Docetaxel for the adjuvant treatment of early node-positive breast cancer: a single technology appraisal

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List of abbreviations

AC:	intravenous doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2, on day 1 of a 21-day cycle
AC-CMF	AC followed by CMF
AT	doxorubicin and docetaxel
CAF	oral cyclophosphamide 100 mg/m^2 on days 1-14, intravenous doxorubicin 30 mg/m^2 and fluorouracil 500 mg/m^2, on days 1 and 8 of a 28-day cycle
cCMF	classic (Bonadonna) CMF
CEF	oral cyclophosphamide 75 mg/m^2 on days 1-14, intravenous epirubicin 60 mg/m^2 and fluorouracil 500 mg/m^2, on days 1 and 8 of a 21-day cycle
CMF	cyclophosphamide, methotrexate, and fluorouracil
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
EC	intravenous epirubicin 60 mg/m^2 and cyclophosphamide 500 mg/m^2, on day 1 of a 21-day cycle
E-CMF	epirubicin 100 mg/m^2 3-weekly followed by CMF 4-weekly
EMEA	European Medicines Agency
FAC	intravenous fluorouracil 500 mg/m^2, doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2, on day 1 of a 21-day cycle
FDA	Food and Drug Administration
FEC	intravenous fluorouracil 500 mg/m^2, epirubicin 50-100 mg/m^2 and cyclophosphamide 500 mg/m^2, on day 1 of a 21-day cycle
G-CSF	granulocyte-colony stimulating factor
HER2	human epidermal growth factor receptor 2

1 SUMMARY

1.1 Scope of the submission

The scope of the manufacturer's submission is limited to docetaxel in combination with doxorubicin and cyclophosphamide (TAC) for the adjuvant treatment of women diagnosed with operable node-positive breast cancer (ie the relevant licensed application), compared with anthracycline-based chemotherapy.

The scope thus excludes women with high-risk node-negative cancers. Such women, who are at intermediate risk of recurrence, would, in clinical practice, be considered for adjuvant chemotherapy. The scope also excludes docetaxel used in sequential therapy (i.e. following or preceding several cycles of other cytotoxic drugs), although current clinical opinion appears to favour such regimens rather than combination regimens such as TAC. The limitation of the comparators to anthracycline-based regimens excludes paclitaxel, another taxane which, like docetaxel, is licensed for use in the UK as adjuvant therapy for operable node-positive breast cancer, in sequential therapy following treatment with doxorubicin and cyclophosphamide.

1.2 Summary of submitted clinical effectiveness evidence

There is evidence from a randomised controlled trial (RCT) that, compared with the anthracycline-based regimen FAC, TAC is associated with superior disease-free and overall survival at 5 years (hazard ratio 0.72, 95% CI 0.59-0.88, p=0.001, and 0.70, 95% CI 0.53-0.91, p=0.008, respectively). The absolute risk reduction at five years in patients treated with TAC, compared with those treated with FAC, was 7% for disease-free survival and 6% for overall survival, and the number of patients who had to be treated with TAC rather than FAC to for one additional patient to benefit was 14 for disease-free survival and 17 for overall survival. However, TAC was associated with significantly greater toxicity than FAC.

There is also RCT evidence that a sequential regimen, FEC100-T, in which docetaxel is used after the anthracycline-based regimen FEC100, is associated with superior disease-free and overall survival at 5 years (adjusted hazard ratio 0.83, 95% CI 0.69-0.99, p=0.041, and 0.77, 95% CI 0.59-1.00, p=0.05, respectively) compared with FEC100. The estimated absolute risk reduction at five years in patients treated with FEC100-T compared with those treated with FEC100 was 5.1% for disease-free survival and 4.0% for overall survival, and the number of patients who had to be treated with FEC100-T rather than FEC100 for one additional patient to benefit was 20 for disease-free survival and 25 for overall survival.

1.3 Summary of submitted cost effectiveness evidence

An economic model is developed, based primarily on the single trial BCIRG001. This submission model generates central estimates of the cost per life year gained and cost per QALY gained of TAC compared to FAC of £7900 and £9800 respectively.

The manufacturer's submission predicts a cost effectiveness of £15,000-£20,000 per QALY gained for TAC compared to E-CMF. This estimate is based upon an indirect comparison of absolute disease-free survival rates.

Based upon the randomized controlled trial of FEC100-T compared to FEC100, the manufacturer's submission estimates the cost effectiveness of FEC100-T to be £8,200 (£3500, £56,000) per QALY compared to FEC100.

1.4 Commentary on the robustness of submitted evidence

The submitted clinical evidence depends primarily on an interim analysis from one trial, BCIRG 001, which uses docetaxel in its licensed regimen (TAC). This is a large study carried out in a population which appears to be representative of the population for whom adjuvant docetaxel is licensed and who are expected to be eligible to receive it. However, there is no evidence that the study outcome assessors were blinded to treatment allocation, although the FDA recommends such blinding when disease-free survival is measured, and consider it necessary to minimize bias in the assessment of drug toxicity. FAC, the anthracycline-based regimen used as the comparator in the trial, is not in common use in the UK, and therefore the submitted evidence does not indicate whether TAC is superior to the anthracycline-based regimens which are in common use.

No evidence of systematic bias has been found in the primary economic analysis of TAC compared to FAC, presented within the manufacturer's submission. It is the ERG's opinion that a revised model taking into account a number of modelling issues identified by the ERG may generate higher estimates of cost effectiveness, but it is unlikely that these estimates would exceed £35,000 per QALY gained. The industrial submission presents a probabilistic sensitivity analysis of uncertainty in the economic estimates; the certainty in the cost effectiveness estimates is overestimated.

1.5 Key issues

Two key issues have been identified. The first relates to safety. TAC is associated with significantly greater toxicity than FAC. However, the manufacturer's submission ignores the premature termination of the French RAPP 01 trial following three fatal or life-threatening adverse events in patients receiving docetaxel with doxorubicin, and does not mention EMEA's concern regarding

TAC's long-term side effects, as a result of which intensive monitoring for cardiotoxicity, secondary leukaemia, and serious gastrointestinal toxicity is ongoing.

The second key issue relates to the choice of FAC as the main comparator anthracycline-based regimen. FAC is not in common use in the UK, where the most common anthracycline-based regimens are FEC and E-CMF. On the basis that the onus is on the manufacturer's submission to prove efficacy and cost effectiveness, what has to be demonstrated is that TAC is more economically attractive than FEC75-100 and / or that FAC is more economically effective than E-CMF. In the absence of direct RCT evidence, the crucial links are the indirect comparisons between FAC and FEC75-100 or E-CMF.

The manufacturer's submission claims that FAC is equivalent to FEC. It supports this claim with reference to clinical opinion and direct comparisons carried out in metastatic cancer. These studies compare FAC with a doxorubicin dose of 50 mg/m^2 to FEC with an epirubicin dose of 50 mg/m^2. Studies in adjuvant therapy have identified a dose response for epirubicin, but not for doxorubicin.

The evidence would appear to indicate that the effectiveness of FAC lies somewhere between that of FEC50 and FEC100. The cost effectiveness of TAC compared to FEC75-100 depends crucially on where within this range the efficacy of FAC lies. If FAC is equivalent to FEC50, as suggested by the studies referred to in the submission, then a crude indirect comparison based upon the relative risks of disease-free survival up to 5 years suggests that TAC may not be more effective than FEC100, and would in that case be dominated economically by FEC100. Whilst this may be an extreme assumption, the economic superiority of TAC compared to FEC100 should, on the basis of the industrial submission, be considered unproven.

It should be noted that it was not possible within the constraints of this review to undertake a systematic review of the evidence concerning the relative efficacies of FAC and FEC in metastatic cancer.

Similarly, since E-CMF has been shown to be superior to CMF, in the absence of direct comparisons between FAC and E-CMF, the relative efficacy of FAC and CMF becomes important. No evidence has been identified from direct comparisons which demonstrates that standard-dose FAC is statistically significantly superior to CMF in adjuvant therapy. The manufacturer's submission supports its assumption that FAC is superior to CMF by reference to the meta-analysis carried out by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). However, it is not clear from published data exactly which studies are included in this meta-analysis, and consequently it is possible that the results are driven by studies of dose-intensive regimens. The relative efficacy of TAC to E-CMF is therefore unclear.

The industry submission predicts a cost effectiveness of £15,000-£20,000 per QALY gained for TAC compared to E-CMF. This estimate is based upon an indirect comparison of absolute disease-free

survival rates, and as such is severely flawed. The review of the clinical evidence concludes that the superiority of TAC over E-CMF is unproven; an exploratory analysis based on an indirect comparison of relative risks suggests a cost per QALY may be in the order of £60,000.

In summary, therefore, the relevance of the cost effectiveness estimates put forward in the manufacturer's submission depend on subjective judgments regarding the likely superiority of TAC over FEC75-100 or E-CMF.

2. BACKGROUND

2.1 Description of underlying health problem

2.1.1 Epidemiology

Breast cancer is the most common cancer amongst women in England and Wales. Around one in nine women will be diagnosed with breast cancer at some time in their lives. In 2002, 37,134 new cases of breast cancer were diagnosed in women in England and Wales.[1]

The risk of breast cancer increases with age. Over 80% of cases occur in women aged over 50.[1]

2.1.2 Prognosis

In breast cancer, prognosis is related to a number of factors, including the extent of disease progression identified at diagnosis or initial surgery. Progression may be assessed using a clinical staging system which takes into account the size of the primary tumour, the extent of spread to regional lymph nodes, and whether there are distant metastases (see Table 1). Ductal carcinoma in situ (cancer which is confined to the milk ducts) is non-invasive. In Stages I and II, the disease is locally invasive: that is, it has spread into the breast tissue and may also have spread, in Stage II, to the regional lymph nodes (those in the armpit on the same side of the body as the breast cancer). In Stage III, the disease may have spread into the skin, chest wall or supraclavicular lymph nodes, and Stage IV (advanced or metastatic) disease has spread to more distant parts of the body. Thus early breast cancer, in which identifiable disease is limited to the breast or regional lymph nodes and can be removed surgically,[2] includes Stage I, Stage II and some Stage IIIA disease.

Table 1 Simplified American Joint Committee on Cancer clinical staging system (after Singletary et al. 2002[3])

TNM stage	Description	Simplified explanation	
		Tumour and regional lymph nodes	**Distant metastases**
0	Non-invasive	Cancer in situ, no lymph nodes affected	No
I	Early	Tumour no more than 2 cm in greatest dimension, no lymph nodes affected	No
IIA		Tumour no more than 2 cm in greatest dimension, spread to movable lymph nodes in armpit or tumour over 2 cm but no more than 5 cm in greatest dimension, no spread to lymph nodes in armpit	No
IIB		Tumour over 2 cm but no more than 5 cm in greatest dimension, spread to movable lymph nodes in armpit or tumour over 5 cm in greatest dimension, no spread to lymph nodes in armpit	No
IIIA	Early or locally advanced	Tumour no more than 5 cm in greatest dimension, spread to non-movable lymph nodes in armpit or tumour over 5 cm in greatest dimension, spread to movable or non-movable lymph nodes in armpit	No
IIIB	Locally advanced	Tumour of any size with invasion of skin or chest wall, with or without spread to lymph nodes in armpit	No
IIIC		Tumour of any size with more severe regional lymph node involvement	No
IV	Advanced or metastatic	Tumour of any size, with or without spread to lymph nodes in armpit	Yes

In the UK, around 10-15% of women with breast cancer present with ductal carcinoma in situ,[4] and fewer than 5% present with metastatic (Stage IV) disease.[5] Of the remainder, about 50% present with Stage I disease,[5] leaving approximately 35% who present with Stage II or III disease. There is

evidence that around 30% of women who present with non-metastatic disease and a tumour no greater than 5 cm (ie Stage I and IIA, and some Stage IIB and III) are node-positive.[6] However, it is not clear from this what proportion of women who present with early breast cancer have node-positive disease.

Age at diagnosis is a prognostic factor for survival. After adjusting for tumour size, lymph node status, and histological grade, 5- and 10-year survival has been found to be significantly lower in women aged under 40 at diagnosis than in those aged 40-69. However, if the tumour is small (<2 cm) and the lymph nodes are not affected, there is no significant difference in survival between women aged under 40 and those aged 40-69 at diagnosis.[7]

Some breast cancers contain oestrogen and progesterone receptors, and are termed endocrine-responsive. Other cancers do not contain such receptors, and are termed endocrine non-responsive. Endocrine-responsive and endocrine non-responsive breast cancer appear to be separate subtypes of the disease.[8] The majority of breast cancers are endocrine responsive. Women with endocrine-responsive tumours have a better general prognosis; they also benefit from antihormonal therapies such as tamoxifen.[9]

Some breast cancers overexpress the human epidermal growth factor receptor 2 (HER2). Such tumours are associated with a worse prognosis than those which are HER2-negative.[10]

2.1.3 Treatment of early breast cancer

The primary treatment for early breast cancer is surgical removal of the tumour and, if necessary, any affected axillary lymph nodes. Radiotherapy may also be used to control local disease. However, over 50% of women with operable breast cancer who receive only such locoregional treatment die from metastatic disease, indicating that micrometastases were present at the time of initial diagnosis.[10] Adjuvant systemic cytotoxic chemotherapy is given with the aim of eradicating such micrometastases. Patients with endocrine-responsive cancers usually also receive hormonal therapy (most commonly tamoxifen).

Because cytotoxic chemotherapy is not without risk, current international guidelines do not recommend its use in women at low risk of disease recurrence. This risk is related to a number of factors, of which the most important is axillary node involvement[11] (spread to the lymph nodes in the armpit; see Table 2).

Table 2: Definition of risk categories for patients with operated breast cancer (St Gallen 2005)[11]

Risk category	
Low	*Node negative **and** all of the following*: Primary tumour ≤2cm Histological and/or nuclear grade 1 No peritumour vascular invasion HER2 negative Age ≥35 years
Intermediate	*Node negative **and** at least one of the following*: Primary tumour >2cm Histological and/or nuclear grade 2-3 Peritumour vascular invasion HER2 positive Age <35 years *Node positive (1-3 involved nodes) **and*** HER2 negative
High	*Node positive (1-3 involved nodes) **and*** HER2 positive *Node positive (≥4 involved nodes)*

Data from the control groups of randomised studies provide some indication of the absolute risk of breast cancer mortality in women who receive surgery without adjuvant chemotherapy or endocrine therapy (see Table 3). Because of subsequent trends towards earlier diagnosis and better treatment, the absolute risk of breast cancer mortality may be higher in these women, who were first treated many years ago, than it would be in comparable women today if they were not given adjuvant chemotherapy or endocrine therapy.[2] However, it is clear that, without adjuvant therapy, women with node-positive disease are at substantially higher risk of death than are those with node-negative disease. Although the relative reductions in the risk of recurrence and breast cancer mortality achieved with polychemotherapy are very similar in node-negative and node-positive disease,

especially in women aged under 50 at diagnosis, the absolute benefit of therapy is greater for women with node-positive disease because it depends on the baseline level of risk, and this is considerably higher in node-positive disease.[2]

Table 3: Risk of breast cancer mortality in women diagnosed with early breast cancer who did not receive adjuvant chemotherapy or endocrine therapy[2]

	5 years	10 years	15 years
Endocrine-receptor-poor, node-negative	16%	25%	32%
Endocrine-receptor-poor, node-positive	42%	58%	66%
Endocrine-receptor-positive, node-negative	7%	20%	31%
Endocrine-receptor-positive, node-positive	23%	51%	63%

The St Gallen 2005 definition of risk categories no longer regards endocrine responsiveness as a risk factor (see Table 2) but as the primary determinant of treatment choice. However, in the context of the choice of treatment modalities, the same document indicates that there are by definition no low-risk endocrine non-responsive cancers[11] (see Table 4).

Table 4: Choice of treatment modalities for early breast cancer (St Gallen 2005)[11]

Risk category	Endocrine responsive	Endocrine response uncertain	Endocrine non-responsive
Low	Endocrine therapy or nil	Endocrine therapy or nil	Not applicable
Intermediate	Endocrine therapy alone, or Chemotherapy followed by endocrine therapy (Chemotherapy + endocrine therapy)*	Chemotherapy followed by endocrine therapy (Chemotherapy + endocrine therapy)*	Chemotherapy
High	Chemotherapy followed by endocrine therapy (Chemotherapy + endocrine therapy)*	Chemotherapy followed by endocrine therapy (Chemotherapy + endocrine therapy)*	Chemotherapy

Nil: no adjuvant systemic therapy

*There is evidence to suggest that chemotherapy and tamoxifen should be delivered sequentially. However, there is no such evidence for aromatase inhibitors or ovarian function suppression/ablation. [11]

Suitability for adjuvant cytotoxic chemotherapy is influenced by other factors in addition to the risk of recurrence: these include age, general health, and patient acceptability. There is evidence to suggest that, in early breast cancer, both the relative and absolute benefits of polychemotherapy compared with no chemotherapy are greater in younger than in older women. Polychemotherapy is associated with an overall relative reduction in the annual event rate of 37% (SE 0.034, $2p<0.00001$) for recurrence and of 19% (SE 0.02, $2p<0.00001$) for breast cancer mortality in women younger than 50 at diagnosis, compared with 29% (SE 0.04, $2p<0.00001$) and 12% (SE 0.03, $2p<0.00001$) respectively in women aged 50-69 at diagnosis. This translates to a reduction in the 15-year probabilities of recurrence and breast cancer mortality of 12.3% and 10.0% respectively in younger women, but only 4.1% and 3.0% respectively in older women.[2]

2.2 Critique of manufacturer's description of underlying health problem

The manufacturer's description of the underlying health problem is very brief. It defines early breast cancer as cancer that is confined to the breast and/or local lymph nodes and where the primary tumour can be removed surgically (ie Stages I, II and operable Stage III disease in the staging system summarised in section 2.1.2 above). The submission further indicates, in Table 5, that chemotherapy is commonly used in high-risk Stage II disease as well as in Stage III and IV disease; however, high-risk Stage II disease is not defined.

The submission does not discuss the implications of the prognostic factors used to define the subgroups for which it presents analyses, namely age, menopausal status, number of positive nodes, hormone receptor status, and HER2 status.

2.3 Overview of current service provision

A number of agents may be used for adjuvant cytotoxic chemotherapy in early breast cancer. The three main groups include:

- CMF (cyclophosphamide, methotrexate, and fluorouracil)
- anthracycline antibiotics, specifically doxorubicin or epirubicin
- taxanes (docetaxel and paclitaxel).

The classic (Bonadonna) CMF regimen consists of 100 mg/m^2 oral cyclophosphamide on days 1-14, and intravenous methotrexate 40 mg/m^2 and fluorouracil 600 mg/m^2 on days 1 and 8 of a 28-day cycle.[12] It has been demonstrated to be significantly superior to intravenous CMF in metastatic breast cancer.[13]

The NICE Guidelines for breast cancer state that women with early breast cancer who are at intermediate or high risk of recurrence should normally be offered four to eight cycles of anthracycline-based chemotherapy.[5]

As no gold-standard regimen for anthracycline-based chemotherapy has yet been established, a variety of regimens may be used. These include:

- FAC: intravenous fluorouracil 500 mg/m^2, doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2, on day 1 of a 21-day cycle
- CAF: oral cyclophosphamide 100 mg/m^2 on days 1-14, intravenous doxorubicin 30 mg/m^2 and fluorouracil 500 mg/m^2, on days 1 and 8 of a 28-day cycle
- AC: intravenous doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2, on day 1 of a 21-day cycle
- EC: intravenous epirubicin 60 mg/m^2 and cyclophosphamide 500 mg/m^2, on day 1 of a 21-day cycle
- FEC: intravenous fluorouracil 500 mg/m^2, epirubicin 50-100 mg/m^2 and cyclophosphamide 500 mg/m^2, on day 1 of a 21-day cycle
- CEF: oral cyclophosphamide 75 mg/m^2 on days 1-14, intravenous epirubicin 60 mg/m^2 and fluorouracil 500 mg/m^2, on days 1 and 8 of a 21-day cycle
- E-CMF: epirubicin 100 mg/m^2 3-weekly followed by CMF 4-weekly.

The manufacturer's submission notes that FEC and E-CMF are the anthracycline-based regimens most commonly used in the UK.

The manufacturer's submission also indicates that, in 2004-5, docetaxel was in occasional use in the UK, in a number of different regimens. Data from the IMS Healthcare Oncology Analyzer suggest that the main regimens used were TAC and FEC-T, although market research carried out for Sanofi-aventis did not identify either of those regimens. FEC-T is understood to be commonly used in current private practice in the UK because it is less toxic than E-CMF, and requires fewer hospital visits.[14]

2.4 Critique of manufacturer's description of current service provision

The submission quotes market research carried out for Sanofi-aventis. This states, on the basis of data relating to 221 patients being treated by 71 physicians, that in 2005 FEC was the most popular anthracycline-based regimen in the UK, followed by E-CMF, and that FAC was not used. 2004-5 data from the IMS Healthcare Oncology Analyzer, based on 473 patients, are very similar. These data are consistent with the views of clinicians consulted in relation to this review. However, no information is provided which indicates how representative the sampled physicians and patients are likely to be.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

3.1 Population

Clinically, the relevant patient population is women diagnosed with operable invasive early breast cancer who are suitable for cytotoxic chemotherapy. This population includes women with node-positive disease, who are at high risk of disease recurrence, and those with high-risk node-negative cancers, who are at intermediate risk of recurrence. However, in line with the relevant licensed indication,[15] the manufacturer's definition of the decision problem limits the population to women with early node-positive breast cancer, thus excluding women with high-risk node-negative disease who would in clinical practice be considered for adjuvant chemotherapy.

3.2 Intervention

Docetaxel is a member of the taxane group of drugs. It has marketing authorisation within the UK for use, in combination with doxorubicin and cyclophosphamide, for the adjuvant treatment of patients with operable node-positive breast cancer.[15] The recommended regimen is docetaxel 75 mg/m^2, administered one hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2, every three weeks for six cycles.[16] The scope of the manufacturer's submission is essentially limited to this regimen.

The only specified contraindications to docetaxel therapy are:

- hypersensitivity to the active substance or any of the excipients
- a baseline neutrophil count of <1,500 cells/mm^3
- pregnancy or breast-feeding
- severe liver impairment.[16]

Unless contraindicated, premedication with an oral corticosteroid such as dexamethasone is recommended; this should be given for three days, starting one day prior to docetaxel administration. Prophylactic granulocyte-colony stimulating factor (G-CSF) may also be used to reduce the risk of haematological toxicities,[16] and is recommended by the US National Comprehensive Cancer Network for adjuvant regimens such as TAC which carry a high risk of febrile neutropaenia.[17]

Because of the risk of neutropaenia and associated infections, frequent monitoring of complete blood counts is recommended for all patients receiving docetaxel.[16] In addition, because of the risk of heart failure, patients should be monitored for symptoms of congestive heart failure during therapy and follow-up.[16]

Clinical opinion in the UK currently favours sequential regimens such as FEC-T, and it is therefore considered unlikely that TAC will come into common use.[14]

3.3 Comparators

As noted in section 2.3 above, NICE recommends the use of multiple-agent chemotherapy which includes anthracyclines in women with early breast cancer at intermediate or high risk of recurrence.[5] The most obvious comparator for docetaxel is therefore anthracycline-based chemotherapy. Although a number of anthracycline-based regimens may be used (see section 2.3 above), market research suggests that those most commonly used in the UK are FEC and E-CMF, and that FAC is not in current use.[18] Until recently, the UK standard for FEC was 6 cycles of FEC60 (ie FEC with an epirubicin dose of 60 mg/m^2). However, following evidence from the FASG 05 study that 5-year disease-free and overall survival are significantly improved in patients receiving FEC100 compared with those receiving FEC50,[19] FEC is now generally used in the UK with an epirubicin dose between 75-90 mg/m^2.[20]

Paclitaxel (Taxol®) should also be considered as a comparator as it is licensed for use in the UK as adjuvant therapy for node-positive breast cancer following treatment with doxorubicin and cyclophosphamide (AC).[16] It is currently under consideration by NICE.

Thus, in an NHS context, the relevant comparators for docetaxel regimens are FEC 75-90 mg/m^2, E-CMF, and AC-paclitaxel. However, whilst the submission identifies anthracycline-containing regimens including FEC, E-CMF, AC and EC as relevant comparators, it does not mention paclitaxel. Moreover, whilst the submission states that FEC and E-CMF are the anthracycline-containing regimens most commonly used for adjuvant therapy in the UK, that AC or EC are also used, and that FAC is seldom or never used, the discussion of clinical effectiveness is limited to studies which compare docetaxel regimens with FAC or FEC100 (FEC with an epirubicin dose of 100 mg/m^2).

The manufacturer's submission cites, in section 2.9, the view of its clinical panel that FAC could reasonably be assumed to be equivalent in efficacy to an unspecified dosage of FEC. This assumption was based on the similar mechanism of action of doxorubicin and epirubicin, and on the results of two studies which directly compared FAC50 and FEC50 in metastatic cancer, and found no significant difference between them.[21,22] The submission also cites as evidence the indirect comparison contained in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analyses[2] even though, in the same article, the EBCTCG demonstrated the unreliability of indirect comparisons relative to direct comparisons in relation to CMF-based and anthracycline-based chemotherapy regimens (see section 4.2.3 below).

3.4 Outcomes

The relevant outcomes in relation to adjuvant chemotherapy for early breast cancer are:

- Overall survival
- Disease-free survival
- Health-related quality of life
- Adverse events
- Health economic outcomes (ie. Cost and cost effectiveness).

Disease-free survival, the manufacturer's submission's primary outcome measure, is clearly important. However, overall survival is also generally considered important because of the unpleasantness of adjuvant cytotoxic chemotherapy, both at the time of treatment and for some time thereafter: an overall survival gain is required to compensate for the time spent undergoing and recovering from therapy. A systematic review of studies carried out in women who had undergone adjuvant chemotherapy for early breast cancer found that around 50% thought that an extra 6 months' survival was needed to make such chemotherapy worthwhile.[23] However, a more recent study in similar women who had received adjuvant chemotherapy with AC, AC-CMF, or CMF alone found their preferences to be surprisingly diverse. When asked to imagine that they had a life expectancy of 15 years without adjuvant chemotherapy, over 50% would undergo such chemotherapy for an additional day's survival, and 80% for an additional year, but 2-4% would not do so for an additional 20 years' survival. The investigators caution that these results are only representative of women who accepted adjuvant chemotherapy, not to those who were offered and refused it.[24]

For all drugs, adverse events form an important outcome measure. However, in relation to adjuvant chemotherapy regimens, adverse events are not straightforward outcome measures. Such regimens are associated with a high level of adverse effects which are at best unpleasant and at worst fatal. As

the anti-cancer activity of cytotoxic drugs is linked to their ability to damage normal tissue, some adverse events may be associated with an improved prognosis – indeed, it has been suggested that regimens which do not cause neutropaenia, the adverse event most frequently associated with adjuvant chemotherapy, may be less effective than those which do.[25] Similarly, adjuvant chemotherapy can induce permanent amenorrhoea in pre-menopausal women, and this is associated with poorer quality of life attributable to factors such as the age inappropriateness of the menopause, the menopausal symptoms themselves, and, among younger women, the associated infertility.[26] Early menopause is also associated with an increased risk of osteoporosis and increased cardiovascular risk. However, there is evidence that chemotherapy-induced amenorrhoea is significantly associated with better outcomes, and thus may act as a surrogate marker for an effective chemotherapy dose.[27,28]

3.5 Time frame

Lengthy studies are required to assess the efficacy of adjuvant chemotherapy. Although the risk of distant recurrence of breast cancer is highest during the first decade after diagnosis, it may still be substantial during the second decade.[2] Meta-analyses which compare polychemotherapy with no chemotherapy suggest that, whilst most of the effect of polychemotherapy on the risk of recurrence is seen in the first five years after randomisation, and is apparently maintained thereafter, more time is needed to demonstrate the full effect of therapy on the risk of breast cancer mortality as, while there is some gain during years 0-4, there is further gain thereafter, such that the absolute gain is generally at least twice as great for 15-year survival as for 5-year survival.[2] Clearly, therefore, a five-year study is not long enough to demonstrate the full impact of adjuvant chemotherapy on overall survival. Ideally, the follow-up period should extend for at least 20 years. However, in practice a ten-year follow-up period would be a reasonable compromise.

In addition, although some adverse events occur during, or shortly after, the actual treatment period, others may not manifest until many years after therapy. Prolonged follow-up is therefore needed to reliably assess long-term toxic effects such as secondary leukaemia, myelodysplastic syndrome and cardiac failure.[29]

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

4.1.1 Was the search strategy appropriate?

Only four electronic databases were searched (Medline, Embase, the Cochrane Central Register, and ASCO). Other potentially relevant databases which were not searched include CINAHL, BIOSIS, the Science Citation Index, and the proceedings of the European Society for Medical Oncology (ESMO) and the San Antonio Breast Cancer Symposium. The most recent search was undertaken on 6th December 2005.

Sufficient detail was provided to allow the search strategies to be reproduced. The Medline search strategy was rerun: it did not identify the submission's key study, BCIRG 001,[30] which was excluded by the attempt to limit the search to studies of early breast cancer (search string 14). As an equivalent search string was included in the search strategies used for the other databases, this would presumably have prevented the identification of that study, and possibly therefore other relevant studies, in those databases also; however, this was not tested.

The submission states that the electronic searches were supplemented by information from undescribed internal company data sources. The stated purpose of this was to try to identify unpublished studies. However, given the shortcomings of the electronic search strategies, it is likely that recourse to these data sources was necessary to identify published studies such as BCIRG 001.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection

There is some ambiguity in terms of the statement of inclusion/exclusion criteria used in the study selection. The criteria used to identify the studies included in the list of all RCTs comparing docetaxel with alternative therapies were:

- Population: women with node-positive early (operable) breast cancer
- Intervention: docetaxel in any dose/regimen
- Comparator: any
- Outcome: not specified
- Study type: any RCT.

However, the criteria used to identify studies for inclusion in the systematic review were more stringent:

- Population: women with node-positive early (operable) breast cancer
- Intervention: docetaxel in combination with anthracyclines
- Comparator: FAC or FEC
- Outcome: not specified
- Study type: phase III RCTs.

4.1.3 Details of studies which were identified and included in the submission

60 studies were identified which compared docetaxel with any comparator. Only five of these were said to have reported (see Table 5).

Table 5: Studies of docetaxel as adjuvant therapy of early breast cancer said in the submission to have reported

Study	Population	Intervention	Comparator	Publication status
BCIRG 001[30]	Node-positive	6 cycles of TAC	6 cycles of FAC	Peer-reviewed journal (second interim analysis only)
PACS 01[31]	Node-positive	3 cycles of FEC100 followed by 3 cycles of docetaxel 100mg/m^2	6 cycles of FEC100	Conference abstract and presentation
ECOG 2197[32]	Node-positive and high-risk node negative	4 cycles of AT	4 cycles of AC	Conference abstracts
GEICAM 9805[33]	High-risk node-negative	6 cycles of TAC	6 cycles of FAC	Conference abstracts and poster (safety data only)
USO 9735[34]	Node-positive and high-risk node-negative	4 cycles of TC	4 cycles of AC	Conference abstracts and slides (interim results)

Only one study, BCIRG 001,[30] was identified which fully met the submission's inclusion criteria by comparing the docetaxel-containing regimen recommended in the UK (TAC) with an anthracycline-containing regimen (FAC) in women with operable node-positive breast cancer.

The submission also draws data from a second study, PACS 01,[31] which has not yet been published in full. This study did not meet the submission's inclusion criteria because it used an unlicensed docetaxel regimen (FEC100-T). Sanofi-aventis did not have access to the full data from PACS 01, though they requested it.

The submission ignores data from four other potentially relevant studies which do not meet the inclusion criteria in full: these are the ECOG 2197, GEICAM 9805 and USO 9735 studies listed in Table 5 above, and the RAPP 01 trial mentioned in section 4.1.4 below. Although the populations of all four studies include women with high-risk node-negative disease, data from studies which include this patient group are not irrelevant since there is generally considered to be no evidence of heterogeneity of effect between node-positive and node-negative disease.

4.1.4 Details of any relevant studies which were not included in the submission The submission's list of all RCTs which compared docetaxel with other therapies is not complete. Additional potentially relevant studies which were not included are listed in Table 6.

Table 6: Additional potentially relevant studies of docetaxel as adjuvant therapy

Study	Population	Intervention	Comparator	Publication status
ADEBAR[35]	Operable breast cancer ≥4 positive nodes	EC4-T 100 mg/m^2 x 4 + radiotherapy	FEC6 + radiotherapy	Abstract only. Study ongoing
EORTC-p53[8]	Large operable or locally advanced breast cancers	T (unspecified dose)-EC	FEC6 or CEF6	Unpublished
Goim 9902[36]	Operable node-positive breast cancer	T 100 mg/m^2 x 4 - EC4	EC4	Abstract only. Enrolment commenced in May 1999
Taxit-216[37]	Operable node-positive breast cancer	E4-T 100 mg/m^{2}4-CMF4	E4-CMF4	Abstract only. Enrolment completed in May 2002; first planned interim analysis by May 2003

In addition, the submission stated that the French RAPP 01 trial, the North American Breast Cancer Intergroup Trial E1199, and the British TACT trial were yet to report. However, results from RAPP 01 were published in JAMA in May 2005,[38] and results from E1199 were presented at the San Antonio symposium in December 2005[39] (the same symposium at which were presented the USO 9735 results mentioned in the submission). Quality of life data from the TACT trial have also been published in abstract form.[40]

4.1.5 Description and critique of manufacturer's approach to validity assessment

The submission does not reference a quality assessment tool. Quality is assessed in relation to the three criteria required by the STA specification: randomisation, blinding and adequacy of follow-up.

It is not clear from published sources that a secure randomisation method was used in either BCIRG 001 or PACS 01. However, section 2.4.1 of the manufacturer's submission states that both studies used a secure randomisation method in which the randomisation sequence was kept away from the clinical area and administered by staff not directly involved in patient care. It is not clear how the manufacturer obtained this additional information in relation to PACS 01, given that they state that they did not have access to unpublished data from this trial, and that they state in Table 14 that information on the method of randomisation is not available for PACS 01.

The patients and clinical staff do not appear to have been blinded in either BCIRG 001 or PACS 01; this is claimed to be normal for cancer trials. It is not clear from the publications relating to either study whether the outcome assessors were blinded to treatment allocation, but the submission's response suggests that, in BCIRG 001, they were not. The US Food and Drug Administration (FDA) state that, although blinding is not essential when the outcome being measured is overall survival, it is preferred when the outcome is disease-free survival, and is necessary to minimise bias in the assessment of drug toxicity.[41]

Very few patients in either trial were lost to follow-up (fewer than 2% in BCIRG 001, none in PACS 01).

The submission states that the trial populations were representative of the population expected to be eligible for the intervention, with the exception of patients aged over 70 years or with Karnofsky performance status less than 80%. Both these groups were excluded from BCIRG 001, and patients aged over 65 were excluded from PACS 01; it is not known whether patients were excluded from PACS 01 on the basis of performance status. However, clinical advice suggests that, because of the toxicity of the chemotherapy regimens involved, the exclusion of patients aged over 70 or with Karnofsky performance status less than 80% is representative of clinical practice, and the population of BCIRG 001 is therefore representative of the population expected to be eligible for the intervention.

The submission provides details of baseline characteristics for BCIRG 001 and PACS 01, but does not highlight any differences between study groups. In BCIRG 001, the two groups appear broadly similar. However, in PACS 01 there is an excess of primary tumours $\geq$2cm in the control arm (66.5% vs 60.9%), and an excess of oestrogen-positive tumours in the docetaxel arm (76.3% vs 71.1%); these imbalances both favour docetaxel.

4.1.6 Description and critique of manufacturer's outcome selection

The primary outcome measure used in BCIRG 001 was disease-free survival, defined as time from randomisation to date of a clinical relapse, a second cancer (except skin cancer other than melanoma, ductal or lobular carcinoma in situ of the breast, or in situ carcinoma of the cervix), or death, whichever occurred first. The secondary outcome measures were overall survival (defined as time from randomisation until death from any cause), health-related quality of life, and toxic effects.

These outcome measures are appropriate. In adjuvant therapy, the prolongation of disease-free survival appears to represent intrinsic benefit rather than acting only as a surrogate for overall survival. However, the FDA advises that the magnitude of that benefit should be carefully weighed against the toxicity of the treatment.[41] As noted earlier, an overall survival gain is generally felt to be required to compensate for the toxicity of the therapy.

The tools used in BCIRG 001 to measure health-related quality of life, the EORTC QLQ-C30 and the breast cancer-specific QLQ-BR23, are appropriate for this purpose.

4.1.7 Description and critique of the statistical approach used

The submission appears to contain unbiased estimates of relative treatment effects expressed in terms of hazard ratios, adjusted when necessary to take account of possible imbalances in prognostic factors. Meta-analysis was not undertaken as only one trial was identified which used docetaxel in its licensed application.

4.1.8 Summary statement

The manufacturer's submission is complete on its own terms in that it both identifies the only study which fully fulfils the inclusion criteria and provides a full account of the relevant data which have been published in relation to that study. However, it is inconsistent in also providing a similar level of detail in relation to another study, PACS 01, which does not fully meet the inclusion criteria as it does not use docetaxel in accordance with its licensed regimen. In this respect, the submitted evidence deviates from the decision problem defined in the submission.

However, the submission is arguably incomplete in terms of clinical relevance, in that it is limited by its scope to node-positive cancer, and therefore ignores relevant data, including important safety data, from studies of docetaxel in node-positive and high-risk node-negative disease.

4.2 Summary of submitted evidence

4.2.1 Summary of results

Disease-free and overall survival

The BCIRG 001 study randomised 1491 women and followed them up for a median of 55 months. When adjusted for nodal status, TAC was associated with a hazard ratio relative to FAC of 0.72 for 5-year disease-free survival (95% CI 0.59-0.88, p=0.001), and of 0.70 for overall survival (95% CI 0.53-0.91, p=0.008). The absolute risk reduction at five years was 7% for disease-free survival and 6% for overall survival in patients receiving TAC compared with those receiving FAC.

Subgroup data are reported which indicate that TAC is associated with a statistically similar improvement in disease-free survival relative to FAC regardless of number of positive nodes (1-3 vs $\geq$4), hormone receptor status, HER2 status and menopausal status. As randomisation was only stratified by centre and node status, only the first of these is a true randomised comparison.

The PACS 01 study randomised 1999 women and followed them up for a median of 5 years. Relative to FEC100, FEC100-T was associated with an adjusted hazard ratio for 5-year disease-free survival of 0.83 (95% CI 0.69-0.99, p=0.041), and for overall survival of 0.77 (95% CI 0.59-1.00, p=0.05). The estimated absolute risk reduction at five years was 5.1% for disease-free survival and 4.0% for overall survival.

Subgroup data are reported which show that FEC100-T is associated with a greater improvement in disease-free survival than FEC100 in women with 1-3 positive nodes; in women with 4 or more positive nodes, the point estimate favours FEC100-T, but the difference between treatment groups is not statistically significant. FEC100-T is also shown to be significantly more effective than FEC100 in women of 50 and over but, surprisingly, appears to be of no benefit in those aged under 50. As randomisation was stratified by centre, node status, and age, both these subgroup analyses are true randomised comparisons. However, clinically, it seems inherently improbable that FEC100-T should benefit older and not younger women.

Adverse events

In the BCIRG 001 study, TAC was associated with a significantly higher incidence of grade 3 or 4 neutropaenia, febrile neutropaenia, and neutropaenic infections, and also with a significantly higher incidence of grade 3 or 4 anaemia, asthenia, stomatitis, diarrhoea, myalgia, amenorrhoea, and allergy, but with significantly less grade 3 or 4 nausea and vomiting. 36% of patients randomised to TAC experienced grade 3 or 4 or severe non-haematological adverse events, compared with 27% of those treated with FAC (p<0.001), and 6% of patients randomised to TAC (45/745) discontinued treatment because of adverse events, compared with 1% (8/746) randomised to FAC (p<0.001). 28.8% of patients randomised to TAC had febrile neutropaenia despite the use of a prophylactic antibiotic

(ciprofloxacin) in that arm of the trial:[30] such antibiotic prophylaxis is not current standard practice in the UK. As the submission notes, evidence from the GEICAM 9805 study of TAC versus FAC in women with high-risk node-negative cancers indicates that toxicity in patients receiving TAC can be substantially reduced by primary prophylaxis with G-CSF.[33]

In PACS 01, the results from cycles 4-6 suggest that docetaxel alone may be less toxic than FEC100: it was associated with a significantly lower incidence of grade 3 or 4 neutropaenia and nausea and vomiting than FEC100, but with a significantly higher incidence of moderate to severe oedema and nail disorders. Overall, FEC100-T was associated with significantly more grade 3-4 febrile neutropaenia than was FEC100, but with significantly less cardiotoxicity. No information was presented on the number of patients discontinuing treatment because of adverse events.[31]

As noted earlier, the FDA considers blinding of outcome assessors to be necessary to minimise bias in the assessment of drug toxicity.[41] As there is no evidence that this was done in either trial, the possibility of bias cannot be excluded.

Quality of life

The BCIRG 001 study measured health-related quality of life using the EORTC QLQ-C30 and the breast-cancer-specific QLQ-BR23 at baseline, before cycles 3 and 5, 3-4 weeks after the last cycle, and 6, 12 and 24 months after the last cycle. Mean quality of life in both groups was said to be similar at baseline, decreasing slightly in both groups by the end of treatment, and returning to near baseline at 6 months and to slightly above baseline at two years. PACS 01 is not said to have measured health-related quality of life.

4.2.2 Critique of submitted evidence synthesis

As noted earlier, no meta-analysis was undertaken. This was appropriate: no two trials which have yet published efficacy data have used both the same docetaxel regimen and the same comparator regimen.

4.2.3 Summary of clinical effectiveness

Overall and disease-free survival

The submission contains an unbiased estimate of the treatment effects seen in BCIRG 001. It also contains an unbiased estimate of the treatment effects seen in PACS 01, although these are not strictly relevant. Although in PACS 01 the treatment groups were unbalanced in relation to key prognostic factors (see section 4.1.5 above), the reported hazard ratios were adjusted to take account of these, and other, prognostic factors.

However, although both studies expressed the treatment effects as relative hazards with confidence intervals, neither published either the confidence intervals or the standard error relating to the estimated 5-year disease-free and overall survival rates. Whilst this is not surprising in PACS 01, which has not yet been published in full, it is a surprising omission from the full publication of BCIRG 001, especially since it includes confidence intervals for the mean quality of life scores.

Neither study published the numbers needed to treat to benefit (NNTB). Although these can be calculated by the method of Altman and Andersen,[42] confidence intervals for the NNTB can not be calculated in relation to either study in the absence of either the confidence intervals or the standard error relating to the estimated 5-year disease-free and overall survival rates.

The data from BCIRG 001 suggest that, if TAC is given instead of FAC, the NNTB is 14 for disease-free survival and 17 for overall survival, while PACS 01 indicates that, if FEC100-T is given instead of FEC100, the NNTB is 20 for disease-free survival and 25 for overall survival. These results suggest that the superiority of TAC over FAC is greater than the superiority of FEC100-T over FEC100.

The submission does not refer to the results of the other trials of adjuvant docetaxel versus anthracycline-containing regimens. The ECOG 2197 and USO 9735 studies were carried out in women with node-positive or high-risk node-negative breast cancer: their main results are set out in Table 7 below. ECOG 2197 found that AT was equivalent to AC. In USO 9735, TC appeared more effective than AC, although an excess of oestrogen-positive tumours in the docetaxel arm (69% vs 65%) may have favoured the intervention. The French RAPP-01 study of 4 cycles of AT versus 4 cycles of AC was also carried out in women with operable node-positive or high-risk node-negative breast cancer: this was terminated prematurely, and at that time the median follow-up of 24 months was too short to demonstrate a difference in the primary endpoint, disease-free survival at 5 years.[38] As yet, only interim safety data are available from the GEICAM 9805 study of 6 cycles of TAC versus 6 cycles of FAC in women with operable node-positive or high-risk node-negative breast cancer.[33,43]

Table 7: Docetaxel in women with node-positive or high-risk node-negative breast cancer

Study Intervention/ comparator	**Median follow-up**	**Number of patients**	**Outcome**	**Intervention**	**Comparator**	**Hazard ratio (95% CI)**	**Absolute risk reduction**
ECOG 2197[32] 4 cycles of AT 4 cycles of AC	53 months	2952	4-year disease-free survival	87%	87%	1.08 (0.89-1.31), p=0.43	0%
			Death	Not reported	Not reported	1.09 (0.84-1.43), p=0.48	Not calculable
USO 9735[34] 4 cycles of TC 4 cycles of AC	66 months	1016	Estimated 5-year disease-free survival	86%	80%	0.67 (0.50-0.94), p=0.015	6%
			Estimated 5-year overall survival	90%	87%	0.76, p=0.131	3%

The E1199 study found no significant difference between docetaxel and paclitaxel used following four cycles of AC in women with node-positive or high-risk node-negative breast cancer.[39]

Adverse effects

The submission does not mention the existence of safety data from the French RAPP 01 trial, published in JAMA in May 2005: it claims that this study has not reported. In RAPP 01, primary G-CSF prophylaxis was not given, and 41% of patients who received AT developed febrile neutropaenia, compared with 7% of those who received AC ($p<0.001$). The trial was prematurely terminated following three severe adverse events involving febrile neutropaenia with gastrointestinal disorders in patients receiving AT: two of these patients died and the third required extensive intestinal surgery. The trial investigators therefore recommended that AT should not be used outside carefully designed clinical trials.[38] While the incidence of febrile neutropaenia is lower in BCIRG 001 than in RAPP 01, presumably because of the use of a prophylactic antibiotic, the incidence is considerably higher than that generally observed with traditional chemotherapy regimens.[38]

The interim safety data available from GEICAM 9805 also indicate that, without G-CSF prophylaxis, TAC is considerably more toxic than FAC.[33,43]

EMEA considers TAC to raise "serious concerns in terms of hematotoxicity, cardiotoxicity, colitis, and leukaemia". It notes that TAC has a worse profile than FAC in relation to long-term side effects (alopecia, ongoing neuro-sensory toxicity, peripheral oedema, cardiac failure and acute leukaemia). Intensive monitoring of TAC for cardiotoxicity, secondary leukaemia, and serious gastrointestinal toxicity is ongoing.[44]

Quality of life

The BCIRG 001 study measured health-related quality of life using the EORTC QLQ-C30 and QLQ-BR23, but did not report the QLQ-BR23 results. The submission indicates that, as measured by the EORTC QLQ-C30, mean quality of life was similar in the TAC and FAC groups at baseline, end of treatment, and 6 months and 2 years after the end of treatment. Although data were also collected before cycles 3 and 5, and 12 months after the end of treatment,[30] these data were not reported, and it is therefore in theory possible that TAC is associated with worse quality of life than FAC both during treatment and, more worryingly, a year after the end of treatment.

PACS 01 did not report quality of life data. However, the TACT trial, which compared FEC4-T4 with FEC8 or E4-CMF4 in patients with operable early stage breast cancer, measured quality of life using the EORTC QLQ-C30, QLQ-BR23 and the Hospital Anxiety and

Depression Scale. This study found that, after the 8th, final, cycle of chemotherapy, FEC-T was associated with significantly worse global quality of life than FEC, and with significantly decreased physical function compared with either FEC or E-CMF. However, the magnitude of these differences was not considered to be clinically relevant, and no other significant differences in quality of life were found.[40]

Relevance of comparators

Recent meta-analyses of adjuvant chemotherapy in early breast cancer undertaken by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG)[2] suggest that, compared with no adjuvant chemotherapy, polychemotherapy (generally involving 6 or 12 months of CMF-based therapy or about 6 months of anthracycline-based treatment using combinations such as FAC or FEC) is associated with an overall relative reduction in the annual event rate of 23% (SE 0.02, $2p<0.00001$) for recurrence and of 17% (SE 0.02, $2p<0.00001$) for breast cancer mortality. When compared with no chemotherapy, CMF-based and anthracycline-based chemotherapy regimens appear comparable in efficacy. However, the more robust evidence from direct randomised comparisons of the two regimens favours anthracycline-based regimens: the latter were associated with an overall reduction in the annual event rate of 11% (SE 0.03, $2p<0.001$) for recurrence and of 16% (SE 0.03, $2p<0.00001$) for breast cancer mortality, and with an absolute difference for both recurrence and breast cancer mortality of about 3% at 5 years and 4% at 10 years, additional to that achieved with CMF.[2]

The EBCTCG study published only very limited information regarding the relative efficacy of individual anthracycline-based regimens, and did not state which studies provided the data which were combined in their meta-analyses.[2] However, it seems probable that the meta-analysis which compared anthracycline-based and CMF-based chemotherapy combined the results from studies of standard-dose and dose-intensive anthracycline-based regimens. Two more recent systematic reviews have provided details of the included randomised studies which directly compared CMF and anthracycline-based chemotherapy as adjuvant therapy in early breast cancer.[45,46] The results of the most relevant of those studies are summarised in Table 8, together with the results of the NEAT study which was too recent for inclusion in either review. As Trudeau et al note,[46] standard-dose anthracycline-based regimens generally display no benefit relative to CMF although dose-intensive regimens such as the Canadian CEF regimen are associated with improved outcomes.

The best evidence relating to the anthracycline-based regimens used either in the UK or as comparators in the docetaxel trials can therefore be summarised as follows:

- Two large, adequately-powered, trials have found that, in both node-positive and node-negative cancers, 4 cycles of AC appear to be equivalent to, and less toxic than, 6 cycles of classic CMF.[47,48] It therefore seems possible that 6 cycles of AC may be more effective than 6 cycles of CMF, but this has not yet been demonstrated.
- In the GEICAM trial, which was also large and adequately powered, a trend favouring FAC did not reach statistical significance, and thus 6 cycles of FAC appear to be equivalent to, but somewhat more toxic than, 6 cycles of intravenous CMF in node-positive and high-risk node-negative cancers.[49] As noted above, intravenous CMF appears less effective than classic CMF.
- In node-positive cancer, 6 cycles of FEC50 appear to be equivalent to 6 cycles of classic CMF, but 6 cycles of an intensive FEC50 regimen appear more effective than 6 cycles of an intensive CMF regimen. FEC is more toxic than CMF.[50]
- In node-positive and node-negative cancer, 4 cycles of epirubicin followed by 4 cycles of CMF are more effective than 6 cycles of CMF, with similar rates of adverse events.[51]

Table 8: Anthracycline-based chemotherapy regimens vs CMF as adjuvant therapy of early breast cancer

Study	Comparison (no of cycles)	No of patients	Node status	Length of follow-up	Summary of results (95% CI)	Hazard ratio (95% CI)	Comments
Carpenter 1996[52]	6 CAF (550/50/500 mg/m^2) vs 6 CMF (600/40/600 mg/m^2)	528	Node-positive	Median 5 years	5-year OS: CAF: 74% (67-81) CMF: 68% (55-81) P=NS	Not reported	Study underpowered to show a difference in overall survival. Toxicity similar in both arms.
Intergroup 0102[53]	6 CAF (as specified in section 2.3 above) vs 6 cCMF	2690	High-risk node-negative	10 years	10-year estimated DFS: CAF: 77% CMF: 75% OS: CAF: 85% CMF: 82%	DFS (CMF vs CAF): 1.09 (0.94-1.27), p=0.13 OS (CMF vs CAF): 1.19 (0.99-1.45), p=0.03	CAF did not increase DFS, and only slightly increased OS. As it also increased toxicity, the investigators did not consider it superior to CMF
GEICAM[49]	6 FAC(as specified in section 2.3 above) vs 6 ivCMF (600/60/600 mg/m^2 on day 1 of 21-day cycle)	985	Node-positive and high-risk node-negative	Median 77.7 months	5-year DFS: FAC: 58% CMF: 50% 7.5-year DFS: FAC: 55% CMF: 47%	Not reported	Randomisation was stratified by node status. There was no significant difference between FAC and CMF either overall or in N+ cancer. However, in N-

Study	Comparison (no of cycles)	No of patients	Node status	Length of follow-up	Summary of results (95% CI)	Hazard ratio (95% CI)	Comments
					P=0.056 5-year OS: FAC: 75% CMF: 69% P=NS		cancer DFS and OS were significantly higher with FAC.
Bang 2000[54]	6 AC (40/600 mg/m^2 on day 1 of 21-day cycle) vs 6 CMF	124	Node-positive	57 months	5-year RFS: AC: 64% CMF: 78% P=0.12 5-year OS: AC: 90% CMF: 86% P=0.96	Not reported	Study underpowered to show a difference in recurrence-free or overall survival.
NSABP B-15[47]	4 AC (as specified in section 2.3 above) vs 6 cCMF	1557	Node-positive	3 years	3- year DFS: AC: 62% CMF: 63% 3-year OS: AC: 83% CMF: 82%	Not reported	No significant difference in efficacy between AC and cCMF; toxicity higher with cCMF. Possibility that 6 AC might have been more effective than 6 cCMF. Results for the

Study	Comparison (no of cycles)	No of patients	Node status	Length of follow-up	Summary of results (95% CI)	Hazard ratio (95% CI)	Comments
							group receiving AC followed by delayed IV CMF not summarised here.
NSABP B-23[48]	4 AC (as specified in section 2.3 above) vs 6 cCMF	2008	Node-negative	5 years	DFS AC: 82% CMF: 83% P=0.6 OS: AC: 90% CMF: 89% P=0.4	Not reported	No significant difference in efficacy between AC and cCMF; toxicity higher with cCMF. Possibility that 6 AC might have been more effective than 6 cCMF.
Levine 1998[12,55]	6 CEF (as specified in section 2.3 above) + antibiotic prophylaxis vs 6 cCMF	710	Node-positive	Median 10 years	5-year RFS: CEF: 63% (57-68) CMF: 53% (48-58) P=0.009 5-year OS: CEF: 77% (73-82) CMF: 70% (65-75) P=0.03	5-year RFS: adjusted HR (CMF vs CEF): 1.3 (1.04-1.65), p=0.02 5-year OS: adjusted HR (CMF vs CEF): 1.22 (0.91-1.64),	CEF is associated with better RFS but greater toxicity

Study	Comparison (no of cycles)	No of patients	Node status	Length of follow-up	Summary of results (95% CI)	Hazard ratio (95% CI)	Comments
					10-year RFS: CEF: 52% CMF: 45% 10-year OS: CEF: 62% CMF: 58%	p=0.17 10-year RFS: adjusted HR (CMF vs CEF): 1.31 (1.06-1.61), p=0.007 10-year OS: adjusted HR (CMF vs CEF): 1.18 (0.94-1.49), p=0.085	
Mouridsen 1999[56]	9 CEF (IV 600, 60, 600 on day 1 of 21-day cycle) vs 9 CMF (IV 600, 40, 600 on day 1 of 21-day cycle)	1195	Group A (n=343): premenopausal, N- Group B (n=531): premenopausal, N+, HR- or unknown Group C (n=321): postmenopausal, N+, HR-	Median 61 months	6-year OS: Group A: CEF: 93% CMF: 83% P<0.01 Group B: CEF: 66% CMF: 60% P=0.2	Not reported	CEF better than CMF only in premenopausal women

Study	Comparison (no of cycles)	No of patients	Node status	Length of follow-up	Summary of results (95% CI)	Hazard ratio (95% CI)	Comments
					Group C: CEF: 50% CMF: 48% P=0.3 Groups A + B: CEF: 76% CMF: 69% P=0.01		
Coombes 1996[50]	6 FEC1 (600/50/600 on day 1 of 21-day cycle) vs 6 CMF1 (cCMF) 6 FEC2 (600/50/600 on days 1 and 8 of 28-day cycle) vs 6 CMF2 (600/40/600 on days 1 and 8 of 28-day cycle)	759	Node-positive	Median 4.5 years	Estimated 5-year OS: FEC1: 71.5% (63.1-78.9) CMF1: 77.7% (70.3-84.0) FEC2: 86.6% (80.5-91.7) CMF2: 73.8% (65.5-81.0) FEC1 vs CMF1 p=0.96 FEC2 vs CFM2 p=0.03	OS: FEC1 vs CMF1: 1.09 (0.71-1.67) FEC2 vs CMF2: 0.55 (0.33-0.91)	RFS and overall survival are better with FEC2 than with CMF2, but FEC1 seems similar in efficacy to CMF1. Toxicity is greater with FEC than with CMF.

Study	Comparison (no of cycles)	No of patients	Node status	Length of follow-up	Summary of results (95% CI)	Hazard ratio (95% CI)	Comments
Gallioioni 1997[57]	4 EC (120/600 on day 1 of 21-day cycle) vs 6 cCMF	207	Node-positive	Median 36 months	Projected 3-year DFS: EC: 72% CMF: 63% P=NS 3-year OS EC: 91% CMF: 89%	Not reported	Toxicity was significantly higher with EC than with CMF
Piccart 2001[58]	8 EC (60/500 on day 1 of 21-day cycle) vs 8 HEC (100/830 on day 1 of 21-day cycle) vs 6 cCMF	777	Node-positive	EC: 52 months HEC: 56 months CMF: 58 months	3-year DFS: EC: 72% (66-78) HEC: 80% (74-86) CMF: 78% (73-83) 3-year OS EC: 89% (85-93) HEC: 92% (89-96) CMF: 91% (87-95)	DFS: HEC vs CMF: 0.96 (0.70-1.31), p=0.80 HEC vs EC: 0.73 (0.54-0.99), p=0.04 OS: HEC vs CMF: 0.97 (0.65-1.44), p=0.87 HEC vs EC: 0.69 (0.47-1.00), p=0.05	HEC was more toxic than EC or CMF

Study	**Comparison (no of cycles)**	**No of patients**	**Node status**	**Length of follow-up**	**Summary of results (95% CI)**	**Hazard ratio (95% CI)**	**Comments**
NEAT/SCTBG BR9601 trials[51]	4 E-4 CMF vs 6 CMF	2391	Node-positive (72%) and node-negative	Median 32 months	No data	RFS: 0.70 (0.58-0.85), p=0.0003 OS: 0.64 (0.51-0.81), p=0.0001	Benefit was seen from E→CMF regardless of age, lymph node status and ER status.

cCMF: classic (Bonadonna) CMF regimen (cyclophosphamide 100 mg/m^2 orally on days 1-14, methotrexate 40 mg/m^2 and fluorouracil 600 mg/m^2 intravenously on days 1 and 8 of a 28-day cycle[12])
DFS: disease-free survival
RFS: relapse-free survival
OS: overall survival
NS: not significant

In summary, neither FAC nor standard FEC50 have been demonstrated to be superior in efficacy to CMF in early node-positive breast cancer. There are no direct randomised comparisons of FAC and FEC as adjuvant therapy of early breast cancer[2] and, as demonstrated above, indirect comparisons of this nature are not robust. However, the manufacturer's submission cites as evidence of equivalence direct comparisons of FAC with FEC50 in patients with advanced breast cancer. This evidence suggests that FAC is equivalent in efficacy to FEC50, and significantly more toxic.[21,22] No randomised trial has been identified which directly compares FEC with E-CMF but, as E-CMF is associated with significantly better relapse-free survival and overall survival than CMF, E-CMF may have greater efficacy than FEC50.

While there is evidence to suggest that no advantage is gained by increasing the dose of doxorubicin in AC in adjuvant therapy from 50 mg/m^2,[59] there is evidence that epirubicin has a dose-related response.[46] Most relevantly, the FASG 05 study found that both disease-free and overall survival were significantly increased in node-positive patients receiving adjuvant therapy with 6 cycles of FEC100 compared with those receiving 6 cycles of FEC50 (5-year disease-free survival 66.3% vs 54.8% respectively, p=0.03; 5-year overall survival 77.4% vs 65.3%, p=0.007).[19] Consequently, as FEC100 is more effective than FEC50, it may also be more effective than FAC, but it is not clear whether one might also expect FEC100 to be more effective than E-CMF.

The manufacturer's submission claims that the anthracycline-based regimens FAC, FEC, AC, EC and E-CMF are more effective than CMF, and that FAC and FEC are more effective than AC. However, the evidence summarised above indicates that neither FAC nor FEC50 have been shown to be significantly superior to CMF in early node-positive disease. Although the evidence for FAC approached statistical significance, the comparator was the apparently inferior intravenous CMF regimen rather than the classic Bonadonna regimen. In addition, although the submission emphasises the evidence that FAC and FEC50 are similar in efficacy in advanced breast cancer, it does not mention the evidence from the same trials that FAC is more toxic than FEC50.[21,22]

The submission further claims that docetaxel-containing regimens (TAC, FEC100-T, and TC) have demonstrated superior efficacy over three different anthracycline-based regimens: FAC (BCIRG 001), FEC100 (PACS 01) and AC (USO 9735) respectively. It does not mention that a fourth study, ECOG 2197, which with nearly 3000 patients is larger than any of the other three trials, found that AT (doxorubicin 60 mg/m^2; docetaxel 60 mg/m^2) was no more effective than AC, but was more toxic.[32,60,61]

5 ECONOMIC EVALUATION

5.1 Overview of manufacturer's economic evaluation

The economic evaluation model has three components:

- Adjuvant chemotherapy decision tree model
  A decision tree is used to calculate expected cost and QALY outcomes associated with the adjuvant chemotherapy treatments under consideration.
- Model of long term disease progression
  A state transition model (Markov model) is used to generate estimates of disease free survival, quality adjusted life years, and monitoring costs. These outcomes are incurred up to disease relapse or death over the lifetime of the model defined as 40 years in the base case.
- Consequences of disease relapse
  Recurrence of locoregional breast cancer or distant metastatic disease is assumed to be associated with constant cost, survival and quality of life outcomes.

The modelling of survival effects, quality of life and costs within these three components are discussed below.

5.2 Adjuvant Chemotherapy Decision Tree Component

5.2.1 Description of decision tree structure

A decision tree is used to calculate expected cost and QALY outcomes associated with the adjuvant chemotherapy treatments under consideration. These effects are assumed to be incurred over the first 6 months of treatment and are fed into the lifetime model at month 7 as a one-off adjustment. The decision tree structure is used to estimate the following:

- Costs
  - chemotherapy drug costs including administration,
  - costs of treating adverse events,
  - cost of infection prophylaxis,
- QALD – Quality adjusted life **days** lost due to adverse events.

The complete outline of the decision tree is shown in the Extract 1.

Extract 1 Complete decision tree

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Each block labelled '#' has an identical structure as shown in Extract 2, these blocks calculate the cost and health outcome payoffs for each node.

The upper arm blocks #1- #8 describe the docetaxel treatment arm, in the baseline analysis this is defined as TAC. The lower arm blocks #9 - #11 are the comparator, in the baseline model this is defined as FAC.

Node N1 is a decision (or management variable) node for including routine infection prophylaxis. In the baseline model this has been set to a policy of no routine infection prophylaxis. Thus the arm including blocks #5 - #8 are inactive and can be ignored. Note that this part of the model has been made inactive in the submission model, the cost effectiveness of TAC with routine G-CSF prophylaxis compared to FAC is not reported in the main dossier

but is reported in Appendix 4 Section 5.4 . Prophylaxis sensitivity analysis in the main report is undertaken on the number of days given not the proportion of people receiving prophylaxis.

Blocks #1 and #4 have identical adverse event profiles, that is probability (p), episodes per patient, cost per episode, duration and utility decrement (see Extract 2), for costs and QALDs, these therefore reflect the results from the whole trial arm not the adverse event subgroup as defined in the tree. Though irregular this is described and justified in Appendix 4 and does not result in any logical errors in the calculations. This is also true of blocks #5 and #8, and blocks #9 and #11.

Extract 2 decision tree block structure

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5.2.2 Adverse events

The marginal cost and quality of life impact of adverse events for TAC versus FAC are shown in Table 8 below.

The submission dossier states that Grade 3 / 4 (severe to life threatening) events were included in the model if they occurred in more than 1% of either arm and there was a difference in incidence of more than 2%.

The main cost impact derives from the increase in febrile neutropenia with docetaxel. There are smaller increases in costs of anaemia and diarrhea but these are balanced by a similar cost

saving from reduced vomiting. Note that the high increase in asthenia (reduced vitility) incurs no cost in the model.

The major quality of life impacts are from increases in febrile neutropenia and asthenia. The increased anaemia experienced with docetaxel is not associated with any quality of life loss in the model.

The cost and quality of life impact of each adverse event episode is assumed to be the same for each treatment, this would appear generally justified since events are classified as grade 3 / 4 . Due to the marked increase in febrile neutropenia, from 9% to 37%, clinical advice was taken on whether this might also be associated with an increase in higher grade adverse events, incurring a higher average cost or utility decrement per episode. This was not thought to be the case.

Adverse events were discussed with clinical advisors, no major issues were raised that would invalidate the modelling of adverse event impacts. No additional types of adverse events were identified as missing from the model.

It should be noted that the model only included adjustments for grade 3 / 4 adverse events. It should be noted that some of the grade 2 toxicities may incur additional healthcare cost. Those adverse events demonstrating a significant grade 2 difference are peripheral edema, myalgia, skin, neurosensory effects, arthralgia.

Table 9: Cost and QALD impact of adverse events with TAC and FAC

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[redacted]

5.2.3 Cost of Chemotherapy and administration

The costs of chemotherapy and administration are detailed in model Extracts 3 & 4 and the implementation of these within the decision tree is summarised in Table 9.

In the TAC arm of the model only 50% of those patients discontinuing due to adverse events receive a 2nd line therapy, 25% receive FEC and 25% CMF. Similarly in the FEC arm only 12.5% of discontinuers receive a 2nd line therapy of CMF. This issue was discussed with clinical advisors and was not deemed unreasonable as patients experiencing adverse events of sufficient severity to warrant discontinuation in the latter cycles may very well not receive further chemotherapy.

Table 10: Costs of chemotherapy and administration

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Extract 3 Costs of treatment and administration 1

Academic in confidence removed

Extract 4 Costs of treatment and administration 2

Academic in confidence removed

The cost of chemotherapy administration appears to be under-estimated, both regimens TAC and FAC are administered as day case procedures, the day case costs do not appear to have been included. These costs would be of the order of £250 (£205 HRG reference cost 2003, J21OP, Cytotoxic therapy breast and endocrine surgery[62] for each day case appointment. Similarly long term monitoring costs for adverse events have not been included in the model for instance monitoring for cardiac toxicity. It should be noted however that both these items will occur to some degree in both arms.

5.2.4 Summary critique of adjuvant chemotherapy decision tree component

The modelling of costs and quality of life impacts of therapy appear to be generally sound.

Costs of therapies have been checked against BNF prices and schedules.[63] Increased costs associated with adverse events in TAC may have been underestimated to some extent by restricting consideration to grade 3 and grade 4 events.

The BCIRG001 trial included quality of life data collection during chemotherapy, but this has not been used in the model, instead the model relies on modelling the specific impact of adverse events. This is justified qualitatively within the industrial submission but it would be reassuring to have the results of the utility model applied to the quality of life data collected within the trial treatment period.

No major issues have been raised by clinical advisors regarding this element of the model.

5.3 Model of long term disease progression

5.3.1 Long term disease relapse

A survival model is fitted to the BCIRG 001 trial data (0-5 years) and then used to predict time to relapse over 40 years. Note that in the economic submission for docetaxel this parametric model is also used to evaluate the within trial effect (0-5 years) as well as the extrapolation effects.

(Note that this modelling forms a key part of the economic analysis presented in the submission, its reporting is not concise but is spread over :

- The main submission dossier
    - Appendix 4 to the dossier
        - Appendix A to Appendix 4

- Part 1a – Embedded file in Appendix A
- Part 1b – Embedded file in Appendix A

- Appendix E to Appendix 4.

This makes it somewhat difficult to critically appraise. It should also be noted that embedded files are not apparent in printed versions of the documents.)

The parametric survival model is a non-standard mixture model. The model can be interpreted as representing for each treatment group the survival of two population subgroups, 'responders' and 'non responders'.

$S_i(t) = p_i.Snr_i(t) + (1-p_i).Sr(t)$ i - 0 FAC
1 TAC

Where $S_i(t)$ = Overall survival in treatment group i at time t,
$Snr_i(t)$ = Survival of 'non responders' in treatment group i,
$Sr(t)$ = Survival of 'responders' and
p_i = Proportion of patients in 'non responding' group.

Loglogistic models are are fitted for Snr_i with treatment specific parameters (2x2 parameters). An exponential model is fitted to Sr with no treatment specific parameters. In order to allow the model to fit low recurrence rates in the early periods, a time lag is also introduced.

The parametric survival model is fitted to the BCIRG 001 trial data, with both treatment groups being fitted concurrently. The survival model is then used to extrapolate the disease free survival out to 40 years. The disease free survival plots for 40 years reproduced from Figure 5 of Appendix 4 of the submission are shown in Figure 1.

As can be seen from Figure 1 the contribution of the Snr is negligible in both treatment groups. The key treatment impact therefore acts through the estimated p_i , that is the proportion of 'non responders' in each treatment group.

The submission model fits the trial data extremely well, but with 7 parameters for both arms the model may be over specified. The submission claims to have "undertaken extensive modelling work" to justify this model. It can be verified that exponential, Weibull, and

loglogistic models do not fit the data well, three simple graphical tests on the BCIRG 001 survival data included spreadsheet demonstrate this in Figure 2.

Figure 1: Extrapolated disease free survival used in submission model

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Figure 2: Simple graphical tests for the three alternative parametric models explored by the submission

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An investigation of the hazards over time estimated by the Kaplan Meier survival analysis indicates that the risk of recurrence is initially very small, increases to a peak between 1 and 2 years and thereafter reduces over time to the end of the trial period. This is a familiar pattern in cancer survival analysis and further explains why the simple parametric survival models investigated in Appendix 4 (and parts 1a and 1b of Appendix A to Appendix 4) fail to fit the data. Since the exponential implies a constant hazard and the Weibull implies a hazard which either increases or decreases monotonically over time. The loglogistic function can replicate this form of hazard, nevertheless, does not fit the trial data particularly well.

An alternative simple model which provides a hazard that increases to a single maximum and decreases over a skewed tail reflecting a prologed period at risk is the lognormal survival distribution. Initial investigations indicate that this model does provide a similarly good fit to each trial arm when modelled independently. In order to model treatment efficacy a baseline lognormal survival distribution could be combined with either a proportional or converging hazard. These alternative model formulations would provide a simpler and more parsimonious model of survival using 3 and 4 parameters respectively, with the advantage that uncertainty in the relative risk over the long term would be captured.

The structure of the two part survival model was discussed with clinical advisors, the structure of the model does not appear to relate to clinical hypotheses about the nature of the disease processes or epidemiology. The clinical validity of the model structure is, therefore, questionable.

The survival modelling is over complex and lacks clear clinical validity. The structure of the model, that is a constant treatment independent hazard superimposed with an early period of high risk, has two implications:

- The fact that the long term constant risk is independent of treatment means that the uncertainty in efficacy will certainly be underestimated to a very great extent.
- The assumption regarding long term risk was discussed with clinical advisors, previous experience with new treatments in breast cancer was that short term gains in disease free survival had been maintained into the longer term.[2] This implies that relative hazards in the short term have been maintained into the long term. On this subjective judgement the assumption of equal risk would be conservative. [For discussion section, the cost per QALY is highly dependent on the time horizon considered and the assumption concerning relative hazards]

5.3.2 Monitoring costs

Extract 5 presents the summary of monitoring cost included in the model.

Extract 5 Monitoring costs description

[redacted]

Clinical advisors validated the modelling of monitoring costs. All clinical advisors consulted suggested that the alternative scenario monitoring schedule most closely reflected current practice in their area. On a minor point there is no sensitivity analysis of either schedules or unit costs within the probabilistic sensitivity analysis undertaken.

5.3.3 Quality of life during disease free survival

The model uses a utility of [redacted] for disease free survival, this is from an analysis of QLQ-C30 data collected in BCIRG 001 after completion of chemotherapy for patients without further event. A non-systematic review of quality of life is presented in an appendix to the submission, the value of [redacted] is lower than the other published evidence identified. On this basis this would appear to be a conservative assumption.

5.4 Post relapse outcomes

5.4.1 Survival post relapse

The mean survival post relapse generated by the models probabilistic sensitivity analysis is presented in Figure 3 below.

Figure 3: Mean survival post relapse from submission model

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The mean survival post relapse is taken from the BCIRG001 trial. A crude truncation appoach is used to adjust survival outcomes for relapses occuring close to the time horizon of the model.

The mean survival used in the model is [redacted] months ([redacted] years) following locoregional recurrence and [redacted] months ([redacted] years) following distant metastases. The Kaplan Meier survival charts for patients experiencing loco-regional recurrence and distant metastases, taken from Appendix 4 - Appendix A Part 2 (embedded), are shown in Figure 4.

Figure 4: Survival post relapse

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It should be noted that the survival curves are truncated on the right, the mean survival figures quoted are given an event occurs.

Thus for distant metastases since the graph appears roughly exponential [redacted], a better estimate of the mean may be provided by the relationship Mean = (Median survival / ln(2)) = [redacted] / ln(2) = [redacted] months. This is a minor adjustment and would probably have little effect on the cost effectiveness.

The survival following locoregional recurrence appears more severely underestimated. Survival after loco-regional recurrence is widely different depending on whether this is recurrence within a conserved breast (good prognosis), isolated chest wall (intermediate) or extensive chest wall / nodal relapse (poor). This variation in survival is reflected in the literature, a non-systematic search for studies reporting survival following locoregional recurrence suggests average survival much longer than the [redacted] years used in the submission. For instance: Doyle et al.[64] in a US study published in 2001 found 5 year overall survival of 86% at 5 years and 69% at 10 years following breast conservation treatment following invasive locoregional breast cancer; Kamby and Sengelov[65] identified a median survival of 89

months (≈ 7.5 years) following locoregional recurrence. In this case the median would be a conservative estimate of the mean.

The impact of this error on the cost effectiveness of TAC is of itself minor, revising the mean post relapse survival to 23 months and 89 months for distant metastases and locoregional recurrence respectively raises the cost per life year gained from £7900 to £8300. It should be noted that the structure of the model means that disease recurrence has a protective effect from all other cause mortality which only acts on the disease free health state. Whilst survival post relapse was under-estimated this would have a modest impact, however the protective effect of relapse in the model will increase with longer post relapse survival times.

5.4.2 Health related quality of life post relapse

Utility weights from Hilner 1991[66] applied to average times in health states from BCIRG 001 plus validation from WGI cohort data for locoregional relapse. Distribution of overall QALYS given below together with implied overall utility weighting through comparison with survival.

Figure 5 Mean QALYs post relapse

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Figure 6 Average Utility Adjustment

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Note that the underestimation of survival post relapse as described above also impacts on the quality of life payoff. The impact of this error on the cost effectiveness of TAC is of itself minor raising the cost per QALY from £9800 to £10200.

A literature review of quality of life in women with early breast cancer is included in an Appendix to the submission. The review does not represent a full systematic review of the evidence in this area either in the scope of evidence sources consulted or in the systematicity of approach, rather a brief discussion is presented of a selection of papers identified. There is no conclusion regarding the strength of evidence. The values in the model have therefore been selected from the published evidence by a 'Clinical Advisory Panel', the basis for their choice is not described. The selected utilities are uniformly the lowest from the range of evidence presented. Whilst the impact of this on the cost effectiveness of TAC is marginal, nonetheless, it does favour docetaxel (though if the disease free quality of life is similarly increased this more than compensates).

5.4.3 Costs post relapse

Costs post relapse include 'hospital', 'hospice' and 'primary care' costs. These are built up on a monthly basis and each is further discussed below.

Primary care costs and hospice costs
Extract 6: from sheet 'Cost post relapse'#1

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Academic in confidence removed

#1 For locoregional and distant recurrence the monthly costs are incurred between months shown. Thus:

For locoregional recurrence

Months 22 – 26 cost is [redacted] x £310.22 = [redacted] - Stable and early disease

Months 27 – 29 cost is [redacted] x £486.81 = [redacted] - Late progressive disease

Month 30 cost is [redacted] x £691.91 = [redacted] - Terminal

Giving an undiscounted total cost of [redacted].

Hospice costs incurred on month [redacted] when included by sensitivity analysis.

For distant mets

Months 1 – 12 cost is [redacted] x £310.22 = [redacted] - Stable and early disease

Months 13 – 18 cost is [redacted] x £486.81 = [redacted] - Late progressive disease
Month 19 cost is [redacted] x £691.91 = [redacted] - Terminal

Giving an undiscounted total cost of [redacted].

Hospice costs incurred on month [redacted] when included by sensitivity analysis.

Hospital costs

Annual hospital costs are estimated from a survey of patients in the Western General Infirmary, Edinburgh. Bootstrapping is used to calculate annual costs (mean and standard error), these are divided by 12 to obtain monthly costs.
Costs for both locoregional and distant first relapses are incurred over 4 years. The mean hospital costs by year are shown in Figure 7.

Figure 7: Mean hospital costs

Academic in confidence removed

Total cost post relapse

Figure 8 presents the timing of costs post relapse and Figure 9 the distribution of total costs generated by the probabilistic sensitivity analysis. Extracts 7 and 8 detail the handling of these costs in the model.

Figure 8: Timing of costs post relapse

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Figure 9: Distribution of mean total cost post relapse

Academic in confidence removed

Hospital costs are estimated as being very similar for both types of relapse, both in total cost and timing of costs. The difference in cost (£[redacted] vs [redacted]) between locoregional and distant relapse in the model is almost totally due to different 'primary care' costs.

Time of occurrence of 'hospital' and 'primary care' and 'hospice' costs is inconsistent. For example in primary care end of life costs occur at months 30 and 19 for locoregional and distant relapse respectively whereas hospital costs continue to accrue until month 60 in both

cases. The impact of this is likely to be small unless considering small time horizons for instance 5-10 years.

The assumption that annual costs are normally distributed leads to negative hospital costs occurring in samples within the sensitivity analysis. The full impact of this has not been assessed though is likely to be small. Annual costs are sampled independently, which may lead to underestimation of uncertainty in costs.

Costs are assumed independent of adjuvant use of docetaxel, this is unlikely to be the case as the use of docetaxel at the early stage will impact on the choice of therapy on recurrence. There is no allowance within the sensitivity analysis for this uncertainty.

It is difficult to validate costs post relapse because of the rapid rate of change in this field, with increasing expenditure on endocrine therapy, chemotherapy including trastuzumab. However, the uncertainty in total costs post relapse would appear to be underestimated, the uncertainty in the model is generated directly from the three unrelated data sources. The generalisability of these data sources to each other and more importantly to the population eligible for TAC is not accounted for. It should be noted that a published paper[67] suggests total costs in the region of £12,500 for stage IV breast cancer, this is lower than the lower 99% CI used in the model. Using this cost, and adjusting the cost of locoregional recurrence pro-rata changes the cost per QALY gained from £9800 to £10500.

Extract 7: from ‘Cost post relapse’ sheet

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Academic in confidence removed

Extract 8: from 'Cost post relapse' sheet

Academic in confidence removed

Academic in confidence removed

5.5 Discounting

Discounting is applied throughout the model at the appropriate annual rate of 3.5% for costs and health benefits alike. This is applied across the full 40 year time horizon of the model.

5.6 Sensitivity analysis

5.6.1 Commentary on univariate sensitivity analysed presented in submission

Two sets of univariate sensitivity analyses are reported in the Appendix 4 to the submission, the first examines parametric uncertainty in the model, the second examines some structural assumptions within the model.

The first univariate sensitivity analysis consists of adjusting all parameters by +/- 50%, the results of this are presented in Table 70 of Appendix 4 to the industry submission. This analysis is flawed in that it represents an analysis of the elasticity of the model rather than reflecting the impact of uncertainty in those parameters. In addition all parameters are subjected to this analysis apart from some cost parameters and crucially the key effectiveness parameters of the two part disease free survival model. This latter is a major omission.

The second set of univariate analyses examine different structural assumptions within the model. It should be noted that the post relapse survival estimates presented in this analysis are not necessarily extreme estimates, but would reflect a best estimate from the available evidence. The major omission in this analysis related to the structural assumption that the long term disease recurrence is the same for both treatments.

5.6.2 Indirect comparisons between docetaxel and current practice

A network of evidence concerning docetaxel is presented in Figure 10. The indirect comparisons of interest, shown in dotted lines, are:
TAC compared to FEC (preferably FEC75/90),
TAC compared to E-CMF,
FEC-T ((preferably FEC75/90-T) compared to FEC (preferably FEC75/90),
FEC-T ((preferably FEC75/90-T) compared to E-CMF.

TAC compared to FEC

As noted in the clinical review concerns have been expressed about the use of FAC as the comparator in BCIRG 001. Fumoleau et al[68] note that they have, for many years, considered FEC100 to be standard treatment for node-positive breast cancer because epirubicin has been

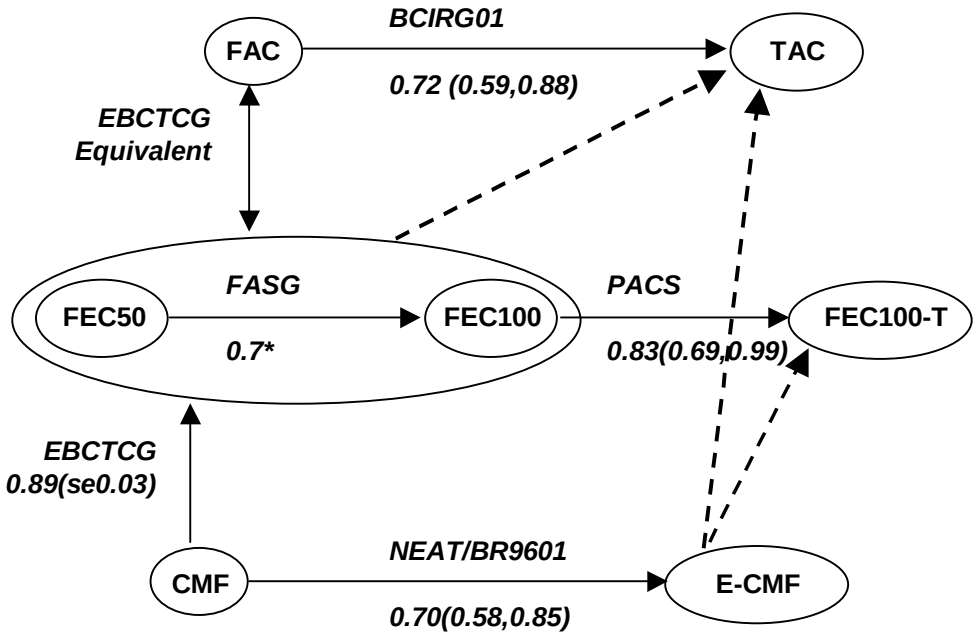
shown to be as effective and less toxic than doxorubicin, and FEC100 has been shown to be more effective than FEC50.[19] This position is compatible with the The Oxford Review,[2] that claims that FAC and FEC "appear to be of comparable efficacy", based upon the indirect comparison that demonstrates "no significant heterogeneity between the anthracycline based therapies". It should be noted that:

- the EBCTCG FEC versus FAC analysis does not take into account the different FEC dose intensities used

- and that the EBCTCG report itself identifies dangers in crude indirect comparisons, for example the indirect comparison between anthracyclines and CMF similarly identifies no significant heterogeneity in effect, whereas the meta-analysis of direct RCT evidence demonstrates a relative hazard of 0.89 (se 0.03).

The importance of this uncertainty is demonstrated by the fact that, if FAC were equivalent to FEC50, then the relative hazard for FEC100 of 0.7 would be very similar to the relative hazard for TAC of 0.72. This indirect comparison would suggest that TAC would be of similar efficacy to FEC100 but with a clear excess cost.

Figure 10: Indirect comparisons



Notes:

1. The figures represent relative hazards of disease free survival taken from 5 year follow-up data.
2. The FASG figure is estimated from the published 5 year disease-free survival rates assuming a constant hazard.
3. Indirect comparisons of interest shown in dotted arrows.

TAC compared to E-CMF

The submission presents an indirect threshold analysis for TAC compared to E-CMF. This is based on considering the 5 year disease free survival E-CMF would need to achieve in a population equivalent to that in the BCIRG 001 trial. Firstly the submission model is used to generate necessary E-CMF 5 year absolute disease free survival thresholds to achieve different levels of cost effectiveness (See Table 65 of the submission dossier) by varying the 'p' model parameter, previously defined, in the FAC arm. A series of adjustments to the NEAT absolute disease free survival rates for E-CMF are then used to justify a predicted cost effectiveness of £15,000-£20,000 for TAC compared to E-CMF. It should be recognised that all indirect comparisons are to some degree flawed. However, the comparison of absolute disease free survival rates between trials and attempts at adjustment for different populations is extremely weak and highly prone to error. A preferred method would be to construct an indirect comparison via the relative risks seen in trials.

By examining the model it is possible to calculate the average monthly relative risk of relapse over the 5 year duration implied by the model. The threshold analysis can then be undertaken using relative risks rather than absolute disease free survival. This is a much stronger

methodology than that presented in the submission. Table 11 presents the equivalent information as Table 65 in the Aventis submission.

Table 11 Relative risk of disease free survival TAC verses E-CMF for a range of IC/QALY values (cf Table 65 Aventis submission)

ICER Threshold (£/QALY)	% Responders in E-CMF arm	Average relative monthly hazard of relapse over 5yrs
£10,000	87.9%	0.75
£20,000	92.3%	0.84
£30,000	93.8%	0.88
£40,000	94.7%	0.90
£50,000	95.2%	0.91
£60,000	95.5%	0.92
£70,000	95.8%	0.93
£100,000	96.2%	0.95
E-CMF indirect estimate		**0.92**

Two possible scenarios are investigated for the next stage of the threshold analysis:

- FAC is equivalent to CMF in women with early node positive breast cancer. This assumption is supported by the review of clinical evidence presented in Section 4. Under this scenario, TAC would be essentially equivalent to E-CMF (relative hazard 0.72/0.7=1.03) and TAC would be dominated by E-CMF.
- If it is assumed that FAC is equivalent to the broad range of anthracycline regimens included in the EBCTCG review, as assumed by the Aventis submission, then the indirect comparison would suggest a relative hazard of (0.72*0.89/0.7=) 0.92 for TAC compared to E-CMF. This would imply a cost per QALY in the region of £60,000 for TAC compared to E-CMF.

Though based on relative risks rather than absolute event rates, these indirect comparisons should still be considered most uncertain. However, they are indicative that the relative efficacy and cost effectiveness of TAC compared to E-CMF must be considered unproven.

FEC-T compared to FEC

The direct RCT evidence for FEC-T[69] relates to FEC100. The key assumption here is whether or not this relative hazard would be maintained when docetaxel is used with lower doses of FEC, that is FEC75/90.

FEC-T compared to E-CMF

Assuming that CMF and FEC50 are equivalent, the indirect estimate of the relative hazard of FEC100-T compared to E-CMF is in the order of (0.83*0.7/0.7=) 0.83. It is difficult to estimate the cost effectiveness of FEC100-T compared to E-CMF from the submission model.

5.6.2 Time horizon

Figure 11 presents the impact of time horizon on the cost per life year gained and cost per QALY gained of TAC versus FAC from the baseline submission model. It can be seen that the cost effectiveness of TAC compared to FAC is very sensitive to the time horizon used up to 15 years. Beyond a horizon of 15 years the economic results are stable. The impact of different model assumptions regarding parameters and structure are likely to be magnified at time horizons up to 15 years.

Figure 11 Impact of time horizon on cost effectiveness of TAC versus FAC

Academic in confidence removed

5.6.3 Paclitaxel versus docetaxel

As discussed in the appraisal of clinical evidence, paclitaxel and docetaxel have been demonstrated to be of equivalent efficacy in a randomised controlled trial reported at the San Antonio Breast Cancer Symposium 2005.[39] This trial compared 4 regimens, all regimens were based upon 4 cycles of AC given 3 weekly, that is doxorubicin 60mg/m2 and cyclophosphamide 600mg/m2, followed by either 3 weekly or weekly paclitaxel or docetaxel. The drug costs for these regimens based upon BNF 2005 prices[63] and an average body surface area of 1.7m^2 are presented in Table 11. Note that these costs exclude the costs of

administration and therefore the weekly dosing costs particularly will be underestimated. The costs presented in Table 12 assume unused vial contents are wasted, some of the cost differential between regimens reflects different wastage rates on a person of average body size. The cost of 3 weekly paclitaxel, both generic and branded, and docetaxel regimens are very similar and would not justify differentiating on economic grounds on this evidence.

Table 12 Costs of paclitaxel and docetaxel in trialed regimens

	Dose	Cost per cycle	Cost per course
Doxorubicin	60mg/m^2	£206	
Cyclophosphamide	600mg/m^2	£8	
Paclitaxel 3 weekly	175mg/m^2	£1,043	£5,029
(generic)		£1,010	£4,895
Docetaxel 3 weekly	100mg/m^2	£1,232	£5,784
Paclitaxel weekly	80mg/m^2	£1,565	£7,116
(generic)		£1,683	£7,587
Docetaxel weekly	35mg/m^2	£977	£4,761

5.7 Results

Table 13 presents the baseline economic results for TAC compared to FAC from the industrial submission. The headline incremental cost per life year gained and cost per QALY gained are approximately £7900 and £9800 respectively.

Table 13 Baseline economic results for TAC compared to FAC presented in the docetaxel submission

Estimates of Costs and Outcomes

	TAC	*FAC*	*Incremental*
Costs (deterministic mean per patient)			
Cost of chemotherapy and administration	£7,173	£1,263	£5,910
Cost of supportive G-CSF	£963	£353	£609
Cost of managing adverse events	£1,014	£499	£514
Monitoring cost for patients in remission	£620	£590	£30
Cost of treatment for relapsing patients	£9,301	£10,257	-£956
Total expected cost	**£19,071**	**£12,963**	**£6,108**
Outcomes (deterministic)			
Patients discontinuing due to AEs (percentage)	6.04%	1.07%	4.97%
Life Years (mean per patient)	10.926	10.155	0.771
QALYs (mean per patient)	8.374	7.753	0.621

The probabilistic results in the table below reflect the most recent run of the probabilistic simulation. If alternative analyses have been made without re-running the probabilistic model, they will not reflect the current analysis.

Incremental Cost-Effectiveness Ratio (ICER) Estimates

	Point Estimate of mean		*95% Confidence Intervals*	
	Deterministic	*Probabilistic*	*Lower*	*Upper*
Incremental Cost /LYS	**£7,924**	£7,956	£7,349	£8,704
Incremental Cost/QALY	**£9,838**	£9,857	£7,788	£16,044

A number of issues have been highlighted in the review that impact on the estimated cost effectiveness of TAC compared to FAC, in order to give an indication of the combined impact of these issues the industrial submission model has been adjusted. These adjustments are limited to modifications to the parameters within the model. Modifications requiring structural amendments were not within the scope of the review.

The following amendments are included:

- Survival duration post relapse increased,
- Cost of relapse reduced in line with published study,
- Quality of life estimates post relapse increased in line with published evidence,
- Monitoring costs schedule utilise alternative schedule,
- Costs of adverse events have been increased by 50%.

Under the adjusted model the incremental cost per life year gained and cost per QALY gained are approximately £9200 and £11800 respectively.

Table 14 Economic results for TAC compared to FAC from an adjusted model

Estimates of Costs and Outcomes

	TAC	*FAC*	*Incremental*
Costs (deterministic mean per patient)			
Cost of chemotherapy and administration	£7,173	£1,263	£5,910
Cost of supportive G-CSF	£963	£353	£609
Cost of managing adverse events	£1,521	£749	£772
Monitoring cost for patients in remission	£769	£737	£32
Cost of treatment for relapsing patients	£5,482	£6,042	-£561
Total expected cost	**£15,908**	**£9,145**	**£6,763**
Outcomes (deterministic)			
Patients discontinuing due to AEs (percentage)	6.04%	1.07%	4.97%
Life Years (mean per patient)	11.238	10.501	0.736
QALYs (mean per patient)	8.798	8.223	0.575

The probabilistic results in the table below reflect the most recent run of the probabilistic simulation. If alternative analyses have been made without re-running the probabilistic model, they will not reflect the current analysis.

Incremental Cost-Effectiveness Ratio (ICER) Estimates

	Point Estimate of mean		*95% Confidence Intervals*	
	Deterministic	*Probabilistic*	*Lower*	*Upper*
Incremental Cost /LYS	**£9,187**	£7,932	£7,289	£8,641
Incremental Cost/QALY	**£11,760**	£9,760	£7,805	£15,561

5.8 Model validation reported within the submission

5.8.1 Survival over the BCIRG 001 trial period

The industrial submission reports validation of the life years generated over 5 years for both treatment arms and the life years gained by the model, this statistic compares well with the results from the trial BCIRG001.

Figure 12 presents the overall survival in the BCIRG 001 trial[30] together with survival curves taken from the submission model. It can be seen that the survival generated by the model does not follow the trial survival curves. This is would appear to be an artefact of the way in which the survival post relapse is modelled. The model combines first order estimates (ie patient level) on disease free survival, with second order (ie mean) estimates of post relapse survival. Though the model does not fit the data well in the short term it is unclear how this impacts on long term estimates of life years and perhaps more importantly life years gained between treatments.

Figure 12 Modelled versus trial survival from BCIRG 001

Academic in confidence removed

5.8.2 Modelling of overall survival over 5 years

The industrial submission reports validation of the modelled disease free survival at 5 years, this statistic compares well with the results from the trial BCIRG001.

The uncertainty analysis presented in the submission is based upon Monte Carlo sampling of the parameters within the 2 part model, the parameters are sampled independently. It is possible to estimate an average relative monthly hazard between the two treatment arms from the information presented in the model. For the baseline analysis using the 2 part model this is estimated at [redacted] with a 95 percentile range of [redacted]. It would appear that, even apart from the long term hazard being assumed equal between treatments, the probabilistic analysis grossly underestimated the uncertainty in efficacy, it should be noted that the relative instantaneous hazard from BCIRG 001 is 0.72 (0.59,0.88). If the 'p' parameter is varied, following the method described in the submission document for the E-CMF threshold analysis, to give 5 year relative monthly hazard similar to the range achieved in the BCIRG 001 trial, the range for the cost per QALY of TAC compared to FAC is (£3,927, £33,460).

5.9 Summary and discussion of manufacturers economic evaluation

TAC compared to FAC

No evidence of systematic bias has been found in the primary economic analysis of TAC compared to FAC, presented within the Aventis submission. There are a number of small issues, however, within this analysis that should be taken into consideration these are summarised below:

- The modelling and extrapolation of relapse is overcomplicated and lacks clinical validity. The model replicates trial duration disease free survival and the assumption of a constant long term treatment independent hazard is probably conservative. Two issues may impact adversely on cost effectiveness
    - If long term survival in the comparator FAC arm is underestimated the relative risk for TAC will overestimate the benefit of treatment.
    - The use of constant post relapse survival in the model may disguise any mediating effects of other cause mortality in the model.
- Post relapse survival and QALYs have been underestimated by using the data from the BCIRG trial. This particularly effects survival post locoregional recurrence and favours docetaxel.
- Costs post relapse may have been overestimated, though it should be born in mind that costs in this area have been increasing rapidly over recent years with the advent of new more expensive therapies. If this is the case then this favours docetaxel.
- Uncertainty is grossly underestimated. Two sources of uncertainty have not been adequately captured in the economic submission model, both relate to the 2 part model used to model disease recurrence.
    - Firstly, the parametric uncertainty incorporated does not generate relative risks of disease recurrence in the same order as seen in the BCIRG 001 trial. That is the model generates relative risks of recurrence in the range [redacted] compared to (0.59,0.88) within the trial.
    - Secondly and with potentially an even greater impact, the structure of the model precludes any uncertainty about the relative long term efficacy of docetaxel.

  Since both these uncertainties relate directly to the effectiveness of therapy, the uncertainty in cost effectiveness will be skewed. Increasing this uncertainty will have a tendency to increase the mean cost effectiveness.

The submission model generates central estimates of the cost per life year gained and cost per QALY gained of TAC compared to FAC of £7900 and £9800 respectively. It is the ERGs opinion that a revised model taking into account the issues identified here may generate higher estimates of cost effectiveness but it is unlikely that these estimates would exceed £35,000 per QALY gained.

Indirect comparisons with current practice

FAC is not in common use in the UK. On the basis that the onus is on the manufacturer's submission to prove efficacy and cost effectiveness, what has to be demonstrated is that TAC is more economically attractive than FEC75-100 and / or E-CMF. In the absence of direct RCT evidence, the crucial links are the indirect comparisons between FAC and FEC75-100 or E-CMF.

The manufacturer's submission claims that FAC is equivalent to FEC. It supports this claim with reference to clinical opinion and direct comparisons carried out in metastatic cancer. However, whilst these studies show no difference in effectiveness, they compare FAC with a doxorubicin dose of 50 mg/m^2 and FEC with an epirubicin dose of 50 mg/m^2. Furthermore, studies in adjuvant therapy have identified a dose response for epirubicin, but not for doxorubicin.

The evidence together with clinical opinion would appear to indicate that the effectiveness of FAC lies somewhere between that of FEC50 and FEC100. The cost effectiveness of TAC compared to FEC75-100 depends crucially on where within this range the efficacy of FAC lies. If FAC is equivalent to FEC50, as suggested by the studies referred to in the submission, then a crude indirect comparison based upon the relative risks of disease-free survival up to 5 years suggests that TAC may not be more effective than FEC100, and would in that case be dominated economically by FEC100. This may be an extreme assumption, though has some support in evidence presented by the French Adjuvant Study Group,[68] the economic superiority of TAC compared to FEC100 must therefore be considered unproven on the basis of the industrial submission.

Similarly, there is no direct statistically significant evidence that FAC is superior to CMF in adjuvant therapy. The manufacturer's submission refers to the meta-analysis carried out by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG)[2] to support their assumption that FAC is superior to CMF. However, this meta-analysis lumps together all anthracycline-based therapies, and consequently the results are driven by dose-intensive regimens such as the Canadian CEF regimen. As E-CMF has been shown to be superior to CMF, the relative efficacy of TAC to E-CMF is unclear.

The industry submission predicts a cost effectiveness of £15,000-£20,000 per QALY gained for TAC compared to E-CMF. This estimate is based upon an indirect comparison of absolute disease-free survival rates, and as such is severely flawed. The review of the clinical evidence concludes that the superiority of TAC over E-CMF is unproven; an exploratory analysis based on an indirect comparison of relative risks suggests a cost per QALY may be in the order of £60,000.

Comparison of the unlicensed regimen FEC-T

The industry submission estimates the cost effectiveness of FEC100-T to be £8,200 (£3500, £56,000) per QALY compared to FEC100.

In considering FEC-T compared E-CMF an indirect comparison of relative risks from randomised controlled trials would suggest a potential relative risk in the order of 0.83, it has not been possible from the economic model in the industry submission to estimate the associated cost per QALY for FEC-T compared to E-CMF.

6 DISCUSSION AND CONCLUSIONS

6.1 Summary of clinical effectiveness results

There is RCT evidence that, compared with the anthracycline-based regimen FAC, TAC is associated with superior disease-free and overall survival at 5 years (hazard ratio 0.72, 95% CI 0.59-0.88, p=0.001, and 0.70, 95% CI 0.53-0.91, p=0.008, respectively). The absolute risk reduction at five years in patients who had received TAC, compared with those who had received FAC, was 7% for disease-free survival and 6% for overall survival, and the number of patients who had to be treated with TAC rather than FAC to for one additional patient to benefit was 14 for disease-free survival and 17 for overall survival. However, TAC was associated with significantly greater toxicity than FAC.

There is also RCT evidence that, compared with the anthracycline-based regimen FEC100, FEC100-T, a sequential regimen in which docetaxel is used after FEC100, is associated with superior disease-free and overall survival at 5 years (adjusted hazard ratio 0.83, 95% CI 0.69-0.99, p=0.041, and 0.77, 95% CI 0.59-1.00, p=0.05, respectively). The estimated absolute risk reduction at five years in patients who had received FEC100-T compared with those who had received FEC100 was 5.1% for disease-free survival and 4.0% for overall survival, and the number of patients who had to be treated with FEC100-T rather than FEC100 for one additional patient to benefit was 20 for disease-free survival and 25 for overall survival.

However, there is no evidence that TAC, the docetaxel regimen which is licensed for use in the UK, is superior to either of the two anthracycline-based regimens in most common use in the UK, E-CMF and FEC with an epirubicin dose higher than 50 mg/m^2. Consequently, the evidence that TAC is superior to FAC is of limited interest since it is not clear that FAC is superior to either E-CMF or FEC75-100.

6.2 Summary of cost effectiveness results

An economic model is developed, based primarily on the single trial BCIRG001. This submission model generates central estimates of the cost per life year gained and cost per QALY gained of TAC compared to FAC of £7900 and £9800 respectively.

The manufacturer's submission predicts a cost effectiveness of £15,000-£20,000 per QALY gained for TAC compared to E-CMF. This estimate is based upon an indirect comparison of absolute disease-free survival rates.

Based upon the randomized controlled trial of FEC100-T compared to FEC100, the manufacturer's submission estimates the cost effectiveness of FEC100-T to be £8,200 (£3500, £56,000) per QALY compared to FEC100.

6.3 Commentary on the robustness of results

The submitted clinical evidence depends primarily on an interim analysis from one trial, BCIRG 001, which uses docetaxel in its licensed regimen (TAC). This is a large study carried out in a population which appears to be representative of the population for whom adjuvant docetaxel is licensed and who are expected to be eligible to receive it. However, there is no evidence that the study outcome assessors were blinded to treatment allocation, although the FDA recommends such blinding when disease-free survival is measured, and consider it necessary to minimize bias in the assessment of drug toxicity. FAC, the anthracycline-based regimen used as the comparator in the trial, is not in common use in the UK, and therefore the submitted evidence does not demonstrate that TAC is superior to the anthracycline-based regimens which are in common use.

No evidence of systematic bias has been found in the primary economic analysis of TAC compared to FAC, presented within the manufacturer's submission. It is the ERG's opinion that a revised model taking into account a number of modelling issues identified by the ERG may generate higher estimates of cost effectiveness, but it is unlikely that these estimates would exceed £35,000 per QALY gained. The industrial submission presents a probabilistic sensitivity analysis of uncertainty in the economic estimates; the certainty in the cost effectiveness estimates is overestimated.

The economic evidence for docetaxel compared to therapies in current use in the UK is less robust than that for TAC versus FAC, as there is no direct evidence that addresses the key underlying relative efficacies between TAC and current therapies. The uncertainty in efficacy carries through to the economics of TAC so that an economic benefit of TAC compared to FEC100 or E-CMF is unproven.

6.4 Issues requiring further work

A number of issues have been raised with the completeness of the uncertainty analysis in the economic elements of the submission, particularly with respect to the disease free survival modelling. Since the uncertainty in cost effectiveness is liable to be skewed this is liable to impact on the central estimates of cost per life year gained and cost per QALY gained. The extent of this impact is hard to assess without further analytical work outside the scope of this review.

6.5 Conclusions

Docetaxel has been licensed for use in combination with doxorubicin and cyclophosphamide (TAC) for the adjuvant treatment of women diagnosed with operable node-positive breast cancer.

Evidence from a large randomised controlled trial demonstrates that TAC is superior to the anthracycline-based FAC regimen in terms of disease-free and overall survival at 5 years. However, the same evidence suggests that TAC is associated with significantly greater toxicity than FAC.

Importantly, FAC is not commonly used in clinical practice the UK. The most common adjuvant chemotherapy regimens currently in use in the UK are FEC using an epirubicin dose of 75mg/m^2 or greater or E-CMF (that is, epirubicin in sequential therapy with CMF). FAC has not been demonstrated to be superior to these anthracycline regimens.

The industrial submission fails to report the premature termination of the French RAPP 01 trial following three fatal or life-threatening adverse events in patients receiving docetaxel with doxorubicin. Furthermore, the submission does not mention the EMEA's concern regarding TAC's long-term adverse events, as a result of which intensive monitoring for cardiotoxicity, secondary leukaemia, and serious gastrointestinal toxicity is ongoing.

There also exists RCT evidence that docetaxel, in an unlicensed sequential regimen FEC100-T, is associated with superior disease-free and overall survival at 5 years compared to FEC100.

The health economic model, submitted by the Sanofi-Aventis estimates that TAC has a cost effectiveness in the order of £10,000 per QALY gained compared to FAC. Indirect comparisons presented within this review suggest that the economic case for TAC in comparison to current UK practice is not proven. As part of the unlicensed FEC100-T regimen, the industrial submission estimate of cost effectiveness for docetaxel is in the order of £10,000 per QALY gained compared to FEC100, a comparator that is currently used in the UK.

It should be noted that the scope, as currently defined within the submission, excludes women with high-risk node-negative cancers and does not include docetaxel used in sequential therapy, although current clinical opinion appears to favour such regimens rather than combination regimens such as TAC. The limitation of the comparators to anthracycline-based regimens excludes paclitaxel, another taxane which, like docetaxel, is licensed for use in the UK as adjuvant therapy for operable node-positive breast cancer, in sequential therapy following treatment with doxorubicin and cyclophosphamide.

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