

6.02 CETUXIMAB, solution for intravenous (IV) infusion, 100 mg in 20 mL & 500 mg in 100 mL, Erbitux[®], Merck Serono Australia Pty Ltd.

1 Purpose of Application

1.1 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 (SCC) of the oral cavity and with a World Health Organization (WHO) performance status of 0 or 1.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough. The ESC recommended that the following note should also apply to the continuing criteria: “No increase in the maximum number of repeats may be authorised.” The Pre-Sub-Committee-Response (PSCR, p.3) proposed to remove the clinical criterion of “previously untreated” to provide consistency with the TGA-approved indication.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Amt	Proprietary Name and Manufacturer
CETUXIMAB				Erbitux SG
Injection, 100 mg/20 mL	880 mg	0	Public: \$ [REDACTED]*	
Injection, 500 mg/100 mL			Private: \$ [REDACTED]*	

Category / Program	Section 100 – Efficient funding of chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Recurrent and/or metastatic
Condition:	Squamous cell carcinoma of the head and neck
PBS Indication:	Recurrent and/or metastatic squamous cell carcinoma of the head and neck
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required – Electronic <input checked="" type="checkbox"/> Streamlined (PUBLIC HOSPITAL ONLY)

Public Summary Document – March 2016 PBAC Meeting

Clinical criteria:	<p>The condition cancer must be located in the oral cavity</p> <p>AND</p> <p>Patient must have a WHO performance status of 0 or 1</p> <p>AND</p> <p>The condition must be previously untreated</p> <p>AND</p> <p>The treatment must be commenced in combination with platinum-based chemotherapy The treatment must be in combination with platinum based chemotherapy</p>
Definitions	<p>The oral cavity is defined as the vermilion border of the lip, buccal mucosa, alveolar ridge, retromolar trigone, floor of the mouth, hard palate, anterior two-thirds of the tongue.</p>
Administrative Advice	<p><u>Note</u> Special Pricing Arrangements apply</p> <p><u>Note</u> No increase in the maximum number of repeats may be authorised.</p>

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Amt	Proprietary Name and Manufacturer
CETUXIMAB				Erbitux SG
Injection, 100 mg/20 mL	550 mg	24 22	Public: \$ [REDACTED]*	
Injection, 500 mg/100 mL			Private: \$ [REDACTED]*	

Category / Program	Section 100 – Efficient funding of chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Recurrent and/or metastatic
Condition:	Squamous cell carcinoma of the head and neck
PBS Indication:	Recurrent and/or metastatic squamous cell carcinoma of the head and neck
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required – Electronic <input checked="" type="checkbox"/> Streamlined Section 100 (Efficient Funding of Chemotherapy (EFC)) Private Hospital/Private Clinic Authority Required Public Hospital Authority Required (STREAMLINED)
Clinical criteria:	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition</p> <p>AND</p>

	Patient must not have progressive disease
Administrative Advice	<p><u>Note</u> Special Pricing Arrangements apply</p> <p><u>Note</u> No increase in the maximum number of repeats may be authorised.</p>

* This represented the published price. The sponsor proposed a confidential [REDACTED] % rebate.

- 2.2 Listing was requested on a cost-effectiveness basis compared with a comparator of platinum-based chemotherapy alone.
- 2.3 The submission stated that cancers of the oral cavity include cancers of the buccal mucosa, alveolar ridge, retromolar trigone, floor of the mouth, hard palate and the anterior two-thirds of the tongue. The submission stated that cancers of the lip are more likely to be treated with surgery and/or radiation rather than with systemic therapy, and were therefore excluded from further consideration in the submission. The proposed PBS listing did not define the oral cavity, nor specify if the location in the oral cavity represented the origin site of the primary tumour. The PSCR (p.3) stated that feedback from clinicians indicated that differences in the interpretation of the phrase “oral cavity” are unlikely; nonetheless the sponsor accepted the proposal to include a definition in the listing proposed by the Secretariat.
- 2.4 The submission provided various arguments to limit use to patients with SCC in the oral cavity, which included additional risk factors for SCC in the oral cavity, a higher impact on quality of life, poorer prognosis (disease progression and mortality), limited response to therapies other than cetuximab, and high response to cetuximab.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

3 Background

- 3.1 Cetuximab was approved by the TGA for the treatment of patients with squamous cell cancer of the head and neck in combination with platinum-based chemotherapy for recurrent and/or metastatic disease on 5 January 2010.
- 3.2 The requested PBS-listing was narrower than the TGA-approved indication as it limited use to patients with previously untreated (i.e. first-line treatment of) metastatic and/or recurrent SCC of the oral cavity and with a WHO performance status of 0 or 1.
- 3.3 This was the first submission to the PBAC for this indication.
- 3.4 Cetuximab, in combination with radiotherapy, is currently PBS-listed for the treatment of patients with Stage III, IVa or IVb squamous cell cancer of the larynx, oropharynx or hypopharynx, who are unable to tolerate or have a contraindication to cisplatin.

4 Clinical place for the proposed therapy

- 4.1 The submission stated that most of the patients with recurrent and/or metastatic SCC of the head and neck are treated with combination chemotherapy, with platinum-

based chemotherapy the most commonly used. The extent of use of combination chemotherapy relative to the other identified treatment options (particularly best supportive care) was unclear. However, it appeared reasonable to expect that chemotherapy would be considered in patients who are unsuitable for other therapies, but are suitable for systemic therapy. The ESC agreed with this view.

- 4.2 The submission proposed that cetuximab be added to platinum-based chemotherapy among patients with SCC of the head and neck whose primary tumour site was the oral cavity and for whom systemic therapy was appropriate (represented by those with a WHO performance status of 0 or 1).

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

- 5.1 The submission nominated "no treatment", better described as platinum-based chemotherapy alone. Cetuximab was proposed to be used in combination with platinum-based chemotherapy, and platinum-based chemotherapy was the most commonly used regimen. The ESC agreed that this was the appropriate comparator.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. In lieu of a formal hearing, a clinician's letter of support was presented to the Committee at the meeting. The clinician stated the particularly negative impact of oral cavity cancers on functionality and the limited treatment options currently available to these patients. The clinician also noted the relatively low toxicity of cetuximab compared with other systemic agents.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from Rare Cancers Australia via the Consumer Comments facility on the PBS website. The comments described the impact of head and neck cancers on patients, and stated that the availability of cetuximab would provide hope, time and an effective treatment to these patients.

Clinical trials

- 6.3 The submission was based on one open-label head-to-head randomised trial (EXTREME; N=442) comparing cetuximab in addition to cisplatin or carboplatin and 5-fluorouracil versus cisplatin or carboplatin and 5-fluorouracil. The submission presented post hoc analyses in a subgroup of patients for whom the primary tumour site of origin was in the oral cavity and with a Karnofsky Performance Status (KPS) ≥ 80 at baseline (N = 78), which provided the key evidence for the submission.

- 6.4 The submission did not specifically present information to justify the post hoc subgroup analyses. The PSCR (pp. 1-2 and Table 3, p. 7) provided information in support of the presentation of a subgroup analysis.
- 6.5 A biologically plausible explanation to support the claim that SCC of the oral cavity were more likely to respond to cetuximab therapy compared to SCC of the head and neck at other locations was unclear. The PSCR (pp.1-2) presented a range of arguments for biological plausibility, including that shrinkage of tumours in this site may profoundly influence Quality of Life and the nutritional status of the patient. The ESC noted that the un-blinded nature of the trial would potentially impact upon a subjective endpoint such as Quality of Life, and may therefore indirectly influence related endpoints such as appetite and nutritional status. Overall, the ESC considered the PSCR provided limited support for the biological plausibility of the subgroup.
- 6.6 The main publication of the trial by Vermorken et al (2008) stated that the significant interaction with the primary tumour site could be due to chance because of repeated testing. The ESC noted that the main publication of the trial warns against over-interpretation of the subgroup analyses and acknowledges the small proportion of patients in the some subgroups.
- 6.7 The submission presented a Bonferroni adjustment for multiplicity of analyses to aid justification of the subgroup selection. Given the method of application of the adjusted p-value (deflating the p-value significance cut-off for the number of multiple comparisons), arguably every subgroup category would be a separate independent hypothesis (51 subgroup categories were specified in the trial report). Additionally, it was unclear the level at which a Type I error of 0.05 should be preserved (e.g. whether all independent hypothesis testing should be included in the correction for multiple comparisons). The trial report stated that the p-values of the subgroup analyses were purely exploratory. Overall, the post hoc adjustment for multiplicity should be interpreted with caution. Regardless, the pre-specified subgroup of patients whose site of origin of the primary tumour was the oral cavity did not represent the nominated post hoc subgroup used as key evidence to support the requested PBS-listing.
- 6.8 The PSCR provided additional explanation: “Whilst not pre-specified, the submission presented a simple Bonferroni adjustment for multiplicity of analyses. All subgroup analyses, including that for patients with oral cavity tumours, were stipulated in the protocol. A simple post hoc Bonferroni adjustment to the p-value for this subgroup confirms the validity of the 6.6 month survival benefit demonstrated in this group of patients (HR 0.417, p=0.0003). The pre-specified analyses included 51 patient subgroups. To preserve the probability of a Type 1 error at 0.05 across the 51 subgroups, the overall p-value of 0.05 must be divided by 51 ($0.05/51=0.00098$). This value can then be used as the p-value for oral cavity. Since the actual p-value for OS in this group was 0.0003, which is less than 0.00098, the HR for mortality in the oral cavity subgroup remained statistically significant even after a Bonferroni adjustment for multiplicity of analyses.”
- 6.9 However, the ESC considered that whilst the described adjustment is appropriate for correcting comparisons for multiplicity, this is no substitute for a formal test of interaction for a subgroup treatment effect. Thus ESC considered that tests of

interactions, particularly with the complement (all other patients not in the post hoc subgroup) would be informative for PBAC consideration.

- 6.10 In addition, the ESC also noted that the PSCR did not: (i) provide justification for excluding patients with SCC of the head and neck outside the oral cavity, who may also benefit from cetuximab treatment, from PBS-subsidised cetuximab; or (ii) to address the potential equity issues relating to the exclusion of these patients.
- 6.11 The Pre-PBAC Response presented an analysis of the complement of the proposed PBS population (all anatomical sites except oral cavity or Karnofsky Score <80). In this analysis, the Hazard Ratio for mortality for the complement population was 0.90 (p=0.3926). Therefore, the sponsor argued, whilst the proposed population for reimbursement demonstrated a statistically significant 65% reduction in the risk of mortality for cetuximab in combination with chemotherapy compared to chemotherapy alone (Hazard Ratio 0.35, p<0.0001), the corresponding reduction in the complement was non-significant. The sponsor claimed that the addition of cetuximab to chemotherapy in the proposed PBS population resulted in a statistically and clinically significant additional 7.1 months of overall survival. In contrast, the sponsor viewed that the result in the complement population was a non-significant trend for an additional two months of survival. The sponsor also noted that the formal test of interaction for a subgroup treatment effect between the proposed PBS population and its complement subgroup reached statistical significance (p=0.0013).
- 6.12 The Pre-PBAC Response further suggested that it was appropriate to exclude patients with SCC of the head and neck outside the oral cavity from PBS-subsided treatment “since no statistically significant overall survival benefit was demonstrated in these patients”.
- 6.13 Details of the trial presented in the submission are provided in the following table.

Table 1: Trials and associated key reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		
EXTREME	Cetuximab (Erbix [®]) in combination with cisplatin or carboplatin and 5-fluorouracil in the first-line treatment of subjects with recurrent and/or metastatic squamous cell carcinoma of the head and neck ("EXTREME") (EMR 62 202-002) Vermorken JB <i>et al.</i> Platinum-based chemotherapy plus cetuximab in head and neck cancer.	8 February 2008 <i>New England Journal of Medicine</i> 2008; 359 (11): 1116-27
	Mésia R <i>et al.</i> Quality of Life of patients receiving platinum-based chemotherapy plus cetuximab first line for recurrent and/or metastatic squamous cell carcinoma of the head and neck.	<i>Annals of Oncology</i> 2010; 21 (10): 1967-73
	Licitra L <i>et al.</i> Evaluation of EGFR copy number as a predictive biomarker for the efficacy of cetuximab in combination with chemotherapy in the first-line treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck: EXTREME study.	<i>Annals of Oncology</i> 2011; 22: 1078-87
	Licitra L <i>et al.</i> Predictive value of epidermal growth factor receptor expression for first-line chemotherapy plus cetuximab in patients with head and neck and colorectal cancer: Analysis of data from the EXTREME and CRYSTAL studies.	<i>European Journal of Cancer</i> 2013; 49(6): 1161-8
	Vermorken JB <i>et al.</i> Impact of tumor HPV status on outcome in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck receiving chemotherapy with or without cetuximab: retrospective analysis of the phase III EXTREME trial.	<i>Annals of Oncology</i> 2014; 25: 801–7
	Vermorken JB <i>et al.</i> Platinum-based chemotherapy (CT) plus cetuximab in recurrent or metastatic squamous cell carcinoma of the head and neck cancer (R/M-SCCHN): 5-year follow-up data for the extreme trial.	<i>Journal of Clinical Oncology</i> 2014; 32 (15 suppl): Abstr 6021; 50 th ASCO Annual Meeting, Chicago, USA May 2014.

Source: Table B.2-2, pp36-37 of the submission

6.14 The key features of the direct randomised trial are summarised in the table below.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Cetuximab + cisplatin/carboplatin + 5-fluorouracil versus cisplatin/carboplatin + 5-fluorouracil						
EXTREME (ITT population)	442	R, OL, MC, PG Median follow-up (ITT population): 19.1 or 18.2 months	Low/ unclear	Recurrent and/or metastatic SCC of the head and neck, KPS ≥70, first-line treatment (nasopharyngeal excluded)	OS, PFS	OS, PFS
<i>Post hoc</i> subgroup: oral cavity & KPS ≥80	78	in each arm respectively (range 12.9-26.0)	High	Primary tumour site: oral cavity and KPS ≥80		

Source: compiled during the evaluation

Abbreviations: ITT = intention-to-treat; KPS = Karnofsky Performance Status; MC = multi-centre; OL = open label; OS = overall survival; PFS = progression-free survival; PG = parallel group; R = randomised; SCC = squamous cell carcinoma

6.15 The risk of bias for the post hoc subgroup analyses, which comprised 17.6% of the overall intention-to-treat (ITT) trial population, was high. It was unclear whether the requested PBS-listing, consistent with the post hoc subgroup, was data-driven. There were potential differences in baseline characteristics between arms, which may favour the cetuximab plus chemotherapy arm. The PSCR (p.2) argued that a

comparison of the baseline characteristics between treatment arms showed a balance of possible tendencies for both worse and better response to treatment, and that differences were therefore unlikely to explain the survival benefit. The ESC noted that only ■ patients were represented in the post hoc subgroup analysis, and considered that the risk of bias was high.

Comparative effectiveness

Table 3: Overall survival in the EXTREME trial (primary outcome)

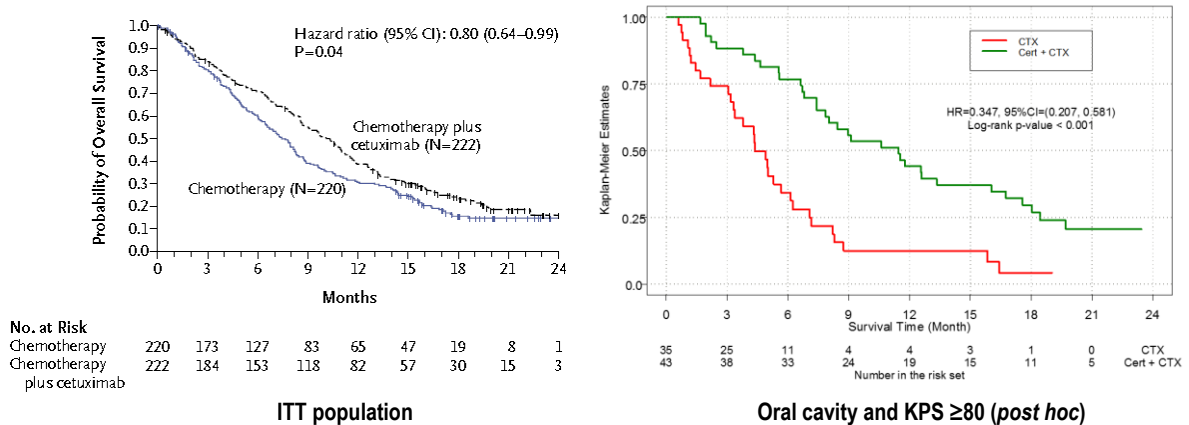
Response variable	ITT population		Oral cavity & KPS ≥80 (post hoc)	
	Cetuximab + CT (N=222)	CT alone (N=220)	Cetuximab + CT (N=43)	CT alone (N=35)
Number of deaths, n (%)	167 (75.2)	176 (80.0)	16 (37.2)	19 (54.3)
OS time in months, median (95% CI)	10.1 (8.6, 11.2)	7.4 (6.4, 8.3)	10.1 (8.6, 11.2)	7.4 (6.4, 8.3)
Hazard ratio (stratified) (95% CI)	0.797 (0.644, 0.986)		0.347 (0.207, 0.581)	
Log rank p-value (stratified)	0.036		<0.0001	

Source: Table B.6-1, p57 of the submission

Abbreviations: CI = confidence interval; CT = chemotherapy; KPS = Karnofsky Performance Status; ITT = intention-to-treat; OS = overall survival

Note: Stratified by previous chemotherapy and KPS, number of months estimated using the Kaplan-Meier method.

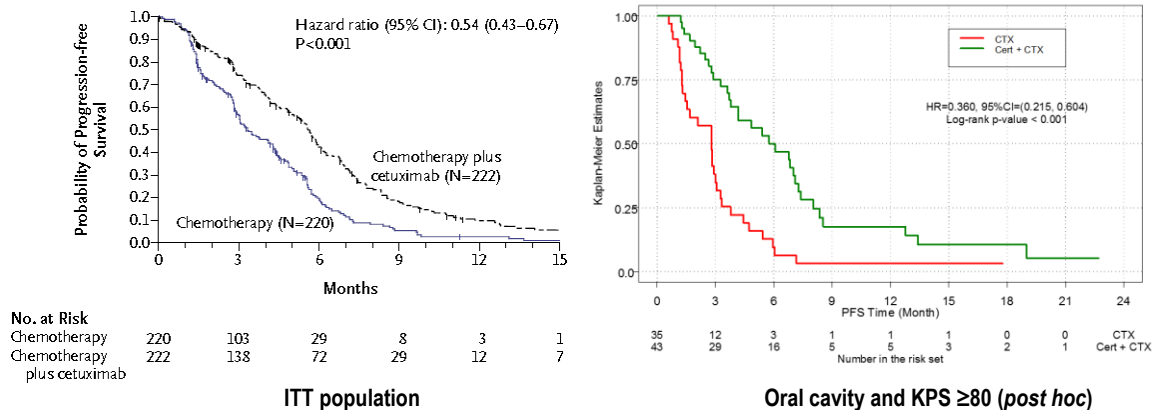
Figure 1: Kaplan-Meier estimates of overall survival in the EXTREME trial



Source: Figure B.6-1, p58 of the submission

Abbreviations: Cert = cetuximab; CTX = Chemotherapy; HR = Hazard Ratio; ITT = intention-to-treat; KPS = Karnofsky Performance Status

Figure 2: Kaplan-Meier estimates of progression-free survival in the EXTREME trial



Source: Figure B.6-2, p61 of the submission

Abbreviations: Cert = cetuximab; CTX = Chemotherapy; HR = Hazard Ratio; ITT = intention-to-treat; KPS = Karnofsky Performance Status

- 6.16 In the overall ITT population, there was a statistically significant difference in the primary outcome of overall survival favouring the cetuximab plus chemotherapy arm over the chemotherapy alone arm. The median overall survival time in the cetuximab plus chemotherapy arm was 10.1 months (95% CI: 8.6, 11.2) versus 7.4 months (95% CI: 6.4, 8.3) in the comparator arm. There was a statistically significant reduction in the hazard of death associated with the addition of cetuximab to chemotherapy (HR=0.797; 95% CI: 0.644, 0.986).
- 6.17 The submission claimed that there was a greater benefit associated with cetuximab treatment among patients with a primary tumour origin site of the oral cavity and a baseline KPS ≥80. The post hoc subgroup analysis found statistically significant improvements in overall survival associated with the addition of cetuximab to chemotherapy. The median overall survival time in the cetuximab plus chemotherapy arm was [redacted] months (95% CI: [redacted], [redacted]) versus [redacted] months (95% CI: [redacted], [redacted]) in the comparator arm. There was a statistically significant reduction in the hazard of death associated with the addition of cetuximab to chemotherapy (HR=0.347; 95% CI 0.207, 0.581). The submission claimed that the Kaplan-Meier curves indicated that patients responded early to cetuximab treatment, which becomes more apparent with time. An alternative interpretation could be that the claimed “greater benefit” was driven by the poor survival of the comparator arm for the post hoc subgroup.
- 6.18 The main publication of the trial by Vermorken et al (2008) 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”. Overall, the results of the post hoc subgroup analyses were not robust and should be interpreted with caution.
- 6.19 The ESC noted that the 2008 publication was silent on the impact of human papillomavirus on treatment outcomes. The ESC noted a subsequent publication (“Impact of tumor HPV status on outcome in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck receiving chemotherapy with or without cetuximab: retrospective analysis of the phase III EXTREME trial”, *Annals of*

Oncology, 2014, April 25(4):801-7), suggested HPV-positive tumours have a much better prognosis.

- 6.20 The abstract by Vermorken (2014) reported that six patients treated with cetuximab plus chemotherapy and two patients treated with chemotherapy alone were still in the EXTREME trial and known to be alive at 5 years. The submission claimed that the appropriateness of the extrapolation of the overall survival for the post hoc subgroup was demonstrated by its correlation with these data. This claim could not be verified as the data reported in Vermorken (2014) was not limited to the nominated post hoc subgroup. The ITT model of the economic analysis, extrapolated using different parametric distributions, appeared to overestimate survival at 5 years for both arms compared to the data reported in Vermorken (2014), assuming that no survivor was lost to follow-up.

Table 4: Survival at 5 years based on Vermorken (2014) and at the end of the 5-year model

Population	Cetuximab + CT	CT alone
Vermorken (2014) – ITT population known to be alive	2.3%	0.9%
Modelled ITT population – log logistic extrapolation	5.0%	2.7%
Modelled post hoc subgroup (oral cavity and KPS ≥80) – log normal extrapolation	■%	■%

Source: Constructed during the evaluation based on Vermorken (2014), '2 Copy of Economic evaluation.xlsx' and '3 Copy of Economic evaluation using ITT population.xlsx'.

Abbreviations: CT = Chemotherapy; ITT = intention-to-treat; KPS = Karnofsky Performance Status

- 6.21 The submission also argued that the extrapolation of the curve for the post hoc subgroup was confirmed by the patient level data at two years, which indicated that patients were alive in the cetuximab arm but were censored prior to this point in the comparator arm. This claim could not be verified, as all the longest follow-up time (including censored patients) for both arms of the post hoc subgroup was shorter than 2 years.
- 6.22 In the ITT population, there were statistically significant differences in favour of cetuximab plus chemotherapy over chemotherapy alone for the secondary outcomes of progression-free survival, best overall response rate, disease control rate and time to treatment failure. There were no statistically significant differences between arms for the duration of response.
- 6.23 For the post hoc subgroup of patients with a primary tumour site of origin in the oral cavity and a KPS ≥80 at baseline, there were statistically significant improvements associated with the addition of cetuximab to chemotherapy for progression-free survival, best response rate and disease control rate. Similarly, the post hoc subgroup results should be interpreted with caution.
- 6.24 The submission claimed that the addition of cetuximab did not adversely impact overall quality of life and actually improved some symptoms. The submission noted that there was a significant improvement in the global health status/QoL score in the cetuximab arm ($p=0.0415$); and that improvements in swallowing and pain reached statistical significance. Limited quality of life data were presented in the submission and the accompanying quality of life publication (Mésia et al, 2010). There were concerns of selective reporting of outcomes. The data were limited by the open-label design of the trial and the low completion rate (44% had an evaluable baseline and post-baseline assessment). The trial report acknowledged that the trend toward better quality of life should be viewed with caution because of the low compliance

with completion of the questionnaire. The submission did not present post hoc subgroup analyses among patients whose primary tumour site was the oral cavity and with a baseline KPS ≥ 80 . The PSCR (p.4) acknowledged the limitations of the Quality of Life data presented in the submission.

Comparative harms

Rash, acne, dermatitis acneiform, dry skin, anorexia, diarrhoea, nausea, pyrexia, hypocalcaemia, and hypomagnesaemia were more frequently reported in the cetuximab plus chemotherapy arm than the chemotherapy alone arm of the EXTREME trial. Grade 3 or 4 adverse events occurring more frequently in the cetuximab plus chemotherapy arm were skin reactions, anorexia, hypomagnesaemia, hypocalcaemia, sepsis, and septic shock.

- 6.25 The submission argued that sepsis did not represent a new safety signal, based on the relatedness assessment presumably by the unblinded investigators. However, infectious complications (including pneumonia and sepsis in combination with platinum-based therapy) was an important identified risk associated with cetuximab as per the Periodic Benefit Risk Evaluation Report.
- 6.26 The adverse events of special interest were skin reactions and infusion-related reactions. About two-thirds of subjects in the cetuximab plus chemotherapy group developed skin reactions (67.6%) or acne-like rash (65.8%) of any grade, with more patients experiencing Grade 3 or 4 skin reactions in the cetuximab plus chemotherapy arm (9.1% versus 0.5%). Infusion-related reactions were experienced by 24 subjects (11%) in the cetuximab plus chemotherapy group. Six of the infusion-related events were Grade 3 or 4.

Benefits/harms

- 6.27 A summary of the comparative benefits and harms for cetuximab plus chemotherapy versus chemotherapy alone is presented in the table below.

Table 5: Summary of comparative benefits and harms for cetuximab plus chemotherapy and chemotherapy alone from the EXTREME trial

Benefits						
OS	Cetuximab + CT	CT alone	Absolute Difference	HR (95% CI)		
OS: ITT population						
Deaths*	167/222	176/220	-	0.797 (0.644, 0.986)		
Median (mths)	10.1 (8.6, 11.2)	7.4 (6.4, 8.3)	2.7	-		
OS: Oral cavity & KPS ≥80 (post hoc)						
Deaths*			-	0.347 (0.207, 0.581)		
Median (mths)			7.1	-		
PFS	Cetuximab + CT	CT alone	Absolute Difference	HR (95% CI)		
PFS: ITT population						
Progressed*	168/222	173/220	-	0.538 (0.431, 0.672)		
Median (mths)	5.6 (5.0, 6.0)	3.3 (2.9, 4.3)	2.3	-		
PFS: Oral cavity & KPS ≥80 (post hoc)						
Progressed*			-	0.360 (0.215, 0.604)		
Median (mths)			3.3	-		
	Cetuximab + CT	CT alone	OR (95% CI)	Event rate/100 patients*		RD (95% CI) ^b
				Cetuximab + CT	CT alone	
Best overall response rate^a						
ITT population	79/222	43/220	2.326 (1.504, 3.600)	35.6	19.5	0.16 (0.08, 0.24)
Oral cavity & KPS ≥80 (post hoc)			14.348 (3.051, 67.463)			0.41 (0.23, 0.57)
Harms						
	Cetuximab + CT	CT alone	RR (95% CI) ^b	Event rate/100 patients*		RD (95% CI) ^b
				Cetuximab + CT	CT alone	
Skin reactions						
ITT population	148/219	12/215	12.11 (7.06, 21.13)	67.6	5.6	0.62 (0.55, 0.69)
Grade 3 or 4 skin reactions						
ITT population	20/219	1/215	19.63 (3.41, 114.69)	9.1	0.5	0.09 (0.05, 0.13)
Sepsis (including septic shock)						
ITT population	9/219	1/215	8.84 (1.47, 53.73)	4.1	0.5	0.04 (0.01, 0.07)

Source: Compiled during the evaluation

Abbreviations: CI = confidence interval; CT = chemotherapy; HR = hazard ratio; ITT = intention-to-treat; KPS = Karnofsky Performance Status; mths = months; NR = not reported; OR = odds ratio; RR = relative risk; RD = risk difference

* Median duration of follow-up of 19.1 in the cetuximab plus chemotherapy arm and 18.2 months in the chemotherapy alone arm (ITT population)

^a Best overall response rate was based on subjects with complete or partial response persisting for at least 4 weeks

^b Calculated during the evaluation using StatsDirect

On the basis of direct evidence presented by the submission in the ITT population, the comparison of cetuximab plus chemotherapy versus chemotherapy alone resulted in:

- Approximately 2.7 months difference in median overall survival; and
- Approximately 2.3 months difference in median progression-free survival.

On the basis of direct evidence presented by the submission, for every 100 patients treated with cetuximab plus chemotherapy in comparison to chemotherapy alone in the ITT population;

- Approximately 16 additional patients would have a complete or partial response for at least 4 weeks over a median duration of follow-up of approximately 18.7 months;
 - Approximately 62 additional patients would experience skin reaction(s) over a median duration of follow-up of approximately 18.7 months;
 - Approximately 9 additional patients would experience Grade 3 or 4 skin reaction(s) over a median duration of follow-up of approximately 18.7 months; and
- Approximately 4 additional sepsis events (including septic shock) over a median duration of follow-up of approximately 18.7 months.

Clinical claim

- 6.28 The submission described the addition of cetuximab to platinum-based chemotherapy as superior in terms of comparative efficacy and with manageable safety profile. The submission did not make a comparative safety claim. The claim in terms of comparative efficacy was adequately supported for the overall ITT population with respect to overall survival, progression-free survival and response rates. However, the key efficacy evidence supporting the PBS-listing was a post hoc subgroup analyses among patients whose primary tumour site of origin was the oral cavity and with a baseline KPS ≥ 80 (██████% of the ITT population). The results of the post hoc subgroup analyses were not robust, as it was subject to confounding and likely to be biased in favour of cetuximab.
- 6.29 The ESC considered that the evidence provided supported a claim of superior comparative effectiveness in terms of OS and PFS compared with platinum-based chemotherapy alone for both the ITT and post-hoc subgroup. Based on the ITT analysis, the ESC considered that the addition of cetuximab to platinum-based chemotherapy is inferior to platinum-based chemotherapy alone in terms of comparative safety. The ESC considered it was reasonable to then assume inferiority in terms of comparative safety in the post hoc subgroup.
- 6.30 In proposing that the listing of cetuximab be based on the post hoc subgroup rather than the ITT population in the trial, the ESC considered that the submission implicitly claimed that the effectiveness of cetuximab in the post hoc subgroup population was superior to the ITT population. The ESC noted that there may also be issues of access for patients with non-oral cavity cancers who were shown to derive a benefit in the EXTREME trial, and a subsequent risk of leakage from the proposed restriction. The PSCR (p. 4) considered the suggestion that leakage was likely into other head and neck cancer because those with tumour in the oral cavity were in the ITT population in EXTREME, to be implausible. The ESC disagreed with the PSCR in this regard. The ESC viewed that its fundamental concerns – the uncertainty of the claimed improved effectiveness of the post hoc derived subgroup compared to the ITT population in the trial – remained unresolved.
- 6.31 The PBAC considered that the claim of superior comparative effectiveness was demonstrated for the overall ITT population with respect to overall survival, progression-free survival and response rates, although the magnitude of the benefit was small. While the PBAC considered that a benefit was also observed among the subgroup of patients with oral cavity cancers, it did not consider that the claim of an additional benefit in this population was adequately supported by the data.

- 6.32 The PBAC 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. The PBAC also considered it reasonable to assume inferiority in terms of comparative safety in the post hoc subgroup.

Economic analysis

- 6.33 The submission presented a stepped economic evaluation. A trial-based economic evaluation and an extrapolation model, described as an area under the curve (AUC) analysis, were presented. The economic evaluation compared two treatment arms, cetuximab plus platinum-based chemotherapy and chemotherapy alone.
- 6.34 The economic evaluation was based on a post hoc subgroup analysis of the EXTREME trial in patients with a primary tumour site of origin in the oral cavity and a baseline KPS ≥ 80 . The submission included an additional model based on the ITT population of the EXTREME trial “for comparison purposes only”, with only the base case incremental cost-effectiveness ratio (ICER) presented in the submission.

Table 6: Summary of model structure and rationale

Component	Summary
Time horizon	5 years in the model base case, versus median follow-up of 19.1 months in the cetuximab plus chemotherapy arm and 18.2 months of the chemotherapy alone arm of the ITT population (maximum follow-up of 26.0 months) in the EXTREME trial.
Outcomes	LYG and QALYs.
Methods used to generate results	Cohort expected value analysis. Overall survival and progression-free survival data for each treatment arm were separately extrapolated beyond the duration of the trial, using log logistic distribution for the ITT population and log normal distribution for the post hoc subgroup (oral cavity and KPS ≥ 80). AUC analysis undertaken to estimate accumulated life years with and without disease progression. Utility values from Paleri and Kelly (2008) used to calculate QALYs.
Health states	‘Free from progression’, ‘progressed’ and ‘dead’.
Cycle length	One day intervals used in the AUC analysis.
Costs	Trial-based data were used to estimate drug costs, costs of managing skin reactions, and costs of subsequent therapies. The submission assumed that █% of patients received cetuximab fortnightly, based on UK data which could not be verified during the evaluation. Costs with associated palliative care were applied to death events.
Discount rate	5% for palliative care costs (other costs were not discounted as they were assumed to be incurred in the first year) and 5% for modelled outcomes (LYG and QALY).

Source: compiled during the evaluation

Abbreviations: AUC = area under the curve; ITT = intention-to-treat; KPS = Karnofsky Performance Status; LYG = life-year gained; QALY = quality-adjusted life year

Table 7: Key drivers of the model

Description	Method/Value	Impact
Extrapolation of the treatment effect	Trial data were truncated at 18.7 months for OS and 12 months for PFS. OS and PFS were extrapolated separately for each treatment arm using log logistic distribution for the ITT model and log normal distribution for the post hoc subgroup of patients with oral cavity tumour and a baseline KPS ≥ 80 . The use of the log logistic distribution for the ITT population and the log normal distribution for the post hoc subgroup resulted in long tails of the modelled survival functions (particularly for OS). There were no sensitivity analyses using different parametric distributions for the ITT model. The post hoc subgroup model was sensitive to the use of the Weibull distribution (which has an accelerated failure time).	Moderate, favours cetuximab
Time horizon	5 years, versus a maximum follow-up of 26.0 months in the EXTREME trial (ITT population). Assumed based on a review of models in head and neck cancer (which was not limited to the recurrent and/or metastatic setting).	High, favours cetuximab
Utilities	Utility values obtained from consensus of an oncologist and a surgeon for good and poor symptom control with palliative care from Paleri and Kelly (2008) were applied to the 'free from progression' and 'progressed' states respectively. The PSCR (p.4) acknowledged the limitations of the utility values.	Moderate, favours cetuximab
Cetuximab use	The trial-based cetuximab usage informed the drug cost estimates, which may underestimate use in practice as treatment may be continued until disease progression (rather than until the trial data-cut). There was some subsequent use of cetuximab included in the model, based on anticancer treatment after participation in the trial, which resulted in a small incremental cost-offset as there was more subsequent use of cetuximab in the comparator arm.	High, favours cetuximab
Cetuximab administration costs	Only outpatient drug administration costs were included, based on consultations by the sponsor (documentation not provided). The submission weighted the use between the public and private setting based on apparently selective data extraction from the Australian Hospital Statistics Report 2012-2013. The submission assumed that █% of patients received cetuximab fortnightly, based on UK data for which the citation was not provided. The drug administration costs were likely underestimates as: the exclusion of inpatient costs was inadequately justified as the categorisation between inpatient (or same-day admitted patients) and outpatients may differ between hospitals and states; the number of administration in the public setting may have been underestimated; and the inadequately justified reduction in the frequency of cetuximab administrations.	Moderate-high, favours cetuximab

Source: compiled during the evaluation

Abbreviations: OS = overall survival; PFS = progression-free survival

Table 8: Results of the stepped economic evaluation

Step and component	ITT population			Oral cavity & KPS ≥80 (post hoc)		
	Cetuximab + CT	CT alone	Increment	Cetuximab + CT	CT alone	Increment
Step 1: Trial-based (drug costs, administration costs, cost of treating skin reactions)						
Costs	\$ [redacted]	\$1,803	\$ [redacted]	\$ [redacted]	\$1,557	\$ [redacted]
Responder (complete/ partial)	35.6%	19.5%	16.1%	[redacted]%	[redacted]%	40.8%
Incremental cost/extra responder gained			\$ [redacted]	-		\$ [redacted]
Step 2: Modelled evaluation (extrapolated to 5 year time horizon, cost of subsequent therapies and palliative care)						
Costs	\$ [redacted]	\$8,444	\$ [redacted]	\$ [redacted]	\$8,527	\$ [redacted]
LYs	1.173	0.925	0.248	[redacted]	[redacted]	0.694
Incremental cost/extra life year gained			\$ [redacted]	-		\$ [redacted]
Step 3: Modelled evaluation (transform to QALYs)						
Costs	\$ [redacted]	\$8,444	\$ [redacted]	\$ [redacted]	\$8,527	\$ [redacted]
QALYs	0.816	0.625	0.190	0.846	0.360	0.486
Incremental cost/extra QALY gained			\$ [redacted]	-		\$ [redacted]

Source: Table D.5-4, p118 of the submission; '2 Copy of Economic evaluation.xlsx' and '3 Copy of Economic evaluation using ITT population.xlsx'. Additional data in italics calculated during the evaluation.

Abbreviations: CT = chemotherapy; ITT = intention-to-treat; KPS = Karnofsky Performance Status; LY = life years; QALY = quality-adjusted life year

The redacted table shows an ICER in the range of \$105,000/QALY - \$200,000/QALY and \$75,000/ life year gained (LYG) -\$105,000/ LYG for the ITT population, and \$45,000/QALY - \$75,000/QALY and \$15,000/LYG-\$45,000/ LYG for the post hoc sub group.

- 6.35 The ICER for the ITT population would decrease from \$105,000/QALY - \$200,000/QALY to \$45,000/QALY - \$75,000/QALY if the confidential rebate was increased from [redacted]% (proposed in the submission) to [redacted]%. The PSCR (p.5) stated that this higher rebate was not viable.
- 6.36 There were favourable assumptions in the model for the cetuximab arm including for cetuximab treatment costs, which may have resulted in the underestimation of the ICER for both the ITT population and the post hoc subgroup of patients with a primary tumour site in the oral cavity and a KPS ≥80 at baseline. Regarding the drug administration costs, the PSCR (p.3) argued that the exclusion of inpatient stays in the cost of IV administration is appropriate on the basis of a survey of private hospitals and day oncology centres, which found that it would be rare for a patient to be admitted as an inpatient for treatment. The ESC did not find sufficient evidence to support this claim, and advised that the cost of inpatient stays should be included in the costs of administering cetuximab. There were concerns that the extrapolation of data over the nominated time horizon resulted in the overestimation of treatment benefit associated with cetuximab. The PSCR (p.3) argued that this time horizon was reasonable, and that the sensitivity analyses presented in the evaluation which truncated overall survival data at 3 months and progression free survival data at 12 months were unjustifiably conservative, because: at three months, 75% of patients in the cetuximab arm had yet to progress; while at two years, nearly one quarter of the cetuximab treatment group were still alive; and at five years, six patients treated with cetuximab and two patients treated with chemotherapy alone were still in the EXTREME trial and known to be alive. The ESC noted that response was assessed by the investigator and again noted the low number of patients in each arm. The ESC considered that this time horizon was optimistic. The estimated ICER for the post hoc subgroup model was additionally uncertain given concerns regarding the robustness

of the underlying data. The ESC noted a key driver of the post hoc subgroup model was the modelled survival gain and that this could be driven by the poor performance of the comparator arm in the subgroup as well as the small numbers in the subgroup informing the model inputs.

- 6.37 The results of the sensitivity analyses indicate that both models were sensitive to the cost of cetuximab and its administration costs, the shortening of the time horizon and utility values.

Table 9: Results of key univariate sensitivity analyses (incremental cost per additional QALY gained)

	ITT population			Oral cavity & KPS ≥80 (post hoc)		
	Incremental costs	Incremental QALY	ICER	Incremental costs	Incremental QALY	ICER
Base case	\$ [REDACTED]	0.190	\$ [REDACTED]	\$ [REDACTED]	0.486	\$ [REDACTED]
Using Weibull distribution (b/c: ITT: log logistic; subgroup: log normal)	NR	NR	NR	\$ [REDACTED]	0.424	\$ [REDACTED]
Reduce time horizon to 3 yrs (b/c: 5 yrs)	\$ [REDACTED]	0.157	\$ [REDACTED]	\$ [REDACTED]	0.441	\$ [REDACTED]
Increase confidential rebate to [REDACTED] % (b/c: [REDACTED] %)	\$ [REDACTED]	0.190	\$ [REDACTED]	\$ [REDACTED]	0.486	\$ [REDACTED]
Drug administration cost as per Nov 2014 mCRC submission	\$ [REDACTED]	0.190	\$ [REDACTED]	\$ [REDACTED]	0.486	\$ [REDACTED]
Utilities from Greenhalgh (2008): PF on cetuximab 0.69, PF on CT 0.65, & progressed 0.52 (b/c: 0.8, 0.8 & 0.6) ^a	\$ [REDACTED]	0.178	\$ [REDACTED]	\$ [REDACTED]	0.431	\$ [REDACTED]
Utilities from Greenhalgh (2008): overall utilities without treatment-related utility: PF both arms 0.67 & progressed 0.52 (b/c: 0.8 & 0.6)	\$ [REDACTED]	0.160	\$ [REDACTED]	\$ [REDACTED]	0.413	\$ [REDACTED]

Source: Table D.6-1 p119 of the submission; '2 Copy of Economic evaluation.xlsx' and '3 Copy of Economic evaluation using ITT population.xlsx'. Additional data in italics calculated during the evaluation.

Abbreviations: b/c = base case; CT = chemotherapy; ICER = incremental cost-effectiveness ratio; ITT = intention-to-treat; mCRC = metastatic colorectal cancer; PF = progression-free; QALY = quality-adjusted life year.

Greenhalgh (2008): QoL analyses from the open-label EXTREME trial (ITT population) – mapped from QLQ-C30 to utilities using a cross walk algorithm (abstract in pancreatic cancer setting)

^a The results of the sensitivity analyses could not be verified during the evaluation. As the incremental cost differed from the base case (which should not have occurred), values calculated during the evaluation were used.

The redacted table above shows ICERs for the ITT population for all scenarios in the range of \$105,000/QALY - \$200,000/QALY, except for increasing the confidential rebate, when the ICER would be in the range of \$45,000/QALY - \$75,000/QALY. For the post hoc subgroup, the table shows ICERs in the range of \$45,000/QALY - \$75,000/QALY, except for increasing the confidential rebate, when the ICER would be in the range of \$15,000/QALY - \$45,000/QALY.

- 6.38 The PBAC previously considered a similar methodology of determining administration costs in the July 2015 minor submission for cetuximab (following the November 2014 recommendation for the first-line treatment for metastatic colorectal cancer). At the July 2015 meeting, the Committee decided it would not provide a recommendation in support of an alternative method to determine infusion costs in public and private hospital settings at that point in time. Applying drug administration costs as per the November 2014 submission, the ICER/QALY for the ITT and subgroup populations increased to \$105,000/QALY - \$200,000/QALY and \$45,000/QALY - \$75,000/QALY respectively.

- 6.39 Sensitivity analyses using different parametric distributions for the ITT population model were not included in the submission.
- 6.40 For the post hoc subgroup in patients with a primary tumour origin site in the oral cavity and a baseline KPS ≥ 80 , the submission stated that the ICER was most sensitive to the Weibull parameter distribution, described as the “outlier” distribution. However, the Akaike Information Criterion and Bayesian Information Criterion values for the Weibull distribution were not substantially higher than the other parametric functions that converged. Visual inspection of the extrapolated Weibull function suggested a reasonable fit with the trial data. It appeared that the higher ICER was driven by the accelerated failure time compared the other parametric functions, particularly for overall survival in the cetuximab arm after the trial period.
- 6.41 The PSCR (p. 4) included one new multivariate sensitivity analysis for the economic evaluation in the post hoc subgroup: ex-manufacturer price reduced by 5% (1 April 2016 statutory price reduction) and maximum treatment duration limited to ■ weeks (23.8 doses per patient instead of 24.5 doses in the base case, in line with the proposed risk share arrangement, see below). The resulting ICER was \$45,000/QALY - \$75,000/QALY.
- 6.42 The Pre-PBAC Response presented additional sensitivity analyses to allow for ■% of treated patients to be leakage into the ITT population, a 5% statutory price reduction from year 1, and cost of treatment rebated by the sponsor beyond ■ weeks (as per the initial proposed RSA), which resulted in an ICER of \$45,000/QALY - \$75,000/QALY gained in the subgroup and \$105,000/QALY - \$200,000/QALY gained in the ITT population. The Pre-PBAC Response then proposed a revised RSA under which treatment beyond ■ weeks would be rebated by the sponsor. In addition to the 5% price reduction and ■% leakage, this resulted in an ICER in the subgroup of \$45,000/QALY - \$75,000/QALY gained.

Drug cost/patient/course:

Table 10: Drug cost/patient/course (24.5 doses per course and inclusive of the ■% confidential rebate)

	Drug cost/patient/ course
<i>Post hoc subgroup (oral cavity & KPS ≥ 80) - as per the submission</i>	\$ ■
<i>Post hoc subgroup (oral cavity & KPS ≥ 80) - 5% discount off ex-man price</i>	\$ ■
<i>Post hoc subgroup (oral cavity & KPS ≥ 80) - 5% discount off DPMA</i>	\$ ■
<i>Post hoc subgroup (oral cavity & KPS ≥ 80) - private hospital scripts incur a flat 1.4% mark-up</i>	\$ ■
<i>Post hoc subgroup (oral cavity & KPS ≥ 80) - private hospital scripts incur a flat 1.4% mark-up and 5% discount off ex-man price</i>	\$ ■

Source: compiled during the evaluation from 2 Copy of Economic evaluation.xlsx' and '4 Section E.xlsx'. *Additional data in italics calculated during the evaluation.*

Abbreviations: DPMA = dispensed price for maximum amount; ex-man = ex-manufacturer; KPS = Karnofsky Performance Status

Estimated PBS usage & financial implications

- 6.43 This submission was not considered by DUSC. An epidemiological approach was undertaken to estimate usage and financial implications.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Uptake rate	50%	60%	65%	70%	75%
Number treated					
Number of infusions/ scripts (24.5 pp)					
Total DPMA for cetuximab ^a	\$	\$	\$	\$	\$
Patient co-payments (\$18.82*2 pp)	-\$	-\$	-\$	-\$	-\$
Total DPMA for cetuximab (less co-payment)	\$	\$	\$	\$	\$
Estimated net cost to PBS/RPBS/MBS					
Costs of managing AEs (\$21.53 pp)	\$	\$	\$	\$	\$
Incremental cost of CT (\$365.87 pp)	\$	\$	\$	\$	\$
Total drug administration costs ^b	\$	\$	\$	\$	\$
<i>MBS drug administration cost (item 13918; 75% benefit: \$73.50; 61.8% administrations in private hospitals)</i>	\$	\$	\$	\$	\$
Estimated total net cost					
Net cost to government (as presented in the submission)	\$	\$	\$	\$	\$
<i>Net cost to government (including MBS item 13918 only for administration costs, 75% benefit)</i>	\$	\$	\$	\$	\$

Source: Tables E.2-3 to E.3-3, pp124-130; Tables E.5-1 to E.5-7, pp130-133 of the submission; '4 Section E.xlsx'. *Additional data in italics calculated during the evaluation.*

Abbreviations: AE = adverse event; CT = chemotherapy; DPMA = dispensed price for maximum amount; pp = per patient; SCC = squamous cell carcinoma

^a Number treated multiplied by \$ in Year 1 and \$ (= \$ * 0.95) from Year 2 to Year 5

^b Number treated multiplied by \$. *The drug administration costs, presented as the MBS costs in the submission, included public hospital costs.*

The redacted table shows that at year 5, the estimated number of patients was less than 10,000, and the net cost to Government (including MBS) would be \$10 – \$20 million.

- 6.44 The use of incidence of oral cavity cancers was uncertain. While the literature suggested patients with recurrent and/or metastatic SCC of the head and neck may have a median life expectancy of less than one year, the incidence estimate used in the submission was not limited to those with recurrent and/or metastatic disease. The incidence may not reflect the prevalence of oral cavity cancers (as assumed in the submission), as the reported 5-year survival for oral cavity cancer was 75%. However, the subsequent assumptions in the submission may not be applicable to alternative estimates of the number of patients with SCC of the oral cavity (e.g. prevalence).
- 6.45 There were uncertainties in the rate of recurrent and/or metastatic disease, the proportion suitable for cetuximab and uptake rates in practice, which were largely informed by expert opinion or assumptions based on the clinical context. The submission suggested that rate of recurrent and/or metastatic disease and the uptake rates were unlikely to be exceeded (and therefore were potential overestimates). The estimated financial implications were sensitive to assumptions used to estimate the numbers of treated patients.

- 6.46 There was the potential for leakage among patients with recurrent and/or metastatic SCC of the head and neck (excluding nasopharyngeal carcinoma) whose primary tumour site of origin was outside the oral cavity, as the pivotal EXTREME trial included these patients. Additionally, there was the potential for leakage among patients with SCC of the oral cavity who have experienced disease progression (particularly given the number of requested repeats for the continuing treatment restriction). There was also potential leakage for use as subsequent-line therapy. The ESC agreed that there likely would be uptake in the population outside the proposed restriction. The PSCR (p.4) argued that that clinicians ‘are entirely familiar with the use of PBS restrictions’, and that leakage is unlikely as ‘patients who fail systemic therapy in this setting are likely to receive best standard care’. The PSCR (p.4) also agreed to include a definition of ‘oral cavity’ in the restriction wording to mitigate risk of leakage into the population of patients with other head and neck cancers. The ESC considered that there is a risk of use outside the proposed restriction. The PSCR (p4) stated should leakage occur it would be managed by a risk share agreement. Under the proposed risk share agreement, patients who require treatment beyond ■ weeks would not incur additional charges to Government. This proposal would manage the risk of the duration of use of cetuximab but not uncertainties in the patient population.
- 6.47 Allowing for 10% of treated patients to be leakage into the ITT population, a 5% statutory price reduction, and costs of treatment rebated beyond ■ weeks, the Pre-PBAC Response presented revised net costs to the PBS and Government. At year 5, there were an estimated less than 10,000 additional patients with SCC outside the oral cavity who were being treated with cetuximab, and the net cost to the Government would be \$10-\$20 million. The sponsor noted that this represented a decrease of less than \$10 million on the original submission estimate of \$10-\$20 million.

Quality Use of Medicines

- 6.48 The quality of used medicines activities outlined in the submission were related to the management of skin reactions associated with cetuximab.
- 6.49 The submission claimed that patients with oral cavity cancer represent a subgroup of patients who have a particularly high unmet clinical need.

Financial Management – Risk Sharing Arrangements

- 6.50 The sponsor also proposed a risk-sharing arrangement, in which patients who require treatment beyond ■ weeks would not incur additional charges to the government. It appeared likely that few patients would be treated beyond ■ weeks.
- 6.51 The Pre-PBAC Response then proposed a revised RSA under which treatment beyond ■ weeks would be rebated by the sponsor.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

7 PBAC Outcome

- 7.1 The PBAC decided not to recommend the listing of cetuximab in combination with

platinum-based chemotherapy, for the treatment of patients with metastatic and/or recurrent squamous cell carcinoma (SCC) of the oral cavity, on the basis of uncertain magnitude of clinical benefit and likely high and unacceptable cost-effectiveness.

- 7.2 The PBAC considered that there is a clinical need for treatments patients with metastatic and/or recurrent SCC of the head and neck and noted that the restriction was based on the post hoc subgroup of patients with this disease for whom the primary tumour site of origin was in the oral cavity and with a WHO performance status 0-1 (equivalent to Karnofsky Performance Status ≥ 80). The PBAC noted that the TGA-registered indication for cetuximab included a broader listing of all patients with metastatic and/or recurrent SCC of the head and neck. The PBAC considered there was a high risk of leakage from the restriction, as proposed by the sponsor, into the broader patient population.
- 7.3 The PBAC agreed that platinum-based chemotherapy was the appropriate comparator.
- 7.4 The PBAC noted that the submission presented data from an open-label head-to-head randomised trial (EXTREME; N=442) comparing cetuximab in addition to cisplatin or carboplatin and 5-fluorouracil versus cisplatin or carboplatin and 5-fluorouracil. However, the submission's requested listing relied on post hoc analyses in a subgroup of patients for whom the primary tumour site of origin was in the oral cavity and with a Karnofsky Performance Status (KPS) ≥ 80 (equivalent to WHO performance status of 0 or 1) at baseline (N = ■). The submission did not present adequate justification for the selection of this subgroup. The Pre-Sub-Committee Response then presented a range of arguments to suggest that there was a biologically plausible explanation to support the claim that patients with SCC of the oral cavity were more likely to respond to cetuximab therapy. The PBAC considered this response, and the advice of the ESC, and viewed that the evidence to support this claim remained unclear. The Pre-PBAC Response then presented a formal test of interaction for a subgroup treatment effect between the proposed PBS population and its complement subgroup, which suggested that the treatment effect is different in the subgroup relative to the larger population from which this particular subgroup was selected. While statistically correct, the PBAC viewed that this additional information could not address its overall concern that the difference in median overall survival between the ITT population and post hoc subgroup may be driven by the poor survival of the small number of patients in the control arm subgroup. The PBAC considered that the prognostic differences in the control arm could represent the influence of selection bias or confounding variables, but that the submission and subsequent responses had not provided evidence to account for this issue. Overall, the PBAC considered that the sponsors request to limit cetuximab use to the subgroup was not supported and that ITT analysis of the trial was more informative for determining the clinical benefit of cetuximab.
- 7.5 The PBAC considered that the claim of superior comparative effectiveness was reasonable for the overall ITT population with respect to overall survival, progression-free survival and response rates, although the magnitude of the benefit (such as a median survival of 2.7 months) was small. While the PBAC considered that a benefit was also observed among the subgroup of patients with oral cavity cancers, it did not consider that the claim of an additional benefit of cetuximab treatment in this population over the ITT population was adequately supported.

- 7.6 The submission made no comparative safety claim. The PBAC 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. The PBAC also considered it reasonable to assume inferiority in terms of comparative safety in the post hoc subgroup. However, the PBAC noted that the skin toxicities associated with cetuximab are widely known and well-managed in practice.
- 7.7 In addition, the PBAC considered it would be helpful if additional evidence corroborating the benefit of anti-EGFR antibodies in the setting of metastatic and/or recurrent SCC of the head and neck could be identified. The PBAC noted the results of the SPECTRUM trial of cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic SCC of the head and neck. The publication (Vermorken et al, Lancet Oncol. 2013.14(8):697-710) concluded, 'Although the addition of panitumumab to chemotherapy did not improve overall survival in an unselected population of patients with recurrent or metastatic SCCHN, it improved progression-free survival and had an acceptable toxicity profile.' In this context, the PBAC concluded that any future resubmission for cetuximab use in recurrent or metastatic SCC of the head and neck should consider situating its clinical claim within the wider scientific literature on anti-EGFR antibodies in this setting.
- 7.8 In its consideration of the economic analysis presented in the submission, the PBAC noted that the acceptability of the outputs of the economic model fundamentally relied on the suitability of the post hoc subgroup selection. The PBAC concerns with the selection of this subgroup therefore made the economic evaluation problematic. In addition to the clinical uncertainty, the PBAC also noted a number of other uncertainties in the model which favoured cetuximab including the choice of extrapolation method, the subgroup extrapolation in the context of limited data, the source of the utility values, an optimistic time horizon and drug administration costs.
- 7.9 The PBAC recalled that the Committee had considered a similar methodology of determining administration costs in the July 2015 minor submission for cetuximab (following the November 2014 recommendation for the first-line treatment for metastatic colorectal cancer). At the July 2015 meeting, the Committee decided it would not provide a recommendation in support of an alternative method to determine infusion costs in public and private hospital settings at that point in time. The PBAC noted that applying drug administration costs as per the November 2014 submission would increase the ICER/QALY compared to the base case scenarios presented in the submission.
- 7.10 The PBAC noted that the ICER for the ITT population, calculated during evaluation as \$105,000/QALY - \$200,000/QALY, was greater than the base case ICER for the subgroup presented in the submission (\$45,000/QALY - \$75,000/QALY). The PBAC considered that applying less optimistic assumptions to the model would likely increase the ICER for the subgroup from \$45,000/QALY - \$75,000/QALY (as proposed in the Pre-PBAC response) to a value that the PBAC considered was unacceptably high for this condition.
- 7.11 In view of the clinical uncertainty, the PBAC agreed that there was a high potential for usage outside the proposed subgroup population. The PBAC noted that the Pre-PBAC Response presented additional sensitivity analyses to allow for a ■■■% leakage, a 5% statutory price reduction from year 1, and cost of treatment rebated by the sponsor beyond ■■■ weeks (as per initial proposed RSA) or beyond ■■■ weeks (a

revised proposed RSA). The PBAC also noted the revised updated net costs to Government allowing for ■■■% leakage, 5% statutory price reduction from year 1 and cost of treatment rebated beyond ■■■ weeks. Several of these revised figures could not be verified before the meeting using the available data in the submission and Pre-PBAC Response. Regardless, the PBAC considered the reduction in the treatment cap to ■■■ weeks was of small consequence in view of the trial data, which showed that 7% (3/43) of the post hoc subgroup reported use beyond 70 infusions, and that 6.4% (14/219) of the ITT population received more than 50 infusions. Furthermore, the PBAC noted that the revised figures likely included a reduction in drug administration costs beyond ■■■ (or ■■■ weeks), which the sponsor had not indicated it would rebate. In this respect, the PBAC considered that the revised figures likely underestimated the utilisation and costs to Government.

- 7.12 The PBAC noted that the number of patients would have to be re-estimated if a listing for cetuximab is sought in a broader population that aligns with the ITT population of the trial.
- 7.13 The PBAC considered that a major resubmission would be required to request further consideration of recommending listing of cetuximab for this condition. The PBAC further considered that the resubmission should define a patient population that more closely aligns with the TGA-registered indication and taking into account the evidence supporting the clinical place of anti-EGFR antibodies in the management of head and neck cancer.
- 7.14 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 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.

9 Sponsor's Comment

Merck Serono is pleased that the PBAC recognises that there is a need for new treatments for patients with RM SCCHN and that cetuximab provides an overall survival benefit in this hard-to-treat group of patients. We remain committed to working with the PBAC to find a solution that allows reimbursed access to cetuximab for this patient population.