7.13 CETUXIMAB
Solution for intravenous (IV) infusion, 100 mg in 20 mL and 500 mg in 100 mL, Erbitux®, Merck Serono Australia Pty Ltd.

1 Purpose of Application

1.1 The minor resubmission requested a Section 100 (Efficient Funding of Chemotherapy) listing for cetuximab, in combination with platinum-based chemotherapy, for the treatment of patients with previously untreated metastatic and/or recurrent squamous cell carcinoma of the head and neck (RM SCCHN).

2 Requested listing

2.1 The minor resubmission requested listing for the treatment of all patients with RM SCCHN. This listing was broader than that requested in the March 2016 submission, which requested a listing for the subgroup of patients with RM SCCHN. Proposed wording for the requested listing was not presented in the minor submission.

2.2 The minor resubmission proposed an effective price of $[redacted]/100 mg ([redacted]% reduction from the effective price of $[redacted]/100 mg proposed in the March 2016 submission; [redacted]% reduction from the proposed published ex-manufacturer price in the current resubmission). The effective price proposed in the minor resubmission was the same as the current effective price of cetuximab for the first line treatment of metastatic colorectal cancer (mCRC). The minor resubmission also proposed a risk sharing arrangement with a rebate of [redacted]% beyond agreed thresholds, as already applies to cetuximab for its current listings for locally advanced SCCHN and for mCRC.

3 Background

3.1 Cetuximab is TGA registered for:

a. Treatment of patients with squamous cell cancer of the head and neck:
   - in combination with radiation therapy for locally advanced disease; and
   - in combination with platinum-based chemotherapy for recurrent and/or metastatic disease.

b. Treatment of patients with epidermal growth factor receptor (EGFR)-expressing tumour, RAS wild-type mCRC:
   - in combination with infusional 5-fluorouracil/folinic acid plus irinotecan;
   - in combination with irinotecan in patients who are refractory to first-line chemotherapy;
   - in first-line in combination with FOLFOX; and
   - as a single agent in patients who have failed or are intolerant to oxaliplatin-based therapy and irinotecan-based therapy.

3.2 Cetuximab, in combination with radiotherapy, is currently PBS-listed for the treatment of patients with Stage III, IVa or IVb SCC of the larynx, oropharynx or hypopharynx, who are unable to tolerate or have a contraindication to cisplatin. Cetuximab is also PBS-listed for the treatment of mCRC in patients who meet certain criteria.

3.3 In March 2016, the PBAC considered a submission for cetuximab, in combination with platinum-based chemotherapy, for the treatment of RM SCCHN, specifically for patients with carcinoma of the oral cavity. The PBAC did not recommend the listing of cetuximab for this indication on the basis of uncertain magnitude of clinical benefit and likely high and unacceptable cost-effectiveness. The PBAC considered that there was a clinical need for treatments for all patients with RM SCCHN. Furthermore, the PBAC noted that the restriction was based on the *post hoc* subgroup of patients with this disease for whom the oral cavity was the primary tumour site of origin and with a WHO performance status 0-1 [equivalent to Karnofsky Performance Status (KPS) ≥80]. The PBAC noted that the TGA-registered indication for cetuximab was broader and included all patients with RM SCCHN. The PBAC considered there was a high risk of leakage outside the restriction proposed by the sponsor, into the broader RM SCCHN population. The PBAC recalled that at the March 2016 meeting, it requested that any subsequent resubmission should be made as a major submission.

3.4 The following table summarises the issues raised by the PBAC at the March meeting, and how the sponsor has addressed these.

Table 1: Summary comparison between the March 2016 major submission and the current resubmission

Issue	Previous submission (March 2016)	Current minor re-submission
Requested population	Restricted to oral cavity only	All patients with RM SCCHN. The submission claimed that those with cancer of the oral cavity have the greatest unmet clinical need.
Population chosen for primary economic evaluation	*Post hoc* subgroup of patients with cancer in oral cavity and KPS ≥80 in EXTREME trial (n=78)	ITT population in EXTREME trial (n=442)
Nominated price for cetuximab	AEMP: $[redacted]/100 mg, representing a [redacted]% rebate from proposed published price of $[redacted]/100 mg	AEMP: $[redacted]/100 mg. This is the same effective price for cetuximab as in mCRC.
Nominated cost for infusion	$[redacted] per infusion	$[redacted] per infusion, based on November 2014 submission for cetuximab in mCRC
Risk sharing arrangement	A confidential [redacted]% rebate on published ex-man price	A confidential [redacted]% rebate on published ex-man price, and a rebate of [redacted]% beyond agreed thresholds as for cetuximab in locally advanced SCCHN and for mCRC
Clinical claim for cetuximab relative to other drugs targeting EGFR in the treatment of RM SCCHN	Not evaluated	Clinical claim that cetuximab is the only anti-EGFR agent to demonstrate clinical efficacy in the treatment of RM SCCHN and that efficacy in RM SCCHN is not a class effect.

Source: Compiled during the minor overview.

For more detail on PBAC's view, see section 6 "PBAC outcome"

4 Comparator

4.1 This was unchanged in the minor resubmission. In March 2016, the PBAC agreed that platinum-based chemotherapy was the appropriate comparator.

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

5.2 The PBAC noted and welcomed the input from one individual and one organisation via the Consumer Comments facility on the PBS website. The PBAC noted that the extent of disability associated with head and neck cancers was an important issue for patients. The PBAC also noted the advice from Rare Cancers Australia, which highlighted the stress and trauma associated with currently available treatment options, and referred to trial data indicating the efficacy of cetuximab for head and neck cancers.

Clinical trials

5.3 The key evidence presented (EXTREME) was unchanged from the March 2016 submission. EXTREME was an open-label head-to-head randomised trial comparing cetuximab in addition to cisplatin or carboplatin and 5-flurouracil versus cisplatin or carboplatin and 5-flurouracil in 442 patients with RM SCCHN.

5.4 The minor resubmission also presented a summary of clinical trials for other agents which, like cetuximab, target the EGFR and have been assessed in the treatment of RM SCCHN. As a minor submission, the data presented were not evaluated and it is therefore unknown whether (i) all relevant literature was included in the review and (ii) the interpretation of the results of the trials was reasonable.

5.5 The minor resubmission identified 52 phase II trials and 7 phase III trials which evaluated the efficacy of 13 anti-EGFR agents in the treatment of RM SCCHN. The following conclusions were stated in the minor submission :

- Erlotinib, gefitinib, lapatinib, panitumumab, sorafenib and vandetanib have no demonstrated efficacy in the treatment of RM SCCHN;
- Afatinib, figitumumab, sunitinib, Sym004 and zalutumumab are not efficacious and are associated with significant toxicities;
- Dacomtinib demonstrated efficacy in a single arm phase II trial but has not been evaluated in any phase II or III comparative trials; and
- The addition of bevacizumab did not increase the efficacy of cetuximab or erlotinib.

5.6 The minor resubmission further claimed that a significant overall survival (OS) benefit was not demonstrated for any agent other than cetuximab in any of the identified phase II comparative trials, and that cetuximab is the only EGFR inhibitor that is

approved by the FDA, EMA and TGA for treatment of RM SCCHN.

5.7 The PBAC noted the comprehensive summary of the data available, and that these data suggested that anti-EGFR agents had limited meaningful clinical benefit in the treatment of metastatic head and neck cancer. The PBAC specifically noted that other anti-EGFR antibodies, including panitumumab, were not shown to increase survival and that this was at odds with cetuximab and panitumumab being similarly effective in the treatment of mCRC. This is discussed further below.

Comparative effectiveness

5.8 The results for the ITT population of the EXTREME trial are presented in Table 2. These are unchanged from the March 2016 submission.

Table 2: Efficacy outcomes in the EXTREME trial in the ITT population

Outcome	Cetuximab+Carboplatin or cisplatin and 5FU (n=222)	Carboplatin or cisplatin and 5FU only (n=220)	p value
Overall Response Rate (ORR)	35.6%	19.5%	0.0001
Progression Free Survival (PFS)	5.6 months	3.3 months	<0.001
Overall Survival (OS)	10.1 months	7.4 months	0.036

Source: p29 of the minor submission

5.9 The comparison provided in the minor resubmission of the cetuximab EXTREME and panitumumab SPECTRUM studies is summarised in Table 3.

Table 3. Comparison of EXTREME and SPECTRUM studies

	EXTREME - cetuximab	SPECTRUM – panitumumab
Number of trial participants	442	657
Baseline demographics Median age (years) Male (%) Locoregional recurrence only (%) WHO 0 or 1 Median duration of disease (months)	 57 90% 53% 88% 16	 59 87% 41% 99% 16
Comparator	Cisplatin 100mg/m^2 Carboplatin AUC 300 mg 5FU 4,000 mg/m^2 ≤6 cycles	Cisplatin 100mg/m^2 - 5FU 4,000 mg/m^2 ≤6 cycles
% cisplatin	64%	100%
Overall Survival	10.1 v 7.4 months HR 0.80 [0.64, 0.99] P=0.04	11.1 v 9.0 months HR 0.87 [0.73, 1.05] P=0.1403
Progression Free Survival	5.6 v 3.3 months HR 0.54 [0.43, 0.67] 46% reduction in risk of progression P<0.001	5.8 v 4.6 months HR 0.78 [0.66, 0.92] 22% reduction in risk of progression P=0.0036
Overall Response Rate	36% v 20% OR 2.33 [1.50, 3.60] P<0.001	36% v 25% OR 1.69 [1.15, 2.44] P=0.0065

5FU = 5-flurouracil, AUC = area under the curve

Source: adapted from Table 3 of the submission (p 13)

5.10 The PBAC noted a statistically significant increase in OS was demonstrated with

cetuximab but not panitumumab. The minor resubmission suggested this may be due to differences in the activity of cetuximab and panitumumab at the molecular level. The PBAC considered there may be other reasons related to differences in the trial designs. For example, carboplatin was used in a proportion of patients in the EXTREME cetuximab trial but not in the SPECTRUM panitumumab trial, and carboplatin is generally considered less effective than cisplatin in the treatment of SCCHN. Further, there were differences across the trials in the median OS in the control groups (7.4 months in EXTREME versus 9.0 months in SPECTRUM), and this may have impacted on the relative efficacy observed for the two anti-EGFR antibodies. The PBAC noted that for the treatment of mCRC, cetuximab and panitumumab are considered equally effective, and considered that the lack of an effect of panitumumab on OS in the SPECTRUM trial increased the uncertainty regarding the magnitude of the survival benefit with cetuximab.

Comparative harms

5.11 The adverse events that were reported in a statistically significantly higher proportion of patients in the ITT population of the EXTREME trial are presented in Table 4. These data were not presented or discussed in the minor resubmission.

Table 4: Statistically significant adverse events reported in the EXTREME trial in the ITT population

Event	Cetuximab + chemo (n=219)	Chemo only (n=215)	RR (95%CI)	Event rates per 100 patients		RD (95%CI)
				Cetuximab + chemo	Chemo only	
All Skin Reactions, n (%)	148 (67.6)	12 (5.6)	**12.11 (7.06, 21.13)**	67.6	5.6	**0.62 (0.55,0.69)**
Grade 3 or 4 skin reactions, n (%)	20 (9.1)	1 (0.5)	**19.63 (3.41, 114.69)**	9.1	0.5	**0.09 (0.05, 0.13)**
Sepsis, n (%)	9 (4.1)	1 (0.5)	**8.84 (1.47, 53.73)**	4.1	0.5	**0.04 (0.01,.0.07)**

Source: Table 5, p12 March 2016 PBAC PSD for cetuximab
Bold typography indicates statistically significant differences

Clinical claim

5.12 The minor submission claimed that the addition of cetuximab to platinum-based chemotherapy results in superior efficacy, with an inferior but manageable safety profile compared to chemotherapy alone. This was consistent with the clinical claim in the March 2016 submission.

5.13 The PBAC recalled that in March 2016 it considered that the claim of superior comparative effectiveness was demonstrated for the overall ITT population with respect to OS, progression-free survival and response rates, but the magnitude of the benefit was small.

5.14 The PBAC recalled that in March 2016 it considered that the addition of cetuximab to platinum-based chemotherapy is inferior to platinum-based chemotherapy alone in terms of comparative safety for the ITT population.

Economic analysis

5.15 The March 2016 submission presented a cost-utility analysis based on the oral cavity

subgroup of the EXTREME trial. The minor resubmission did not alter the structure of the economic model but populated it using the ITT population of the EXTREME trial. The respecified base case incremental cost-effectiveness ratio (ICER) (as presented in the resubmission) was verified by the Secretariat. However, as a minor submission, the economic model was not evaluated.

5.16 The following model inputs were revised compared with the March 2016 model:

- Efficacy inputs were based on the ITT population of the EXTREME trial instead of a subset of patients with RM SCCHN in the oral cavity only.
- Price reduced from $[redacted]/100 mg vial to $[redacted]/100 mg vial.
- Cost of intravenous administration increased from $[redacted] per infusion to $[redacted] (consistent with that used in the November 2014 submission for cetuximab for mCRC).

5.17 The estimated cost per Life-year Gained (LYG) and cost per Quality Adjusted Life-year (QALY) gained as presented in the March 2016 submission and the minor resubmission for the ITT population are summarised in Table 5. The redacted table below shows that for the ITT population, the ICER in the March 2016 submission was $105,000 - $200,000 per QALY, the ICER for the minor resubmission with an infusion cost of $[redacted] was $75,000 - $105,000 per QALY, the ICER for the minor resubmission with an infusion cost of $[redacted] was $75,000 - $105,000 and the ICER using calculations from the March 2016 submission was $75,000 - $105,000.

Table 5: Estimated cost effectiveness in the ITT population

Model inputs	Cost per QALY gained	Cost per LYG
March 2016 submission base case for ITT population • Cetuximab cost: $[redacted] per 100 mg vial • Cetuximab dose: 500 mg weekly dose for continuing treatment • Infusion cost: $[redacted] per infusion	$[redacted]	$[redacted]
Minor resubmission for ITT population • Cetuximab cost: $[redacted] per 100 mg vial • Cetuximab dose: 400* mg weekly dose for continuing treatment • Infusion cost: $[redacted] per infusion	$[redacted]	$[redacted]
Minor resubmission for ITT population • Cetuximab cost: $[redacted] per 100 mg vial • Cetuximab dose: 400* mg weekly dose for continuing treatment • Infusion cost: $[redacted] per infusion	$[redacted]	$[redacted]
ITT population using calculations from March 2016 submission • Cetuximab cost: $[redacted] per 100 mg vial • Cetuximab dose: 500 mg weekly dose for continuing treatment • Infusion cost: $[redacted] per infusion	$[redacted]	$[redacted]

Source: Table 5, p35 of the minor resubmission
*corrected as noted in pre-PBAC response

5.18 The minor resubmission's ICERs could not be reproduced using the model provided with the March 2016 submission. This was due to the minor submission assuming a 400 mg dose of cetuximab weekly for maintenance instead of 441 mg weekly (rounded up to 500 mg in accordance with Efficient Funding of Chemotherapy (EFC) measures). This change was not documented nor justified in the minor resubmission. The pre-PBAC response (p1) clarified that the minor resubmission assumed a maintenance dose of 394 mg (rounded up to 400 mg in accordance with EFC

measures) and that the lower maintenance dose reflects the lower dose intensity for maintenance infusions in the ITT population compared with the oral cavity subgroup.

5.19 Additionally, the minor resubmission altered the composition of cisplatin vials from 4 x 50 mg vials in the March 2016 submission to 2 x 100 mg vials, resulting in a slight increase in the cost per dose of cisplatin from $140.41 to $143.41. This change was not documented in the resubmission but has negligible impact on the ICER.

5.20 The minor resubmission also presented an updated analysis for the subgroup of patients with RM SCCHN in the oral cavity only and a KPS ≥80 / WHO 0 or 1. The minor resubmission claimed that cetuximab is more effective in these patients (additional 7.1 months vs 2.7 months OS). The PBAC noted that it previously considered that the evidence to support this claim is unclear, as the oral cavity subgroup was conducted as a *post hoc* analysis and that the difference observed may be driven by the poor survival in the small number of patients in the control arm (March 2016 PBAC Public Summary Document (PSD), paragraph 7.4).

5.21 The PBAC further recalled in the main publication of the EXTREME trial it was stated that "[t]here was a significant interaction with the primary tumo[u]r site, but because of repeated testing, this result could be due to chance. Such subgroup analyses must be interpreted cautiously; the results do not allow us to state with certainty that some groups did not benefit or to speculate on the degree of benefit" (March 2016 PBAC PSD, paragraph 6.18). The PBAC considered that the results of the *post hoc* subgroup analyses were not robust and should be interpreted with caution.

5.22 The estimated cost/LYG and cost/QALY gained in the oral cavity subgroup are summarised in Table 6. The redacted table below shows that for the oral cavity subgroup, the ICER in the March 2016 submission was $45,000 - $74,000 per QALY, the ICER for the minor resubmission with an infusion cost of $[redacted] was $15,000 - $45,000 per QALY and the ICER for the minor resubmission with an infusion cost of $[redacted] was $45,000 - $75,000 per QALY.

Table 6: Results of estimated cost effectiveness in oral cavity subgroup

Model inputs	Cost per QALY	Cost per LYG
March 2016 submission base case for oral cavity population • Cetuximab cost: $[redacted] per 100 mg vial • Cetuximab dose: 500 mg weekly dose for continuing treatment • Infusion cost: $[redacted] per infusion	$[redacted]	$[redacted]
Minor resubmission for oral cavity population • Cetuximab cost: $[redacted] per 100 mg vial • Cetuximab dose: 500 mg weekly dose for continuing treatment • Infusion cost: $[redacted] per infusion	$[redacted]	$[redacted]
Minor resubmission for oral cavity population • Cetuximab cost: $[redacted] per 100 mg vial • Cetuximab dose: 500 mg weekly dose for continuing treatment • Infusion cost: $[redacted] per infusion	$[redacted]	$[redacted]

Source: Table 10, p39 of the minor submission

5.23 For the oral cavity subgroup, the continuation dose was the same as in the March 2016 submission.

Drug cost/patient/course:

Table 7: Drug cost/patient/course (as per the submissions)

	March 2016 submission ($[redacted]/100mg)	Minor resubmission ($[redacted]/100mg)
RM SCCHN	-	$[redacted] (20.1 doses)
Post hoc subgroup (oral cavity & KPS ≥80)	$[redacted] (24.5 doses)	$[redacted] (24.5 doses)

Source: compiled during the preparation of the overview from 2 Copy of Economic evaluation.xlsx' and '4 Section E.xlsx'.

Estimated PBS usage & financial implications

5.24 The changes to the assumptions used to estimate the financial impact of listing cetuximab (compared to the March 2016 submission) are presented in Table 8.

Table 8: Differences in assumptions between the minor resubmission and March 2016 submission for financial impact estimate

Assumption	Previous submission (March 2016)	Minor resubmission
Cost per 100mg cetuximab	$[redacted]	$[redacted]
Incidence of RM SCCHN	0.0056% (oral cavity subgroup only)	0.0135% (ITT population of EXTREME)
Number of infusions/scripts per patient[1]	24.5	20.1 (ITT) 24.5 (oral cavity)
Cost of cetuximab per patient[2]	$[redacted] in year 1 and $[redacted] from year 2 to 5	$[redacted] (ITT) $[redacted] (oral cavity)
Incremental cost of concurrent chemotherapy per patient	$[redacted] (oral cavity)	$[redacted] (ITT) $[redacted] (oral cavity)
Cost of managing AE per patient[3]	$21.53	$21.53
Copayment per script	$18.82	$18.82
Number of administrations per patient for cetuximab	18.38 (oral cavity)	15.08 (ITT) 18.38 (oral cavity)
Number of administrations per patient for chemotherapy (comparator)	3.6 (oral cavity)	4.0 (ITT) 3.6 (oral cavity)
Cost per administration (MBS)	$[redacted]	$[redacted]

[1]Differences due to lower continuing dose assumed in the minor resubmission
[2]Differences due to lower cost per vial and also lower number of infusions per patient
[3]Includes treatment for rash only. Does not include management of sepsis.
Source: Constructed during preparation of the overview

5.25 In addition to the price reduction per vial of cetuximab, the minor resubmission assumed for the ITT population (compared to the oral cavity subgroup):

- fewer scripts per patient reflecting a shorter treatment duration;
- a lower dose of cetuximab in the continuing phase; and
- a lower incremental cost for concurrent chemotherapy.

5.26 The impact of the higher administration cost was offset by a lower number of administrations assumed for patients using cetuximab and a higher number of administrations for patients using chemotherapy only compared to the March 2016 submission.

5.27 The minor resubmission estimated:

- a net cost to the PBS of $10 - $20 million in Year 5 of listing, with a total net cost to the PBS of $30 - $60 million over the first 5 years of listing for the ITT population (Table 9); and
- a net cost to the PBS of $10 - $20 million in Year 5 of listing, with a total net cost to the PBS of $30 - $60 million over the first 5 years of listing for the oral cavity subgroup (Table 10).

Table 9: Financial impact estimates for RM SCCHN (ITT population in EXTREME)

	Year 1	Year 2	Year 3	Year 4	Year 5
Minor submission estimates					
Uptake rate	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Number treated (ITT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of infusion/script (20.1pp)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of cetuximab	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Incremental cost of CT[1]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost of managing AE[2]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Patient copayment	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS[3]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]
Administration costs for cetuximab[4]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Administration costs for CT (comparator)[5]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]
Net cost to Government[6]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]
Previous submission estimates (oral cavity only)					
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of infusion/script (24.5 pp)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to the PBS as per previous submission	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]
Net cost to Government as presented in previous submission[7]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]

CT = Chemotherapy, PP = per patient, AE = Adverse Events

[1]The difference in the cost of chemotherapy treatment when used with cetuximab versus chemotherapy alone

[2]Calcualted as DPMQ of drugs to treat adverse events minus the copayment for these drugs

[3]Calculated as cost of cetuximab +incremental cost of CT + cost of managing AE minus patient copayment

[4]Assumes $[redacted] per patient

[5]Assumes $[redacted] per patient

[6]Sum of cost to PBS and cost to MBS

[7]Oral cavity patients only.

Source: Table 11, p19 March 2016 PBAC PSD for cetuximab, Table 8 and 9, p35 of the minor submission, 3 Section E ITT population_November 2016 Resubmission.xls

5.28 The financial estimates presented in the minor resubmission were arithmetically accurate. The increase in expenditure compared with the March 2016 submission was due to a larger population (ITT vs oral cavity only) and higher administration costs, but the increase was partly countered due to a lower continuing dose, fewer administrations for cetuximab, and higher dose and more administrations for comparator.

Table 10: Financial impact estimates for oral cavity only

	Year 1	Year 2	Year 3	Year 4	Year 5
Minor submission estimates					
Uptake rate	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Number treated (ITT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of infusion/script (24.5pp)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of cetuximab	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Incremental cost of CT[1]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost of managing AE	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Patient copayment	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS[3]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]
Administration costs for cetuximab[4]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Administration costs for CT (comparator)[5]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]
Net cost to Government[6]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]
Previous submission estimates					
Number treated (oral cavity only)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of infusion/script (24.5 pp)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to Government as presented in previous submission[7]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]

CT = Chemotherapy, PP = per patient

[1]The difference in the cost of chemotherapy treatment when used with cetuximab versus chemotherapy alone

[2]Calcualted as DPMQ of drugs to treat adverse events minus the copayment for these drugs

[3]Calculated as cost of cetuximab + incremental cost of CT + Cost of managing AE minus patient copayment

[4]Assumes $[redacted] per patient

[5]Assumes $[redacted] per patient

[6]Sum of cost to PBS and cost to MBS

[7]Oral cavity patients only.

Source: Table 11 and 12, p38 of the minor submission, 3 Section E oral cavity population_November 2016 Resubmission.xls

Financial management – Risk Sharing Arrangements

5.29 The minor resubmission proposed a risk sharing arrangement with a rebate of [redacted]% beyond agreed thresholds, as already applies to cetuximab for its current listings for locally advanced SCCHN and for mCRC.

6 PBAC Outcome

6.1 The PBAC decided not to recommend cetuximab in combination with platinum chemotherapy for previously untreated metastatic and/or recurrent squamous cell carcinoma of the head and neck (RM SCCHN) on the basis of uncertain clinical effectiveness and uncertain and unfavourable cost-effectiveness.

6.2 The PBAC considered that there is a clinical need for treatments patients with RM SCCHN. However, the PBAC also noted the toxicity and uncertain clinical effectiveness associated with cetuximab plus chemotherapy over chemotherapy alone.

6.3 Based on the summary of clinical trials presented in the minor resubmission for

agents, which like cetuximab, target the EGFR, the PBAC noted that no meaningful clinical benefit was demonstrated for these agents in the treatment of RM SCCHN.

6.4 The PBAC noted a statistically significant increase in OS was demonstrated with cetuximab in the EXTREME trial but not for panitumumab in the SPECTRUM trial. The PBAC considered that this may be due to differences in the trial designs. For example, carboplatin was used in a proportion of patients in the EXTREME trial but not in the SPECTRUM trial, and carboplatin is generally considered less effective than cisplatin in the treatment of SCCHN. Further, there were differences across the trials in the median OS in the control groups (7.4 months in EXTREME versus 9.0 months in SPECTRUM), and this may have impacted on the relative efficacy observed with the two anti-EGFR antibodies. The PBAC noted for the treatment of mCRC that cetuximab and panitumumab are considered equally effective, and that the lack of an effect of panitumumab on OS in the SPECTRUM trial increased the uncertainty regarding the magnitude of the survival benefit with cetuximab.

6.5 The PBAC reaffirmed its conclusion from the March 2016 meeting that the incremental benefits with cetuximab plus chemotherapy over chemotherapy alone in the treatment of RM SCCHN were small, and that the addition of cetuximab increased toxicity.

6.6 The PBAC considered the cost/QALY gained of $75,000 - $105,000 to be high and uncertain, reflecting the uncertain extent of clinical benefit. The PBAC also noted that the economic model did not address all of the issues identified at its March 2016 meeting, including the choice of extrapolation method, the source of the utility values, and the optimistic time horizon.

6.7 The PBAC reaffirmed its view from the March 2016 meeting that a major resubmission would be required to adequately address the issues raised with the previous submission, together with those raised in the current resubmission. The PBAC noted that pooling the results from the panitumumab and cetuximab trials may provide additional certainty regarding the likely magnitude of clinical benefit of anti-EGFR antibodies in the treatment of RM SCCHN. The PBAC considered a listing based on the ITT population of the EXTREME trial was more appropriate than one based on the oral cavity sub-group, and that any subsequent submission should be for the broader population.

6.8 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

8 Sponsor's Comment

Merck is disappointed with a second rejection by the PBAC. Overseas, cetuximab has been the standard of care for patients with RM SCCHN for many years as recommended in European and American Guidelines. We shall discuss with the Department whether there is a way to make cetuximab available for people living with RM SCCHN.