate?	pilot trial, no control in study design	
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	pilot trial, no control in study design, however, compared to other trials similar lesion and patient related risk factors	
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	pilot trial, no control in study design	
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	no control arm	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	study results have not been published yet	The endpoints reported in the presentation comprise residual in-segment stenosis (i.e. procedural success), 9-month clinical angiographic follow-up (i.e. LLL) and MACE up to 3 years. The trial is estimated to complete by May 2011 (www.clinicaltrials.gov).
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	There does not appear to be missing data.
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

4.1.4 Description and critique of manufacturers outcome selection

The outcome measures addressed by the manufacturer's submission are considered to be appropriate. Relevant outcome measures, as outlined in the NICE scope and provided in the manufacturer submission, were restenosis, LLL and MACE. For all of the clinical effectiveness studies, the primary outcome was LLL and the secondary outcomes were MACE, TLR and the angiographic restenosis rate. In addition, adverse events were also considered, with details provided in the appropriate section. As previously stated, information regarding some of the outcomes specified in the scope was not provided by the included clinical studies. Hence some outcomes specified in the NICE scope were not addressed.

The manufacturer describes LLL as a marker for the suppression of intimal hyperplasia and a surrogate marker for the clinical success of the treatment. It is also stated that MACE and TLR are preferable for clinical efficacy, with LLL a strong predictor for angiographic restenosis.

Consistent definitions of the clinical outcomes were used in the studies. LLL was defined as the difference between the in-segment minimal lumen diameter after the procedure and at 6 months, as evaluated by coronary angiography. The definition of TLR was provided as either a percutaneous intervention or coronary artery bypass graft (CABG) involving the target lesion. Restenosis was defined as a stenosis of at least 50% of the luminal diameter at angiographic follow-up.

4.1.5 Describe and critique the statistical approach used

The statistical analyses of four of the five clinical trials were adequately reported, in general, by the manufacturer (note that statistical analysis for the PEPCAD V was not available). The described statistical analyses were appropriate.

The statistical approaches that were used in the clinical effectiveness trials were conducted on an intention to treat (ITT) principle, which is a robust technique that aims to reduce attrition bias. As-treated analyses were also performed for the PEPCAD I and II studies and the ISR I trial, for comparison.

A two-sided P-value of 0.05 was used in all of the included clinical trials to indicate statistical significance.

There is some discrepancy between the sample size and power calculation reported in the submission (page 50) and those reported in the published studies. The handling of missing data, patient withdrawals and sub-group analyses were not included in the studies. Details of subgroup analyses in the submission document (page 50) were incomplete.

There was no additional statistical analysis conducted by the manufacturer. Meta-analysis was not provided on the grounds that it was inappropriate, with further details provided in Section 4.2.2.

4.1.6 Summary statement about the review of clinical effectiveness

The studies included in the submission are relevant to the decision problem, in terms of patient populations and interventions, and the submitted evidence adequately reflects the decision problem. The relevant data from the included studies have been reported in the submission document. It is not possible to determine whether all relevant studies have been included due to incomplete reporting of the search strategy, the searches not being conducted using robust methodology, and certain inconsistencies, as discussed above. It is anticipated that the manufacturer of the SeQuent® Please technology will be aware of the relevant studies which investigate its use, although we cannot say with certainty whether all of these have been included.

The validity assessment of the included studies was adequate, although information on the process such as the number of reviewers *etc.* was absent. The clinical outcomes selected for the assessment of SeQuent® Please relate to those outlined in the NICE scope and the statistical methods undertaken by the included studies were, in general, adequately reported.

4.2 Summary of submitted evidence

The evidence submitted by the manufacturer comprised five studies, as previously described (Section 4.1.2). The findings that were presented from these studies in the submission (pages 54-77) are summarised below.

4.2.1 Summary of results

The results from the included trials have been presented as ITT analyses wherever such data are available[4]. Results were presented for angiographic findings (such as LLL, restenosis rate), TLR, MACE and other complications, amongst other outcomes, by using tables and figures taken directly from the relevant references.

Late lumen loss

The ISR I and II trials, which included 108 coronary in-stent restenosis patients, found that combined in-stent LLL was 0.14±0.46 mm for the 54 patients in the DEB[5] group and 0.81±0.79 mm for the 54 patients in the uncoated balloon group, at 6 months (p = 0.001). In the PEPCAD II trial of 131 ISR patients, in-stent LLL was also found to be significantly lower at 6 months for the DEB group (0.19±0.39 mm) when compared, here, to DES (0.45±0.68 mm).

One of the non-ISR trials (i.e. those focusing instead on small coronary vessels or bifurcations) reported that LLL was 0.21 mm for side branches and 0.38 mm for main branches for bifurcation patients, at 9 months (PEPCAD V). The PEPCAD I trial, investigating small coronary artery patients, found that in-lesion LLL was 0.18±0.38 mm for the DEB only group, and 0.73±0.74 mm for those who used BMS in addition to DEB, at 6 months (p<0.0001).

Target lesion revascularisation

The included studies reported lower TLR rates for the DEB patients when compared to the comparator under consideration. The ISR I and II trials found TLR to be 6% (3/54) at 24 months in the DEB group as opposed to 37% (20/54) in the uncoated balloon group (p = 0.001). The corresponding 12-month results were 4% (2/54) and 37% (20/54), respectively. The PEPCAD II trial reported TLR rates of 6% (4/66) for DEB patients versus 15% (10/65) for DES patients at 12 months. For patients with bifurcations, the PEPCAD V trial

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[4] Note that results for the PEPCAD I are presented in terms of the as-treated analysis.

[5] Note that whenever reference is made to DEB, this indicates the SeQuent® Please technology.

reported the TLR rate at 9 months to be 4% (1/28). The mean TLR rate for the small coronary artery patients in the PEPCAD I trial was 12% (14/118) at 12-month follow-up.

Restenosis

The rate of binary in-stent restenosis was 6% (3/54) for the DEB group compared to 49% (24/54) for the uncoated balloon group, at 6 months, in the ISR I and II trials (p = 0.001). Similarly, the PEPCAD II trial found a lower binary in-stent restenosis rate for the DEB group (7%; 4/66) when compared to DES (17%; 10/65). For small coronary artery patients, the binary restenosis rate (in-lesion) was 6% (4/82) for DEB patients, and 41% (12/32) where BMS had also been used (PEPCAD I), at 12-month follow-up.

Safety

MACE was significantly reduced at 24 months for the DEB group (11%) when compared to the uncoated balloon group (46%) in the ISR I and II trials (p=0.001). Similarly, MACE was reduced for the comparison of DEB versus DES in the PEPCAD II trial. The submission provided 6-month rates of 5% and 18% for DEB and DES, respectively, with reference to page 117-118 of the internal PEPCAD II report (14). The MACE rates are actually provided on page 110-111 and relate to the as-treated analysis. For the ITT analysis, the corresponding 6-month rates are 8% and 17% respectively (12-month rates are 8% and 17%, respectively) (14).

The PEPCAD I trial reported 6-month MACE rates of 6% and 38% for the DEB group and DEB plus BMS group, respectively. The bifurcation patients in the PEPCAD V trial had an associated MACE rate of 11% at 9 months.

The ISR I and II trials reported a reduction in rate of death, stroke and MI associated with DEB use versus the uncoated balloon catheter at 24 months, although the reductions were not statistically significant. The PEPCAD II trial reported death in 3% and 5% of DEB and DES patients, respectively, at 12-month follow-up. Myocardial infarction and noncardiac deaths were lower for the DEB group; however, cardiac deaths were higher (1 cardiac death in the

DEB group as opposed to no deaths in the DES group). At 12-months, the PEPCAD I trial reported zero death rates in both patient groups, with MI rates of 1.3% and 3.1% for the DEB group and DEB plus BMS group, respectively. The PEPCAD V trial reported 0% death rates at 9-month follow-up.

Note: the figures included in the interpretation section do not all correspond to the figures featured earlier in the clinical results sections (i.e. they differ to the tables that have been sourced from the studies). The submission document states that Table 5.5.1.4 relates to the ITT analysis. This is incorrect however; the table in fact relates to the as-treated analysis (Table 2 in Unverdorben *et al.* 2010 (6)).

4.2.2 Critique of submitted evidence syntheses

The manufacturer submission did not undertake meta-analysis or indirect/mixed treatment comparisons on the grounds that meta-analysis was "not meaningful in terms of clinical outcomes, i.e. MACE and TLR/TVR since each lesion specific study has different risk and patient outcome expectations." The EAC agrees that such a meta-analysis would not be worthwhile due to the limited number of studies and differences in patient populations.

The submission provides a summary of clinical findings in relation to LLL and MACE from the included studies. Tables and charts are used to compare the LLL rate across studies, and similarly for MACE rates (pages 65-66). However, when interpreting this data it should be remembered that the different studies involved different patient populations.

5 Assessment of cost analysis

5.1 Overview of manufacturer's economic assessment

5.1.1 Methods

This section assesses the cost analysis submitted by the manufacturer regarding the use of SeQuent® Please.

The manufacturer's submission to NICE included:

- A description of the literature search that was undertaken for the identification of cost and cost-effectiveness studies in relation to SeQuent® Please (pages 81-84; Appendix 6, pages 138-139);

- A report of the *de novo* cost impact analysis that was conducted, including the patient population, model structure, model parameters, assumptions, data sources, base case results and sensitivity analyses (pages 84-119);

- An electronic copy of a Markov model developed using TreeAge;

- An Excel file showing the base case results of the analysis and sensitivity analyses;

- An Excel file containing additional information regarding model parameters.

A summary of the relevant areas of the submission document for the cost analysis can be seen in Table 3.

Table 3: Summary of key information in the submission document for cost analysis

	Reference in submission document	Key tables/figures in submission document
Review of literature	p 81-84, p 105-106, p 134-160 (Appendix 4-9)	Table B10 Figure 6.1.1
Model structure	p 85-88	Figures 6.2.3-6.2.4
States and events	p 88-89	
Transition probabilities	p 94-98, p 101-102	Table 6.3.2, Table B12, Table B13
Comparator	p 88	
Subgroups	p 120-122	Table 6.8.1
Perspective and time horizon	p 90	Table B11
Adverse events	p 109-	Table B16
Resource use and costs	p 104-110, p 158-159	Table B12, Table B14, Table B15, Table B16
Discount rates	p 90	Table B11
Sensitivity analysis	p 111-115, p 118-119	Tables B17-B19, Figure 6.6.4
Results	p 112-118	Tables B20-B22

Identification of studies

The searches for cost-effectiveness studies were reported in Appendix 6: Search strategy for cost-effectiveness and cost studies (Section 6.1). The submission does not include a search of the Cochrane Library or EconLIT, but does include a search of EMBASE and PubMed (which includes Medline and Medline In-process). The submission does not include a search of NHS EED even though the resource is free to search on the internet.

The PubMed search is not extensive and runs the risk of missing relevant studies. As well as 'cost-effectiveness' and 'cost-benefit', additional search terms might be usefully added to the search such as 'cost-utility'. Search

filters to identify economic evaluations on PubMed can be obtained free of charge (http://www.york.ac.uk/inst/crd/intertasc/econ.htm). The subject search seems highly restrictive and unlikely to identify all the relevant records.

The use of limits is unclear with the tables providing conflicting information and the supporting document suggesting no limits. If limits were used the comments noted earlier all apply. The absence of limits would be a positive feature.

The EMBASE search strategy is reported differently in two tables, but we have assumed that the second table represents the DIMDI search which was conducted. However, the search strategy does not seem to be sensitive enough (not enough synonyms) to be confident that all relevant records have been retrieved.

It is helpful to know that www.clusty.com was searched, but the search terms are not presented so the adequacy of the search is unknown.

The searches for the cost analysis seem to be those reported in Appendix 8: Search strategy for Section 6.4 (Measurement and valuation of health effects). Searches were only conducted in MEDLINE, so additional studies may have been missed from EMBASE, NHS EED and EconLIT.

The search strategy for bleeding and post PCI is structured as follows:

Economic analysis

AND

Uk

AND

Coronary heart disease

AND

Mortality

AND

English

AND

Publication years 2005 to 2010

The search is not very focused on bleeding, and is not sensitive enough to have captured all UK studies. The use of the text word term 'uk' is very limited. Records relevant to the UK are indexed with the subject heading 'Great Britain' in MEDLINE and this does not appear in the strategy. In addition 'united kingdom' should also have been searched. The search for 'mortality' as a concept also limits the searches. The economic search concept is quite focused as the 'economics' terms have to appear either with the subheading 'analysis; and the word 'analysis' in any field. This is quite a stringent requirement. For example, 'cost analysis' would not have been returned by this strategy. The subheading 'analysis' is used in the search but its meaning in the context of MEDLINE indexing is as follows:

Used for the identification or quantitative determination of a substance or its constituents and metabolites; includes the analysis of air, water, or other environmental carrier. The concept applies to both methodology and results. For analysis of substances in blood, cerebrospinal fluid, and urine the specific subheading designating the fluid is used.

The search strategy for bleeding and post CABG is structured as follows:

hemorrhage

AND

Coronary artery bypass

AND

Mortality

AND

English

AND

Publication years 2005 to 2010

This search is more sensitive than the previous search although it does not have the spelling variants for 'hemorrhage' such as 'haemorrhage'.

The search strategy for bleeding and CABG and clopidogrel is structured as follows:

hemorrhage

AND

Coronary artery bypass

AND

Clopidogrel

AND

Publication years 2005 to 2010

This search is reasonably sensitive although it does not have the spelling variants for 'hemorrhage' such as 'haemorrhage'.

The search strategy for CABG and death is structured as follows:

hemorrhage

AND

Coronary artery bypass

AND

Death

AND

Risk

AND

mortality

AND

In-hospital

AND

English language

AND

Journal subset AIM

This is a very focused search as all the concepts above are required to be present in a record. Relevant studies are highly likely to have been missed by this search. The use of the concept 'Death' in particular is very limiting especially as 'mortality' terms are also required. The use of 'in-hospital' is very specific and additional terms should have been ORed with this to improve the sensitivity of the search.

The search strategy for cost-effectiveness of coronary heart disease in the UK is structured as follows:

Economic analysis

AND

Coronary disease

AND

Uk

AND

Mortality

AND

English

AND

Publication years 2005 to 2010

The search is not sensitive enough to have captured all UK studies. The use of the text word term 'uk' is very limited. Records relevant to the UK are indexed with the subject heading 'Great Britain' in MEDLINE and this does not appear in the strategy. In addition 'united kingdom' should also have been searched. The search for 'mortality' as a concept also limits the searches. The economic search concept is quite focused as the 'economics' terms have to appear either with the subheading 'analysis; and the word 'analysis' in any field. This is quite a stringent requirement. For example, 'cost analysis' would not have been returned by this strategy. The subheading 'analysis' is used in the search but its meaning in the context of MEDLINE indexing is as follows: Used for the identification or quantitative determination of a substance or its constituents and metabolites; includes the analysis of air, water, or other environmental carrier. The concept applies to both methodology and results. For analysis of substances in blood, cerebrospinal fluid, and urine the specific subheading designating the fluid is used.

Searches to identify resources should be reported in Appendix 9: Resource identification, measurement and valuation (Section 6.4). However, the

databases searched and the strategies used were not reported so it is not possible to judge whether they were adequate.

In total, the search for cost-effectiveness and cost identified 28 references, 11 of which referred to in-stent restenosis, as stated by the manufacturer (page 82). Of the 11 ISR references, 4 were identified as being relevant, with 7 excluded. The included studies comprised Beusterien *et al.* 2002 (15), Reynolds *et al.* 2007 (16), Cohen *et al.* 2002 (17) and Mahieu *et al.* 2007 (18). Two additional references are provided in Table B10; 'HTA Austria 2009' and 'Spetaris 2009'. However, data from the identified studies have not been used for the model. Further studies appear to have been used for the model, such as Ovrum *et al.* 2010 (19) and Ko *et al.* 2010 (20), although details of their identification have not been provided.

Details of the excluded studies were not included in the submission but were supplied by the manufacturer when requested by the EAC (information provided in Appendix 1).

Model structure

A *de novo* cost impact analysis was undertaken through the development of a simple 'within-trial' Markov model. In general, the model was presented appropriately although a more comprehensive description of some aspects would have been useful. Patients enter the model with ISR, as the analysis focuses on patients with ISR only (i.e. patients with small calibre coronary arteries and bifurcation patients were not considered). Appropriately, the analysis is taken from the perspective of the NHS and Personal Social Services (PSS).

The comparator was the DES, as previously discussed (Section 3.3). Specifically, the Taxus® stent was included, which also uses paclitaxel but involves a different release mechanism (stent mediated paclitaxel release versus balloon). Hence, the model has two arms in order to compare SeQuent® Please against the DES. The model uses monthly Markov cycles, a one-year time horizon and applies a half-cycle correction.

The model compares the two treatment options in terms of the costs associated with treatment, device, medication and serious complications, along with the associated survival. The model aims to capture the impact of some serious adverse events, such as stroke, MI and bleeding complications.

Health states and events

The manufacturer states that relevant health states for the model are (pages 88-89):

- survival without TVR;
- survival with TVR which can be subdivided in:
  - survival with TVR by CABG;
  - survival with TVR by re-intervention (re-PCI);
- survival without MI;
- survival with MI which can be subdivided in:
  - survival with TVR by CABG;
  - survival with TVR by re-intervention (re-PCI);
- cardiac death ;
- non-cardiac death, i.e. death from other causes (e.g. malignancy);
- bleeding complications from extended dual anti-platelet therapy (DAPT).

The four main health states included in the model, however, are:
- alive pre-revascularisation;
- alive post-revascularisation;
- alive post-TVR;
- dead.

Events are then incorporated for each health state, such as revascularisation and various complications, including bleeding, MI and stroke. The likelihoods of the different events are estimated using probabilities (Tables B12 and B13).

All ISR patients enter the model in the 'alive pre-revascularisation' state where they face the possibility of having initial revascularisation procedures, where complications may be encountered (i.e. alongside the procedure there may be no complications, or complications such as MI, stroke or bleeding, or death). Patients subsequently move into one of the remaining three health states; either 'alive post-revascularisation', 'alive post-TVR' or 'dead', according to the transition probabilities. Patients stay in the 'alive post-revascularisation' state until TVR is required. Following TVR, patients move to the 'alive post-TVR' state, where they remain until death. 'Dead' is an absorbing state.

Assumptions

The submission did not provide any assumptions in the relevant section (page 103), with the manufacturer stating that the 'within-trial' model was used with minimal assumptions (i.e. extrapolations into the long-term and across trials were not undertaken). However, the EAC notes the following assumptions that featured in other sections of the report here. The assumption was made that transition probabilities did not vary with time. In addition, the lowest HRG (health-related group) tariff is used for the intervention cost (page 104) (assuming PCI will be an elective procedure rather than non-elective, page 104).

Data sources

The model uses data predominantly from the PEPCAD II trial (the only non-PEPCAD II data to be used are for some of the probabilities, taken from additional studies (19, 20)). In addition, the NHS National Tariff 2010-2011 was used. Details of the sources for the various model inputs can be found in the corresponding sections below.

Resources and costs

The costs included in the model are based on those to the NHS and PSS, as specified for the NICE reference case. The model included costs for the devices, treatment procedures and co-medication, as shown in Table B14 (page 108). Costs for administration, monitoring and tests were not

incorporated, as it was stated that there would be no additional costs involved for these areas. The costs associated with the different health states included some complication costs. Costs were provided in 2010 pounds.

Costs were applied in the model each cycle according to the event that occurred in that particular cycle. For instance, where a PCI occurred, the corresponding cost of this intervention was applied. Details of the costs associated with the different events (termed health states in the submission) and adverse events can be seen in Tables B15 and B16 of the submission document, which are summarised in Table 4 below.

All of the costs for the procedures and adverse events were taken from the National Tariff 2010-2011. Specifically, the admitted patient care and outpatient procedure tariff was used. Although these details were not provided in the submission document, additional files were supplied by the manufacturer including the relevant tariff file and information regarding the HRG codes that were used. This information was verified by the EAC. The application of a cost for the PCI procedure and also a separate cost for the complication, both sourced from the National Tariff, may include some degree of double-counting although the extent of this cannot be determined. The EAC acknowledges the approach used here is appropriate. The adverse event costs do not incorporate long-term costs, such as rehabilitation costs associated with stroke. However, this approach is conservative given that stroke is more likely for the DES arm.

The cost of a PCI intervention was based on the HGR code EA31Z which refers to PCI (0-2 stents). The PCI cost was applied similarly for both treatment arms, apart from the cost differential (of £200) associated with the devices being added to the SeQuent® Please arm. Wherever a PCI occurred in the SeQuent® Please arm, this indicated use with SeQuent® Please each time, as clarified by the manufacturer. The manufacturer states that price variations occur in the UK market for the devices in the analysis. As a result, the model uses a cost differential between DES and SeQuent® Please of £200. Hence, whenever SeQuent® Please is used, an additional cost of £200 is applied.

The cost of co-medication using clopidogrel was applied monthly (i.e. per cycle), based on prices from NICE HTA 182 (21) and applied for the durations used in the PEPCAD II trial. The corresponding durations applied for the model were 3 months for SeQuent® Please and 12 months for DES.

The costs included in the model can be seen in Table 4, based on information provided in the submission document, with additional information added by the EAC regarding the corresponding HRG codes.

Table 4: Costs used in the model

Variable Name	Default Definition (£)	HRG Code
c_monthly_clopidogrel	38.66	NA
c_PCI_PES	3306	EA31Z
c_PCI_SQP	3306+200	EA31Z
c_rePCI_PES	1635	EA35Z
c_rePCI_SQP	1635+200	EA35Z
Adverse events:		
c_bleed	1191	FZ38B
c_CABG	8226	EA14Z
c_MI	1569	EB10Z
c_stroke	3759	AA22Z

Based on Tables B15 and B16 from submission document; all costs sourced from NHS National Tariff 2010-2011, with the exception of the clopidogrel cost.

Impact on further resources

The submission document notes the difficulty in capturing costs which may arise for caretakers and rehabilitation. Such costs are not included in the analysis, with it being acknowledged that productivity loss is also not considered, which is appropriate given the NHS perspective of the analysis.

Transition probabilities

The model uses transition probabilities based on the rates of TLR or target vessel revascularisation (TVR). These are noted by the manufacturer to be the main cost drivers. The transition probabilities have been derived from the PEPCAD II trial, in addition to two studies (Ko *et al*. 2010 (20) and Ovrum *et al*. 2010 (19)) for probabilities related to CABG and bleed-related mortality

(Table 6.3.2). In the base case it was assumed that transition probabilities did not vary according to time.

Time horizon

A one-year time horizon was used for the analysis. There was no extrapolation from this short-term time horizon to the long-term. The manufacturer referred to analysis over 12 months, to be extended to several years in Table B11. However, this extension into the future has not been undertaken, as described later in the submission. The justification of the time horizon was provided (Table B11 and page 103).

Discounting

Due to the one-year time horizon of the model, discounting was not undertaken, which is appropriate.

Sensitivity analysis

Deterministic sensitivity analysis was undertaken. Probabilistic sensitivity analysis was not featured in the submission. The following model parameters were investigated using sensitivity analysis:

- mortality rates;
- TVR rates;
- DAPT (i.e. clopidogrel) duration;
- cost for SeQuent® Please[6];
- costs for TVR and MI;
- time dependence for events (i.e. time-dependent transition probabilities).

A tornado diagram (Figure 6.6.4, page 118) was used to assess the robustness of the base-case results to various costs in terms of the

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[6] Note: the results of this sensitivity analysis were not provided in the submission document, although were provided in an additional Excel file.

incremental costs. This involved varying the inputs for initial revascularisation cost, MI cost and post-revascularisation TVR cost by +/- 20%.

5.1.2 Results

Results are presented in terms of the expected cost and life expectancy for the two treatment arms. The incremental cost and incremental life expectancy are then displayed. Overall costs are reported, in addition to a breakdown of costs associated with technology, treatment, administration, monitoring, tests and medication.

In addition to the base case results, sensitivity analyses were also presented in the submission (as described above). As previously reported, the manufacturer did not carry out subgroup analyses. A full description of the results presented by the manufacturer can be seen in Section 5.3.

5.1.3 Model validation

The manufacturer stated that the model is a refined version and the outcome of several iterations, with the use of tracker variables[7] to test the robustness of the model outcomes (page 119). However, further details were not provided. For instance, it was not reported that the model structure had been validated by a clinical expert.

5.2 Critique of approach used

The manufacturer states that the model is a simplification of real clinical practice to treat patients with ISR. On the whole, the EAC considers the model to be an accurate representation in terms of capturing the main events likely to occur for ISR patients over a one-year time period. Due to actual trial data being implemented in the model, there was no need for data extrapolation or approximation. Details of different aspects of the approach taken by the manufacturer are provided below.

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[7] Tracker variables can be used to track a patient's history in the Markov process, to report additional output quantities or to manipulate various inputs or conditions of the model that may depend on a patient's history (http://www.treeage.com/products/healthDetails.html).

Comparator

The manufacturer's choice of comparator is based on the assumption that, in the absence of SeQuent® Please, the majority (90%) of ISR patients are treated with DES (page 88). Although details of whether there is anything to support the assumption are not given, the DES is considered by the EAC to be the appropriate comparator. However, investigation of further alternatives would be useful.

Model

As previously discussed, the time horizon of the model is one year, whereas the NICE scope outlined that long-term costs should be incorporated. The manufacturer states that when the next (3-year) follow-up period of the PEPCAD II trial is reached, the existing model can be updated. At this time, additional data sources will be used such as the ongoing ISR trials and the International Registry results (page 103). We acknowledge that extrapolation into the future using short-term data would introduce uncertainty into the model. However, it would be useful for the model to take the 12-month trial data out to a longer time period, perhaps looking at the medium-term (e.g. 5 years) in the first instance.

Given the time horizon of the model, an appropriate cycle length and use of half-cycle correction was incorporated. The clinical continuation rule has not been included in the submission (page 92).

Model inputs

Clinical experts did not assess the applicability of model values or the assumptions underlying the model. It would be ideal to obtain feedback from such experts to ensure the model accurately represents real clinical practice in the UK as far as possible. The use of the PEPCAD II trial data means that the model is based on relevant findings for the patient population under consideration. The use of relevant national cost data means that the cost inputs are applicable for the UK.

The assumption that transition probabilities were not time-dependent seems sensible given the one-year time horizon. If a longer time horizon were incorporated, however, this consideration would need to be addressed.

There is discrepancy between the description of the model health states in the report and those featured in the model. The health states described by the manufacturer on page 88 relate to aspects that are picked up by the model. However, the four actual health states included in the model are as described in Section 5.1.1.

The submission states that "the full potential of the Markov model relative to higher bleeding complications in the DES group has not yet been applied" (page 124). That is, the model currently uses zero probabilities for bleeding complications in both arms. The model assumes that the same probabilities have been applied for the events that occur during the post-revascularisation state and those that occur during the post-TVR state. Therefore the occurrence of TVR has not been taken into account here.

Resources and costs

The cost analysis took a conservative approach around the use of intervention cost for PCI. The use of a price differential between SeQuent® Please and DES seems sensible given the range of costs available for the devices. However, it would be useful to see details of the sources used for the ranges (in addition to information on page 10). In particular, as the list prices of the devices are £1,035 and £750 for SeQuent® Please and paclitaxel DES respectively (NICE Medical Technologies Guidance: SeQuent® Please), generating a price differential of £285, it is important to see more detail about the justification for the £200 price differential used in the model. The EAC notes the sensitivity analysis undertaken around an alternative cost for SeQuent® Please, as supplied in the Excel file additional to the submission. However, further investigation around the price differential using sensitivity analysis would be valuable. It may be useful to incorporate more detail relating to resource use, such as physician visits, outpatient consultations *etc*, into the model.

The cost for clopidogrel medication was applied for 3 months for SeQuent®
Please and 12 months for DES. The submission stated that these durations
were based on the PEPCAD II trial. In this trial, after 6 months, it was reported
that 29% of SeQuent® Please patients and 65% of DES patients were using
clopidogrel (5). After 12 months, 18% and 42% in the SeQuent® Please and
DES groups, respectively, were using clopidogrel. Hence, although over 40%
of DES patients were using this medication at 12 months, so too were some
SeQuent® Please patients. The application of the clopidogrel durations in the
model is therefore questionable. The cost of clopidogrel has been shown to
have an impact on the overall results (shown in Table 6); hence it is important
to investigate the impact of varying the duration of time that clopidogrel is
applied for in the DES arm (for instance, considering 6 months of clopidogrel,
as featured in the methods of the PEPCAD II trial (5)). A point to note is that
the use of clopidogrel for 12 months for DES patients has been recommended
by the BCIS and the American College of Cardiologists/American Heart
Association in NICE HTA guidance 152 (22).

As highlighted by the manufacturer, the model is influenced by the co-
medication costs. The analysis incorporates (non-generic) clopidogrel, which
is the generally accepted drug of choice for the high-risk ISR patient
population.

Literature search

The literature search undertaken for studies relating to costs and cost-
effectiveness associated with SeQuent® Please was not extensive. The cost
section also includes additional studies that do not appear to have been
identified via the literature searches, but full details relating to their
identification have not been provided. Details of the searches for resource use
data were unclear (pages 105-106, 158-160). However, searches were
conducted in relation to adverse events, although details of how these were
used for the model were unclear.

Analysis

The analysis evaluated the cost impact for ISR treatment with SeQuent® Please in comparison to DES. The main costs associated with such treatment options were included, such as procedure, device, complication and co-medication costs. Sensitivity analyses were provided which explored a range of model parameters, although only one-way deterministic sensitivity analysis was undertaken.

5.3 Results included in manufacturer's submission

The results of the model are reported in page 112-122 of the submission document. The base case analysis found that the average per-patient cost over the one-year time horizon was £4,134 for the SeQuent® Please treatment arm and £4,873 for the DES arm. This indicates a cost saving of £739 per patient through use of Sequent® Please compared to DES. The expected life expectancy was estimated to be 0.987 versus 0.979 years for Sequent® Please and DES, respectively; hence an improvement of 0.01 years.

The results section of the submission mainly comprised tables, with little explanation surrounding these. The base case results from the submission can be seen below in Table 5.

Table 5: Base case results

Base case						
	SeQuent Please		Taxus		Incremental (SQP - PES)	
	Costs (£)	Life expectancy (years)	Costs (£)	Life expectancy (years)	Costs (£)	Life expectancy (years)
Statistic	C(SeQuent Please (SQP))	E(SeQuent Please (SQP))	C(Taxus (PES))	E(Taxus (PES))		
Mean	4.133,77	0,987	4.873,20	0,979	**-739,43**	0,01
Std Dev	1.326,52	0,089	1.890,30	0,11	-563,78	-0,02
Minimum	3.563,99	0,125	3.363,99	0,125	200,00	0,00
2,50%	3.641,31	0,875	3.595,95	0,625	45,36	0,25
10%	3.641,31	1	3.769,92	1	-128,61	0,00
Median	3.641,31	1	3.769,92	1	-128,61	0,00
90%	7.205,30	1	7.075,92	1	129,38	0,00
97,50%	7.263,29	1	10.381,92	1	-3.118,63	0,00
Maximum	17.955,26	1	20.299,92	1	-2.344,66	0,00
Sum (n*mean)	413.376.732,78	98651,542	487.319.632,23	97934,625	-73.942.899,45	716,92

Table B22 from submission document.

The findings from the model were not compared against other study findings due to the lack of evidence available. The results reported in Table B20 in relation to the summary of costs by health state were not very meaningful.

However, the results in Table B21 regarding the summary of costs by cost category were more useful; the cost of PCI with SeQuent® Please was £3,614 compared to £3,736 for DES, which comprised the cost of the treatment itself, device and co-medication.

Although sub-group analysis was not carried out for the submission, the manufacturer states that the main driver for unfavourable outcomes is the diabetic subpopulation, which accounted for approximately one third of the PEPCAD II study population (page 121).

The results of the deterministic sensitivity analysis are presented in Tables B17-B19 and in the tornado diagram on page 118. In order to demonstrate the impact of the various sensitivity analyses conducted by the manufacturer, the EAC have added a table which provides a summary; Table 6 shows the change in cost savings in relation to the base case. For instance, when the cost of MI was increased by 20% in the sensitivity analysis, the corresponding cost saving increased by 2.5%, from £739 to £758.

Table 6: Summary of impact of sensitivity analysis in terms of cost saving

Scenario	Cost saving (£)	Change (in relation to base case)
Base case	**739**	
Same mortality in both arms (i.e. apply DES rate for both)	751	1.6%
Same post revasc. MI rate in both arms (i.e. apply DES rate for both)	716	-3.1%
Same TRV rate in both arms (i.e. apply DES rate for both)	75	-89.9%
Clopidogrel for 1 month after SQP PCI (base case assumes 3 months)	839	13.4%
Clopidogrel for 5 months after SQP PCI (base case assumes 3 months)	660	-10.7%
Cost of TVR + 20% (c_rePCI_PES and c_rePCI_SQP + 20%)	744	0.7%
Cost of TVR - 20% (c_rePCI_PES and c_rePCI_SQP - 20%)	742	0.3%
Cost of MI + 20%	758	2.5%
Cost of MI - 20%	733	-0.8%
Time-dependent transition probabilities	707	-4.4%
Intitial revascularisation cost +20% (c_PCI_PE and c_PCI_SQP +20%)	870	17.7%
Intitial revascularisation cost -20% (c_PCI_PE and c_PCI_SQP -20%)	624	-15.6%

Of the parameters that were varied in the sensitivity analysis, the largest impact was demonstrated for TVR rates. In addition, although to a lesser extent, the model was found to be sensitive to co-medication costs (i.e. clopidogrel cost) and initial revascularisation costs.

The manufacturer states that the cost savings are relevant to a 'real world' scenario of an unselected ISR patient population who require additional revascularisation.

5.4 Comment on validity of results presented with reference to methodology used

The results reported in the submission document indicate that SeQuent® Please is likely to be cost-saving over the one-year time horizon that was considered in the analysis. The findings are sensitive to TVR rates, co-medication costs and initial revascularisation costs. The validity of the conclusions is subject to a number of issues and areas of potential uncertainty, which are summarised in Section 5.5.

The EAC attempted to validate the manufacturer's model and inputs as far as was possible given the associated time constraints. The methodology behind the model and construct of the model were not fully explained for some areas. The model was straightforward and the choice of health states and events appears sensible. The incorporation of adverse events was appropriate, although long-term management was not incorporated. By using a Markov modelling approach, it is possible to incorporate the movement between different health states over time whilst incorporating certain events which will influence the overall costs, as in this model.

Trial-based evaluation using one trial may be considered inadequate. However, given the paucity of evidence in this area and the fact that the manufacturer's literature search only identified three relevant studies (ISR I and II, and PEPCAD II) in relation to ISR patients, it seems reasonable to have focused on the PEPCAD II findings in these circumstances. In terms of assessing SeQuent® Please in the longer-term, it would be valuable to extrapolate outside the trial-based approach.

In addition, the model incorporated utilities, although this was beyond the scope of the submission.

5.5 Summary of uncertainties and issues

In general, the EAC considered the manufacturer's submission in relation to the cost impact of SeQuent® Please to be adequate in addressing the decision problem. Sensitivity analysis was conducted in order to explore the robustness of the results to changes in various parameters. The main issues raised by the EAC are summarised below.

Literature searches

The search strategies provided in the submission were not extensive and were inadequately reported. There were inconsistencies in the methods used, therefore we cannot be confident about the identification of studies and whether all relevant studies have been included in the submission.

Data sources

The main source of data for the model was the PEPCAD II trial. This study was conducted in Germany, hence the generalisability to the UK setting is an issue to consider (e.g. whether patient case-mix and routine clinical practice will vary). Unverdorben *et al.* (2009) (6) state that the majority of patients had simple patterns of in-stent restenosis that are associated with a more favourable outcome as a limitation, in addition to the number and selection of patients in the study. The duration of co-medication was based on the PEPCAD II trial. However, there is some uncertainty around whether the appropriate durations have been applied in the model, as previously discussed (Section 5.2).

Follow-up

The one-year follow-up period of the PEPCAD II trial used for the model is shorter than the appropriate time horizon that would ideally be considered for the cost analysis. Any conclusions about the costs associated with SeQuent® Please after this time therefore have not been estimated. It would be useful to

investigate the likely impact in the medium-term (for example, 5 years) by extrapolating the current data.

Patient population

This submission has focused on the use of SeQuent® Please in patients with in-stent restenosis. However, the impact on patients with small calibre arteries and bifurcations has not been investigated and therefore the effect in these patient populations is unknown.

Comparators

The cost analysis has provided findings for SeQuent® Please versus the DES, which was considered to be the most relevant comparator. Due to the model being based on relevant trial data and the short time horizon, the results generated by the analysis are likely to be reliable for this comparison. However, further comparators have not been considered, such as the BMS and uncoated balloon catheter, as they do not feature in the PEPCAD II trial, which was the primary data source. Analyses of such comparators would provide more information about the relative value of SeQuent® Please.

Adverse events

An additional literature search (and review) was conducted in relation to adverse events. However it was not reported whether the results of this were used to inform the choice of adverse events that were used in the model. It is therefore not clear whether all relevant adverse events were captured.

Execution of the model

Details of the model were not reported comprehensively for certain parts of the submission. However, clarification was sought from the manufacturer regarding certain aspects such as the sources used for the transition probabilities, with information subsequently provided in additional files. Another point to raise is that the model was not verified by clinical experts; hence it is unknown whether the model accurately represents reality according to such opinion.

Sensitivity Analysis

Sensitivity analysis was conducted for a range of parameters. However, further investigation around the price differential (between SeQuent® Please and DES) and the duration of clopidogrel for DES patients (e.g. 6 months for DES rather than the 12 months currently applied) would be useful. Some of the sensitivity analyses were illustrated by use of a tornado diagram. Although it is useful to see the findings in this diagram, it would be useful to see the impact on more parameters here.

Additional work undertaken by the External Assessment Centre

Additional work undertaken by the EAC comprised:

- Additional literature searches in order to investigate the reliability of the manufacturer's literature searches that were used to identify the clinical data. Details of these are provided in Section 4.1.2, along with a detailed critique of the literature searches in Sections 4.1.1 and 5.1.1.

- Comments have been provided alongside the manufacturer's critical appraisal of the included clinical effectiveness studies.

- Additions such as the additional table to demonstrate the change in cost savings compared to the base case, for the sensitivity analysis that was conducted by the manufacturer.

6 Discussion

6.1 Summary of clinical effectiveness issues

The literature search for the clinical effectiveness studies relating to paclitaxel-coated balloon catheters was not extensive and the description of the search strategy lacked detail. Therefore the EAC cannot be confident that all relevant studies were identified. In addition to inconsistencies around the searches, full details of the review process were not provided. The five included studies comprised three RCTs and two non-randomised trials; the three RCTs related specifically to ISR patients.

The included studies on which the clinical effectiveness was based were all conducted in Germany, funded by B. Braun or another manufacturer and of limited follow-up. The studies focused on different comparators; SeQuent® Please was compared against the uncoated balloon catheter, DES and also the addition of BMS was considered. The validity of studies was assessed which raised some issues; the selection of patients, size of the trials (and therefore power of the findings), *etc.*

The outcomes addressed by the submission were considered appropriate and relevant, including restenosis, LLL, TLR and MACE, although not all of the outcomes outlined in the NICE scope were addressed. Consistent definitions of the outcomes were used and the presented evidence demonstrates a reduction in restenosis, LLL, TLR and MACE associated with SeQuent® Please treatment.

6.2 Summary of cost issues

For the comparison of SeQuent® Please and DES, the cost model represented real clinical practice and was therefore considered to be a justifiable simplification of reality. The use of a within-trial approach meant there was no need for extrapolation or approximation. However, the one-year time horizon does not capture the long-term impact.

As with the clinical searches, the cost literature searches were not extensive and inadequately reported. However, appropriate sources have been used to

populate the cost model. A conservative approach was taken in relation to the PCI procedure cost used in the model. The price differential between the two devices could be explored further, to determine whether this is a key driver of the results. The calculation of the clopidogrel co-medication cost applies clopidogrel for 12 months in the DES arm, although this may be considered too long compared to real clinical practice.

The base-case analysis demonstrated a cost saving of £739 per patient through use of SeQuent® Please compared to DES; the average per-patient cost over the one-year time horizon was £4,134 for the SeQuent® Please treatment arm and £4,873 for the DES arm. The sensitivity analysis identified the key drivers of the results to be TVR rates, co-medication costs and initial revascularisation costs. However, other potentially influential parameters such as the price differential between the two devices and the duration of clopidogrel treatment in the DES arm could have been investigated.

6.3 Implications for guidance and research

The submission has presented evidence that SeQuent® Please for the treatment of ISR results in a reduction in restenosis, TVR rates, LLL, MACE and co-medication (i.e. anti-platelet therapy), in addition to cost savings.

A full evaluation of SeQuent® Please treatment in patients with small calibre coronary arteries & bifurcations would be of value, in addition to the consideration of different comparators. It would also be useful to conduct subgroup analysis in order to identify the relative value of treatment using SeQuent® Please in different patient populations.

The currently available evidence is based on a limited follow-up duration. Longer-term data are required in order to determine the impact of SeQuent® Please in the future, and therefore enabling a robust long-term analysis to be undertaken. There is ongoing research into the use of SeQuent® Please in the long-term and in different patient populations, including the PEPCAD DES, SEDUCE and PEPCAD CTO trials, with results due within the next five years.

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Appendix 1: Excluded ISR studies, from the cost-effectiveness and cost search

Of the 11 ISR studies that were identified, the 7 excluded studies comprised:

- Bejarano 2004: The cutting balloon for in-stent restenosis: a review.

- Chong and Cheng 2004: Early experiences and clinical implications of restenosis and drug-eluting stents: Part 2.

- Mazighi *et al.* 2004: Prevention of in-stent restenosis: towards an in situ treatment?

- IJsselmuiden *et al.* 2003: Direct coronary stent implantation does not reduce the incidence of in-stent restenosis or major adverse cardiac events: six month results of a randomized trial.

- Stent-PAMI trial 2001: Cost-effectiveness of coronary stenting in acute myocardial infarction: results from the stent primary angioplasty in myocardial infarction (stent-PAMI) trial.

- Salame and Douglas 2001: The restenosis story: is intracoronary radiation therapy the solution?

- Waksman 1998: Endovascular brachytherapy: overcoming "practical" obstacles.