NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Dabrafenib for treating unresectable, advanced or metastatic BRAF^{V600} mutation-positive melanoma

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- The manufacturer's submission only includes people previously untreated for BRAF^{V600} mutation-positive advanced or metastatic melanoma, which is a subgroup of the population covered by the marketing authorisation of dabrafenib and that specified in the final scope. The manufacturer highlighted the lack of comparative evidence in people previously treated. Is the Committee satisfied with the population addressed in the manufacturer's decision problem?
- What is the Committee's view on the most appropriate comparator for dabrafenib in clinical practice?
- What is the Committee's view on the generalisability of the BREAK-3 trial to clinical practice in England?

- The ERG did not agree with the manufacturer's explanation that the lack of an overall survival benefit in BREAK-3 was caused by crossover from the dacarbazine arm to the dabrafenib arm. The ERG conducted an analysis of the survival data, which showed that patients in the dacarbazine arm who crossed over did not gain any significant benefit over patients that did not crossover.
  - Does the Committee consider that overall survival could have been underestimated because of crossover?
- The manufacturer adjusted for crossover using the rank preserving structural failure time (RPSFT) method. However the ERG indicated that the inverse probability of censoring weighting (IPCW) method may be more appropriate (see section 4.12 for further details). Which method does the Committee consider to be more appropriate to adjust for crossover in BREAK-3?
- Does the Committee consider the BREAK-3 and BRIM-3 trials to be comparable?
- Does the Committee accept the ERG's view that dabrafenib and vemurafenib cannot reliably be compared using the available data?

Cost effectiveness

- Should the adjusted or unadjusted overall survival results be used in the cost-effectiveness analysis and end-of life considerations?
- What is the Committee's view on the manufacturer's approach to modelling survival, given the following issues highlighted by the ERG:
  - censoring data at the date of last observation rather than at data-cut
  - using a log-normal distribution to represent the whole trial period
  - not using the latest overall survival from the January 2014 data-cut, although unadjusted for crossover
  - generalisability of the AJCC registration data to the UK population
  - estimating overall survival from year 10 to year 30 using mortality rates from UK general population life tables
  - using the proportional hazards assumption to model the dacarbazine and vemurafenib arms
- The ERG noted that the majority of the estimated QALY gain with dabrafenib in the manufacturer's model occurs after disease progression (62% for the

comparison with dacarbazine and 93% for the comparison with vemurafenib). The ERG explained that this is largely attributable the approach used by the manufacturer to model survival (see section 6.14). Does the Committee consider the manufacturer's estimates to be plausible?

- The ERG indicated that any estimated ICERs generated for the comparison with vemurafenib would be unreliable and likely to be misleading, given that the proportional hazards assumption required for the indirect comparison was not valid (please see section 6.15 for more details). The ERG therefore restricted any detailed numerical comparisons to the direct evidence from the BREAK-3 trial for dabrafenib compared with dacarbazine.
  - What is the Committee's view of the ERG's rationale for not providing amended cost-effectiveness results comparing dabrafenib with vemurafenib?
  - What is the Committee's view on the cost-effectiveness of dabrafenib compared with vemurafenib?
- For the comparison with dacarbazine, does the Committee agree with the ERG's exploratory analyses, including the adjustments to the manufacturer's model? Which ICER does the Committee consider to be most plausible?
- Does the Committee consider that dabrafenib has met all the end-of-life criteria required for end-of-life considerations and that the estimates are robust?

1 Background: clinical need and practice

1.1 Melanoma is a type of skin cancer which in its early stages is normally asymptomatic and, if detected early, before it has spread, can be curable by resection. Melanoma can spread to nearby lymph nodes (stage III) or to other parts of the body (stage IV). People with an above-average mole count, sun-sensitive skin, or a strong family history of melanoma are at increased risk. BRAF is part of the RAS/MAPK signalling pathway, which helps to control cell proliferation, differentiation and death. $BRAF^{V600}$ mutation is found in approximately 50% of malignant melanomas.

1.2 There were 11,121 new diagnoses of malignant melanoma and 1,871 deaths registered in England in 2011. In England, melanoma is diagnosed

at a mean age of around 50 years but approximately 20% of cases occur in young adults aged between 15 and 39 years old. Five-year survival rates are approximately 20-30% for stage IIIc melanoma and approximately 7-20% for stage IV melanoma.

1.3 Early recognition of melanoma and accurate diagnosis presents the best opportunity for cure by surgical resection of the tumour. A small minority of people with advanced disease can still have their tumour removed. Current standard of care for people with a $BRAF^{V600}$ mutation is normally vemurafenib, but dacarbazine and ipilimumab are also treatment options. NICE technology appraisal guidance 269 recommends vemurafenib as an option for treating $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma only if the manufacturer provides vemurafenib with the discount agreed in the patient access scheme. NICE technology appraisal guidance 319 recommends ipilimumab as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme.

2 The technology

2.1 Dabrafenib (Tafinlar, GlaxoSmithKline) is a selective ATP-competitive BRAF (serine/threonine-protein kinase BRAF) inhibitor. When the activity of mutant protein kinase is blocked, the cancer cells stop growing and die. Dabrafenib has a marketing authorisation in the UK in monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V^{600} mutation.

2.2 The summary of product characteristics lists the following very common adverse reactions for dabrafenib: papilloma, decreased appetite, headache, cough, nausea, vomiting, diarrhoea, hyperkeratosis, alopecia, rash, palmar-plantar erythrodysaesthesia syndrome, arthralgia, myalgia, pain in extremity, pyrexia, fatigue, chills and asthenia. For full details of

adverse reactions and contraindications, see the summary of product characteristics.

2.3 The list price of dabrafenib is £1,400 per 75 mg, 28-capsule pack and £933.33 per 50 mg, 28-capsule pack (excluding VAT; 'British national formulary' [BNF] edition 67). It is taken orally at a recommended dose of 150 mg twice daily. The manufacturer of dabrafenib has agreed a patient access scheme with the Department of Health, which makes dabrafenib available with a discount of [redacted] applied to all invoices. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of dabrafenib within its licensed indication for the treatment of unresectable, advanced or metastatic BRAF V^{600} mutation-positive melanoma.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	People with advanced or metastatic $BRAF^{V600}$ mutation-positive melanoma	Adults with previously untreated advanced or metastatic $BRAF^{V600}$ mutation-positive melanoma.

The manufacturer stated that there is insufficient evidence from the clinical trials with which to build an economic argument for the use of dabrafenib in people with $BRAF^{V600}$ mutation-positive metastatic melanoma who have received prior therapy. The ERG agreed that relative comparative evidence only exists for treatment naïve patients.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Intervention	Dabrafenib monotherapy	Same as scope

	Final scope issued by NICE	Decision problem addressed in the submission
Comparators	For people with previously untreated melanoma: • dacarbazine (or temozolomide for people whose melanoma has metastasised to the brain) • vemurafenib For people with previously treated melanoma: • dacarbazine (or temozolomide for people whose melanoma has metastasised to the brain) • ipilimumab • vemurafenib	Previously untreated patients • vemurafenib • dacarbazine

The manufacturer stated that there is insufficient evidence from the clinical trials to build economic arguments for comparing dabrafenib with dacarbazine, vemurafenib and ipilimumab in patients with previously treated melanoma and with temozolomide in patients whose disease has metastasised to the brain. The ERG noted that ipilimumab is currently recommended only in people previously treated for malignant melanoma. The ERG also agreed that although temozolimide is an appropriate comparator for patients with metastasis to the brain, relevant evidence is only available for dacarbazine and vemurafenib.

	Final scope issued by NICE	Decision problem addressed in the submission
Outcomes	• progression-free survival • overall survival • response rate • adverse effects of treatment • health-related quality of life	Same as scope

	Final scope issued by NICE	Decision problem addressed in the submission
Economic evaluation	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.	• Cost-effectiveness will be expressed in terms of an incremental cost per quality-adjusted life year, over a lifetime horizon • Costs will be considered from an NHS and PSS perspective • Medication costs (for interventions and comparators) will incorporate available patient access schemes

3.2 The manufacturer proposed dabrafenib as an alternative treatment option to vemurafenib and dacarbazine for previously untreated advanced or metastatic BRAF^{V600} mutation-positive melanoma.

4 Clinical-effectiveness evidence

4.1 The key clinical evidence came from the pivotal phase III trial – BREAK-3, which was an international, multi-centre, randomised, open-label active-controlled trial comparing dabrafenib with dacarbazine in patients previously untreated for unresectable advanced or metastatic BRAF^{V600} mutation-positive melanoma. The manufacturer also provided supportive evidence from 4 other trials of dabrafenib, including 2 randomised-controlled trials (BRF113220 and Combi-d) and 2 non-randomised-controlled trials (BREAK-2 and BREAK-MB). However none of these trials

included comparators relevant to the decision problem; therefore they were not included in a quantitative analysis.

4.2 Patients in BREAK-3 were randomly assigned in a 3:1 ratio to receive either 150 mg of dabrafenib twice daily orally (n=187) or 1000 mg/m^2 of body-surface area of dacarbazine by intravenous infusion every 3 weeks (n=63). Previous immunotherapy (interleukin-2), surgery or radiotherapy was allowed at trial entry. Baseline patient characteristics were generally similar between the treatment groups. The mean age was 53.5 years in the dabrafenib arm and 51.6 years in the dacarbazine arm of the trial. Approximately 67% of patients had an ECOG performance status of 0. The manufacturer stated that most patients had undergone surgery previously and adjuvant immunotherapy with interferon was the most common prior anti-cancer therapy.

4.3 The manufacturer conducted 2 separate analyses based on 2 different cut-off dates (December 2011 and June 2012) for the primary outcome of investigator-assessed progression-free survival and all secondary outcomes. For the outcome of overall survival, the manufacturer conducted a third analysis based on a later cut-off date (December 2012). In response to the NICE request for clarification, the manufacturer presented a more recent overall survival data with a cut-off date in January 2014.

4.4 Table 1 shows that there was a 63% reduction in disease progression at the second analysis time point (June 2012) for patients receiving dabrafenib compared with patients receiving dacarbazine. The median progression free survival was 6.9 months for dabrafenib compared to 2.7 months for dacarbazine, resulting in a statistically significant difference of 4.2 months (hazard ratio [HR] 0.37, 95% confidence interval [CI] 0.24 to 0.58, ($p<0.0001$). The manufacturer reported results from a range of pre-specified subgroups, including age, sex, ECOG performance status, disease stage lactate dehydrogenase levels and number of disease sites.

The results showed that the progression-free survival benefit conferred by dabrafenib treatment was generally maintained across each subgroup.

4.5 Results from the December 2012 analysis of BREAK-3 showed an improvement of 2.6 months in the key secondary outcome of median overall survival, which was 18.2 months in the dabrafenib group compared with 15.6 months in the dacarbazine group. However, the difference between the treatments was not statistically significant (HR 0.76, 95% CI 0.48 to 1.21, p-value not presented).The manufacturer explained that approximately 57% of patients assigned to receive dacarbazine had crossed over to the dabrafenib arm at the time of the analysis conducted in December 2012. Therefore, the manufacturer adjusted the overall survival results using the rank preserving structural failure time (RPSFT) model.The RPSFT-adjusted analysis showed that treatment with dabrafenib reduced the risk of mortality by 45% compared with dacarbazine, although the difference between the treatments was not statistically significant (HR 0.55, 95% CI 0.21 to 1.43). The analysis based on the January 2014 data-cut was not adjusted for crossover, and the results showed a median overall survival of [redacted] in the dabrafenib group compared with [redacted] in the dacarbazine group, with a difference of [redacted] and a hazard ratio of [redacted] The manufacturer specified that a crossover-adjusted analysis of the final data from BREAK-3 would be completed at a later date.

Table 1 Progression-free survival and overall survival results from the BREAK-3 trial comparing dabrafenib with dacarbazine.

All (n = 416)	Dabrafenib (n=187) (95% confidence interval)	Dacarbazine (n=63) (95% confidence interval)	Hazard Ratio Unadjusted ITT population (95% confidence interval)	Hazard ratio RPSFT adjusted (95% confidence interval)
Median Progression free survival (months) at 25th June 2012 data cut	6.9 (5.2 to 9.0)	2.7 (1.5 to 3.2)	0.37 (0.24 to 0.58)	Not applicable
Median Overall survival (months) at 18th December 2012 data cut	18.2 (16.6 to NR)	15.6 (12.7 to NR)	0.76 (0.48 to 1.21)	0.55 (0.21 to 1.43)
RPSFT= Rank Preserving Structural Failure Time, I TT = Invitation to treat, NR=Not reached.				

Source: manufacturer's submission (table1, page 10)

4.6 Health-related quality of life (HRQoL) was assessed in BREAK-3 using the EuroQoL (EQ-5D) utility index. EQ-5D data were collected at screening, week 6, week 12, week 15, at disease progression, and at approximately 30 days after disease progression. HRQoL data was collected for all of the participants in the trial.

Table 2 EQ-5D utility index in the BREAK-3 trial

Treatment	N	Time	N	Mean	SD
Dabrafenib	187	Baseline	184	0.724	0.266
		Week 6	165	0.774	0.215
		Week 12	136	0.795	0.193
		Week 15	135	0.777	0.206
		Progression	37	0.599	0.355
		Week 4 Post-PD	8	0.839	0.256
Dacarbazine	63	Baseline	59	0.717	0.309
		Week 6	33	0.787	0.248
		Week 12	19	0.824	0.179
		Week 15	18	0.845	0.163
		Progression	26	0.671	0.299
		Week 4 Post-PD	3	0.701	0.394
Post-PD=post-progressive disease, SD=standard deviation					

Source: manufacturer's submission (table 25, page 89)

Indirect treatment comparison

4.7 To estimate the effectiveness of dabrafenib compared with vemurafenib, the manufacturer conducted an indirect treatment comparison, using data from the BREAK-3 and BRIM-3 trials, in the absence of head-to-head trials comparing dabrafenib and vemurafenib. BRIM-3 was a phase III, multicentre, randomised, open label, active-controlled trial that compared vemurafenib (960 mg twice daily orally; n=337) with dacarbazine (1000mg/m^2 of body surface area; n=338). The study population comprised of adults who were previously untreated for advanced or metastatic BRAF^{V600} mutation-positive melanoma. Patients in BRIM-3

were similar to patients in BREAK-3 in terms of age, sex, ECOG status and disease stage. However, the trials differed in proportion of patients with elevated lactate dehydrogenase (BREAK-3=34%; BRIM-3=58%), sample size (BREAK-3, n=250; BRIM-3, n=675), ratio of randomisation (BREAK-3, 3:1; BRIM-3, 1:1) and median follow-up time at their latest cut-off points.

4.8 Overall survival and progression-frees survival were joint primary outcomes in BRIM-3. The manufacturer explained that approximately 34% of patients assigned to receive dacarbazine had crossed over to the vemurafenib arm at the time of the analysis conducted at the latest cut-off date (February 2012). The RPSFT method was also used to adjust for crossover. The results using the February 2012 data-cut showed statistically significant differences between vemurafenib and dacarbazine for the primary outcomes as follows:

- progression-free survival (HR 0.38, 95% CI 0.32 to 0.46, p<0.001)
- unadjusted overall survival (HR 0.76, 95% CI 0.63 to 0.93, p-value not presented)
- RPSFT-adjusted overall survival (HR 0.64, 95% CI 0.53 to 0.78, p-value not presented)

4.9 The manufacturer conducted the indirect comparison using the method described by Bucher et al. 1997, based on the assumption that the patient characteristics between BREAK-3 and BRIM-3 were similar. Results of the indirect comparison found no difference in progression-free survival (HR 0.97, 95% CI 0.59 to 1.60) and overall survival (unadjusted HR 1.00, 95% CI 0.62 to 1.62; crossover-adjusted HR 0.86, 95% CI 0.32 to 2.29) between dabrafenib and vemurafenib.

Adverse events

4.10 Data from the December 2012 cut-off showed that the most commonly reported adverse events with dabrafenib were skin-related toxic effects (hyperkeratosis, palmar-plantar erythrodysaethesia, papillomas), pyrexia,

fatigue, arthralgia, alopecia, nausea and headache. These adverse events occurred more frequently in the dabrafenib arm than in the dacarbazine arm, except for nausea, which had a higher incidence in the dacarbazine arm. Treatment-related adverse events, adverse events leading to discontinuation of trial treatment and adverse events leading to dose reduction or interruption were not reported for the December 2012 analysis. However, for the December 2011 analysis, treatment-related adverse events occurred with a higher frequency in the dabrafenib arm (88%) than in the dacarbazine arm (73%), whereas the incidence of adverse events leading to discontinuation of trial treatment or dose reduction were similar between the treatment arms. The manufacturer stated that 1 patient in the dabrafenib arm died from elective euthanasia, but it did not consider this to be caused by dabrafenib treatment.

Evidence Review Group Comments

4.11 The ERG was satisfied that all relevant studies with the appropriate comparisons were included in the manufacturer's analysis. In general, it concluded that BREAK-3 was a good quality trial. The ERG agreed that evidence from the BREAK-3 trial show that treatment with dabrafenib was associated with progression-free survival benefits compared with dacarbazine. However, it did not agree with the manufacturer that crossover in BREAK-3 explained the lack of an overall survival benefit with dabrafenib because an analysis of the survival data showed that patients in the dacarbazine arm who crossed over did not gain any significant benefit over patients that did not cross over.

4.12 The ERG did not consider the RPSFT method used to adjust for cross-over in BREAK-3 to be appropriate for the following reasons:

- survival data is immature as it was not based on the final trial data, but rather an interim analysis with few deaths
- the 'common treatment effect assumption required for the RPSFT method is not valid because the effect of dabrafenib treatment when

received on diagnosis (that is, in the dabrafenib group) would not be the same as when received on disease progression (that is, in the dacarbazine group that crossed over to receive dabrafenib)

- patients in the dabrafenib arm and dacarbazine arm did not receive similar treatments at the time of disease progression, and some received treatments which are not used in routine clinical practice in the UK.

The ERG stated that it would have been more appropriate to use the inverse probability of censoring weighting (IPCW) method to adjust for crossover, given that it could appropriately adjust for all treatment deviations while still estimating the causal estimate of interest. However, it acknowledged that the immaturity of the overall survival data and subsequent small number of deaths may invalidate the use of the IPCW method at present.

4.13 Regarding the manufacturer's indirect treatment comparison, the ERG was satisfied that the BREAK-3 and BRIM-3 trials were broadly similar in terms of patient population and eligibility criteria. However it noted that a greater proportion of patients in BRIM-3 had lactate dehydrogenase levels above the upper limit of the normal range than patients in BREAK-3. The ERG commented that this may have a negative effect on the prognosis of patients in BRIM-3 compared to patients in BREAK-3. The ERG questioned the validity of the approach used to conduct the indirect comparison given that the assumption regarding constant hazard ratios for progression-free survival and overall survival within BREAK-3 and the assumption regarding constant proportional hazards for dacarbazine overall survival between the two trials were not met. The ERG also commented that in view of the issues regarding adjustment for crossover in the individual trials, it is more appropriate to use the unadjusted hazard ratios in the indirect treatment comparison. The ERG also noted that the most recent overall survival data from BREAK-3 trial (January 2014 data cut) had not been used in the manufacturer's indirect treatment

comparison. In view of these issues, the ERG stated that the evidence from the manufacturer's indirect treatment comparison was not robust, therefore it was unable to comment on the clinical effectiveness of dabrafenib compared with vemurafenib.

5 Comments from other consultees

5.1 Consultees commented that patients with the $BRAF^{V600}$ mutation-positive melanoma are currently treated with vemurafenib in clinical practice, and that dacarbazine is not commonly used now in these patients. Consultees noted that dabrafenib is another BRAF inhibitor that could be used in clinical practice as an alternative to vemurafenib or in patients who respond to vemurafenib initially and then become intolerant beyond 2 months. Consultees also noted that ipilimumab immunotherapy recently received a licence for first-line treatment of $BRAF^{V600}$ mutation-positive melanoma and also, other immunotherapies such as PD-1 inhibitors are currently being tested in this patient group. Therefore they suggested that immunotherapy was likely to be used increasingly as a first-line treatment option and BRAF inhibitors used subsequently given that immunotherapy is more effective in patients with good performance status and life expectancy of 12 weeks or more, whereas the BRAF inhibitors target poor performance status and high volume disease progressing rapidly. They also indicated that combination therapy reduce the risks of side effects and may supersede monotherapy in the next few years.

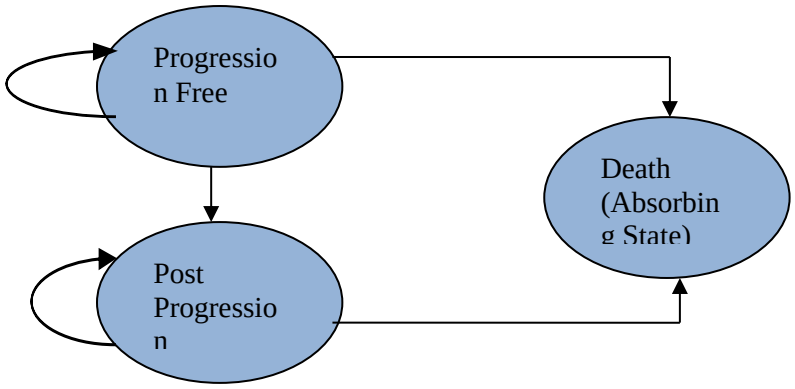
5.2 Comments from Consultees indicated that dabrafenib and vemurafenib have similar side effect profiles in that they can cause cutaneous squamous cell carcinomas. However, dabrafenib is not associated with phototoxicity as seen with vemurafenib, although it is associated with the development of pyrexia and grover's disease in a small proportion of patients. The Consultees stated that treatment with dabrafenib would take place in pre-existing specialist oncology clinics with oncologists and

dermatologists involved, and that additional professional input such as specialist cancer nurses would be needed to support the patients.

6 Cost-effectiveness evidence

6.1 The manufacturer submitted a de novo '3-state partitioned survival' model comparing dabrafenib with dacarbazine and vemurafenib, for previously untreated unresectable advanced or metastatic BRAF^{V600} mutation-positive melanoma. The manufacturer considered a partitioned survival model to be more appropriate than a Markov model because it uses distributions of progression free survival and overall survival as model inputs and therefore ensures that the model results match those observed in the trial for the duration of the trial. Patients were assumed to enter the model in the 'progression-free' health state, and in each cycle could either remain in that state or progress to a worse state, that is, the 'post progression' health state or 'death' state. The model had a lifetime horizon of 30 years consisting of weekly cycles and no half-cycle correction. The manufacturer based the analysis from an NHS and personal social services perspective, and costs and benefits were discounted at an annual rate of 3.5%.The mean age of the model population was 53 years. The manufacturer explained that it was not possible to estimate the cost effectiveness of dabrafenib in adults who had received prior treatment due to insufficient clinical data being available. No subgroup analyses were conducted by the manufacturer.

Figure 1 Model structure



6.2 For the comparison with dacarbazine, the proportion of people in each health state in the manufacturer's model was estimated based on survival functions for investigator-assessed progression-free survival and overall survival using the June 2012 and December 2012 data cut-offs respectively from BREAK-3. The manufacturer fitted independent log-normal distributions to individual patient data for progression-free survival for both treatment arms from time zero using accelerated failure time (AFT) regression. The fitted curves were then extrapolated beyond the trial period (defined as 53.1 weeks for dacarbazine and 71.1 weeks for dabrafenib based on the last censor or observed failure time for progression-free survival) to 30 years. The manufacturer stated that the log-normal distribution provided the best fit to the data based on goodness of fit statistics and area under the curve comparisons.

6.3 The manufacturer modelled overall survival in the dabrafenib arm in 3 phases:

- Phase 1: The manufacturer fitted the log-normal distribution to individual patient data from the dabrafenib arm of BREAK-3 for the trial period only (defined as 96 weeks based on maximum censor or failure time for overall survival) using AFT regression.
- Phase 2: From the end of trial follow-up and up to 10 years, the manufacturer applied hazard rates obtained by fitting the log-logistic distribution to the overall survival data from the American Joint Committee on Cancer (AJCC) registry reported by Balch et al. (2009), which was weighted by the relative proportions of patients according to disease stage in BREAK-3.
- Phase 3: For the remaining duration of the model, the manufacturer modelled survival by applying mortality rates obtained from UK general population Life Tables.

6.4 The manufacturer stated that there are uncertainties associated with fitting parametric curves to the data from the RPSFT analysis for the

dacarbazine arm because of the small number of patient in the analysis. Therefore, it modelled overall survival for the dacarbazine arm as proportional hazards versus dabrafenib using the RPSFT-adjusted hazard ratio from BREAK-3. This hazard ratio was applied for the trial period of 96 weeks, after which no further treatment effect was assumed.

6.5 For the comparison with vemurafenib, the manufacturer applied the progression-free survival and overall survival hazard ratios from the indirect treatment comparison to the parametric survival curves used to model the dabrafenib arm. Proportional hazards were assumed throughout the entire model timeframe for progression-free survival, whereas for overall survival, it was assumed for the trial period of 96 weeks only.

6.6 Treatment-specific EQ-5D utility data for pre-progression and post-progression derived directly from BREAK-3 was used in the model for dabrafenib and dacarbazine. The manufacturer did not calculate the decrement in post-progression utility for dacarbazine because of potential confounding due to crossover in BREAK-3. Given that there was no rationale to assume that health-related quality of life after progression would differ between treatments, the manufacturer assumed that the post-progression utility value for dacarbazine would be the same as that for dabrafenib. In the absence of comparable EQ-5D utility data for vemurafenib, the manufacturer assumed that the vemurafenib utility values would be the same as those for dabrafenib. Disutilities associated with adverse events were not included in the model because the manufacturer considered the impact of adverse events on quality of life to be captured within the pre- and post-progression health state utility values. Health related quality of life was assumed to be constant over time within each health state.

Table 3 Utility estimates in the manufacturer's model.

	Dabrafenib/ Vemurafenib		Dacarbazine	
Decrement in Utility	**N**	**Actual utility value used**	**N**	**Actual utility value used**
Progression-free vs. perfect health	187	0.767	60	0.750
Post-progression vs. progression-free	37	0.677	*	0.677

Source: manufacturer's submission (table 53, page 153)

6.7 Costs incorporated in the manufacturer's model included drug costs, dispensing costs for dabrafenib and vemurafenib, administration cost for dacarbazine, BRAF testing, post-study anti-cancer therapy, costs associated with health states and adverse events. The costs of dabrafenib and vemurafenib were estimated using the patient access schemes provided by the manufacturers, whereas the cost of dacarbazine was based on the list price. The drug and administration costs were adjusted for the relative dosing intensities observed in BREAK-3 to account for dose reductions, treatment interruptions and differences between the distribution of time to discontinuation and the distribution of progression-free survival. The manufacturer applied the same relative dosing intensities for dabrafenib to vemurafenib in the absence of data for vemurafenib. Estimates of the costs of treating adverse events were based on the results of a cost-of-illness study commissioned by the manufacturer. The cost of treating each adverse event was then calculated by multiplying the incidence of the adverse event (derived from BREAK-3 and BRIM-3) by the expected cost of the adverse event. The post study anti-cancer therapy costs were estimated to be £3,013 for dabrafenib and vemurafenib and £6,044 for dacarbazine. In addition, one-off costs of £337 and £6,177 were assumed for treatment initiation and death respectively, regardless of treatment received.

Table 4 Summary of costs in the manufacturer's economic model

Cost Parameter	Value
Technology cost - Dabrafenib	[redacted] with PAS for 28 days
Technology cost - Dacarbazine	£82 for 28 days
Technology cost - Vemurafenib	[redacted] with PAS for 28 days
Dispensing cost - Dabrafenib and Vemurafenib	£13.40 every 28 days
Administration cost - Dacarbazine	£203.16
BRAF testing – Dabrafenib and Vemurafenib	£206.34 per treated patient
Progression-free survival health state cost	£127
Post-progression survival health state cost	£333
Treatment initiation	£337
Death	£6177
Post-study anti-cancer therapy – Dabrafenib and Vemurafenib	£3013
Post-study anti-cancer therapy - Dacarbazine	£6044

Source: manufacturer's submission (tables 54 to 61, pages 159 to 164)

6.8 The base-case results for the incremental analyses are shown in the table below. For the pairwise analyses, the incremental cost-effectiveness ratio (ICER) was £49,019 per quality adjusted life year (QALY) gained for dabrafenib compared with dacarbazine and £11,028 per QALY gained for dabrafenib compared with vemurafenib.

Table 5 Base-case cost-effectiveness results for dabrafenib (with PAS) versus dacarbazine.

	Dacarbazine	Vemurafenib	Dabrafinib
Total costs (£)	[redacted]	[redacted]	[redacted]
Total life year gain	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs (£)	-	[redacted]	[redacted]
Incremental life year gain	-	[redacted]	[redacted]
Incremental QALYs	-	[redacted]	[redacted]
ICER (£) vs baseline (QALYs)	**-**	**60,980**	**49,019**
ICER (£) incremental (QALYs)	**-**	**Extended dominance**	**49,019**

Source: manufacturer's submission (table 70b, page 183)

6.9 The manufacturer's probabilistic analysis showed that if the maximum acceptable amount for an additional QALY was £30,000 then dabrafenib would have a 56% probability of being cost effective compared with vemurafenib and a 6% probability compared with dacarbazine. However, if the maximum acceptable amount for an additional QALY was £50,000 then dabrafenib would have a 43.5% probability of being cost effective compared with dacarbazine.

6.10 The manufacturer conducted a series of deterministic sensitivity analyses (for further details, see table 72 of the manufacturers submission). For the comparison with dacarbazine, overall survival was the key driver of the cost-effectiveness results. When the RPSFT-adjusted hazard ratio for overall survival was varied using the 95% CI, the ICERs ranged from £26,470 per QALY gained to dabrafenib being dominated by dacarbazine. The key driver of the cost-effectiveness result for the comparison with vemurafenib was the progression free survival assumption; varying the hazard ratio using the 95% confidence interval resulted in ICERs ranging from a scenario where dabrafenib dominated vemurafenib to £67,220 per QALY gained. The manufacturer explained that progression free survival determined the duration of treatment, and in this case

[redacted]. The cost effectiveness estimate for dabrafenib compared with vemurafenib was also sensitive to the overall survival hazard ratio used in the model, assuming a class effect between dabrafenib and vemurafenib and using alternative distributions to model survival. Changes to the time horizon, cost parameters and utility values did not have a huge impact on the base-case ICER.

Figure 2 Tornado diagram for dabrafenib vs. vemurafenib

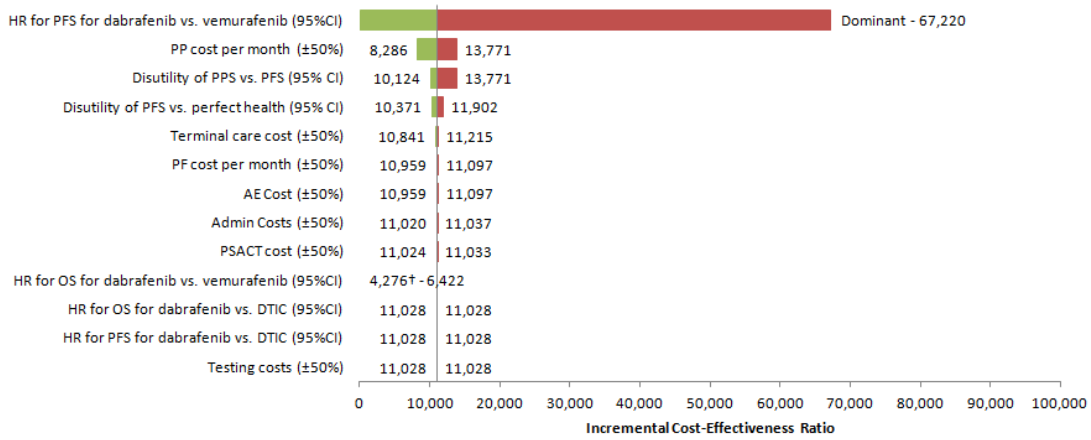
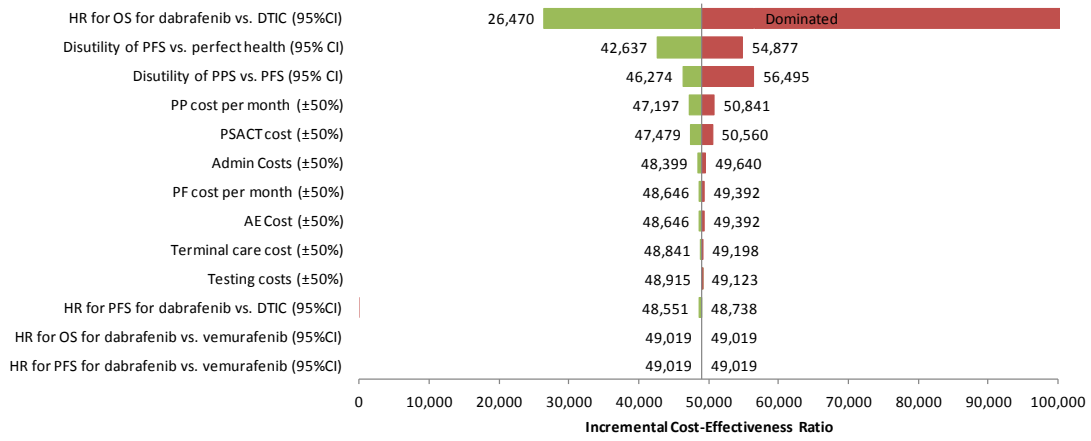


Figure 3 Tornado diagram for dabrafenib vs dacarbazine



Source: manufacturer's submission (Figures 16 and 17, page 185)

Evidence Review Group comments

6.11 The ERG stated that the assumptions around the clinical effectiveness model inputs were the main drivers of the manufacturer's cost effectiveness estimate. The ERG noted that the manufacturer censored progression-free and overall survival data at the date of last observation, which could misrepresent survival projections when used to calibrate parametric survival functions. It considered that censoring survival data at the date of data-cut would have been more appropriate in order to remove any bias from informative censoring.

6.12 The ERG noted that the manufacturer modelled overall survival in 3 phases and it considered this approach to be complex and associated with several limitations:

- Phase 1 (from randomisation until 96 weeks [1.8 years]): The ERG stated that the log normal distribution used to represent the whole period of the trial follow-up was questionable as the log-normal distribution is known to have a long tail, and therefore overestimates overall survival gain. The ERG also considered that it would have been more appropriate to use the most recent overall survival data available from BREAK-3 (January 2014).
- Phase 2 data (from 1.8 to 10 years): The ERG noted that the manufacturer did not present evidence to support the clinical or biological plausibility of the log-logistic distribution fitted to the AJCC registry data used in this phase. It also noted that the registry data is based on a North American population and therefore may not be representative of the UK population.
- Phase 3 data (from 10 to 30 years): The ERG noted that this approach assumes that long term survivors are effectively cured of metastatic disease without any supporting evidence

6.13 The ERG noted that the dabrafenib parametric model was used as a basis for modelling survival for the first 10 years in the dacarbazine and

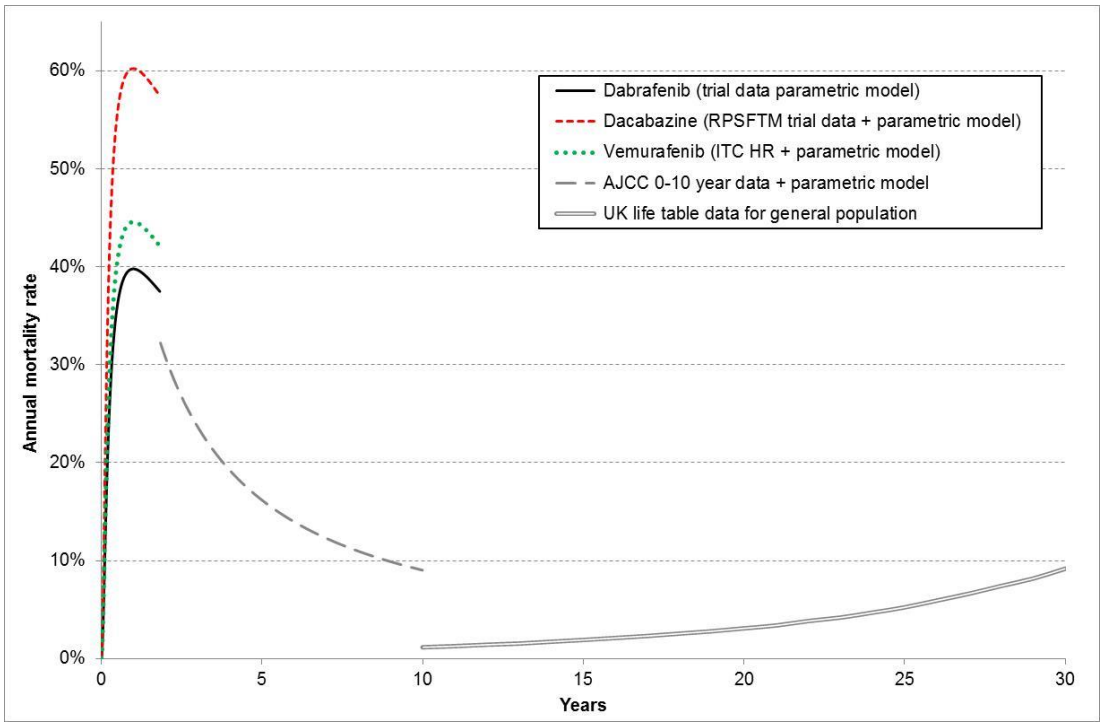
vemurafenib arms and was concerned that the manufacturer's assumption of proportional hazards across the three treatments may not be valid. The ERG indicated that the reliability of this approach was strongly affected by the assumptions around the RPSFT-adjusted hazard ratio from BREAK-3 used to model the dacarbazine arm. It also indicated that the hazard ratio estimated from the indirect treatment comparison with vemurafenib was not reliable and any cost-effectiveness assessment of dabrafenib and vemurafenib using this estimate would not be robust. Therefore the ERG did not conduct any further assessment of the comparison with vemurafenib.

6.14 The ERG noted that the majority of the estimated QALY gain in the manufacturer's model (62% for the comparison with dacarbazine and 93% for the comparison with vemurafenib) arises from the estimated life-years after disease progression. It also noted that the estimated mean survival in the manufacturer's model was 58 months for dabrafenib and 35 months for dacarbazine, which is much larger than is normally observed in clinical trials or in registry data. The ERG explained that 2 aspects of the model contributed to these results, including:

- the use of the RPSFT-adjusted survival data from BREAK-3 resulted in a large survival difference between dabrafenib and dacarbazine after 96 months
- the structure of the model in three phases involves applying mortality rates from different sources which are not compatible, and seriously underestimate death rates, so extending estimated survival times over many years. The ERG drew attention to the sudden changes in mortality rates at 96 months and 10 years in the manufacturer's model, which lack any clinical or epidemiological justification.

These 2 features of the model serve to establish a large early survival advantage for dabrafenib at 96 months, which is then extended over 3 decades by the over-optimistic modelling of mortality.

Figure 2 ERG plot of the mortality rates in the manufacturer's base case analysis



Source: ERG report (Figure 5, page 70)

Evidence Review Group exploratory analyses

6.15 The ERG noted that a comparison of the cost effectiveness of dabrafenib and vemurafenib depends on an indirect treatment comparison between the BREAK-3 and BRIM-3 trials, in order to generate progression-free survival and overall survival hazard ratios. The ERG examined the trial results and found that the proportional hazards ratio assumption was not valid within each trial and between the dacarbazine arms of the trials; therefore, robust hazard ratios for dabrafenib compared with dacarbazine could not be obtained. The ERG concluded that any estimated ICERs generated by this indirect comparison would be unreliable and likely to be misleading. The ERG therefore restricted any detailed numerical comparisons to the direct evidence from the BREAK-3 trial for dabrafenib compared with dacarbazine.

6.16 For the comparison with dacarbazine, the ERG used alternative methods to derive the clinical effectiveness model inputs. The ERG revised the censoring of progression-free survival data for some patients still at risk at the end of the trial to reflect the date of data-cut rather than the date of last observation. It then used the area under the curve approach to model progression-free survival in the early variable segment and an exponential projective function for the latter period. The ERG stated that using their progression free survival estimates in the manufacturer's model resulted in a small increase in the incremental QALYs per patient (+0.16%). However, the increase in the incremental cost per patient was much larger (+6.32%) because of the additional days of treatment with dabrafenib. The ICER resulting from this change increased from £49,019 to £52,035 per QALY gained.

Table 6 Comparison of estimated lifetime progression-free survival between the manufacturer's base case and the ERG's long-term projection method

	Manufacturer's base case PFS estimates (months)		**ERG long-term projection PFS Estimates (months)**	
Treatment	**Dabrafenib**	**Dacarbazine**	**Dabrafenib**	**Dacarbazine**
AUC PFS	-	-	6.69	3.31
Projected PFS	10.69	4.73	4.28	1.46
Total PFS	10.69	4.73	10.97	4.76
PFS gain	+5.96	-	+6.21	-
AUC = Area under the curve, PFS = Progression free survival				

Source: ERG report (table 24, page 81)

6.17 The ERG analysed the latest overall survival data from the January 2014 data-cut and concluded that the risk of bias introduced through the choice of censoring method is small, and could only possibly affect the last few recorded events in each trial arm. The analysis, therefore, was carried out without any post-hoc adjustments. The ERG was aware that the latest overall survival data was unadjusted for cross over. However it noted its earlier analysis which showed no statistically significant survival difference

between the patients in the dacarbazine group who crossed over and the patients who did not cross over (see section 4.11). The ERG then modelled overall survival by using the area under the curve survival data until a long term trend was established and then applying the long-term exponential function throughout the rest of the trial period, that is, 1.8 years. It continued to apply the long-term exponential projection derived from BREAK-3 data throughout the manufacturer's phase 2 time period, that is, up to 10 years. The ERG noted that all patients had died at the end of 10 years; therefore it restricted the modelling to 10 years rather than 30 years assumed by the manufacturer.

6.18 The ERG's analysis resulted in an overall survival gain of [redacted] compared with [redacted] in the manufacturer's base case. To assess the clinical plausibility of its estimates, the ERG used an alternative parametric model used in the appraisal of vemurafenib (NICE technology appraisal guidance 269) to fit the updated BREAK-3 data. This resulted in an overall survival gain of [redacted] with dabrafenib, which is close to the ERG's estimate.The analysis using the ERG's method also showed a large reduction in the incremental life years (-68.3%) and incremental QALYs gained per patient (-35.7%), but a smaller decrease in incremental cost per patient (-11.4%). The ICER resulting from the ERG's analysis increased from £49,019 to £99,560 per QALY gained for dabrafenib compared with dacarbazine.

Table 7 Comparison of estimated mean lifetime overall survival between the manufacturer's base case (RPFSTM-adjusted, December 2012 data-cut) and the ERG long-term projection method (unadjusted, January 2014 data-cut)

	Manufacturer's base case OS estimates (months)		**ERG simple long-term projection OS estimates (months)**	
Treatment	**Dabrafenib**	**Dacarbazine**	**Dabrafenib**	**Dacarbazine**
AUC OS	-	-	[redacted]	[redacted]
Projected OS	[redacted]	[redacted]	[redacted]	[redacted]
Total OS	[redacted]	[redacted]	[redacted]	[redacted]
OS gain	[redacted]	-	[redacted]	[redacted]
AUC = Area under the curve, OS=Overall survival				

Source: ERG report (table 25, page 83)

6.19 The ERG made several amendments to the dacarbazine acquisition and administration cost estimates, which increased the incremental cost by £86 per patient and increased the ICER for dabrafenib compared with dacarbazine by £87 per QALY gained. The amendments include:

- changing the patient body-surface area estimate to a normal distribution as opposed to a log-normal distribution in the manufacturer's submission
- incorporating sex as a factor when calculating the average doses by using data on sex balance in BREAK-3.
- using the most recently reported eMIT prices for dacarbazine applied in a more efficient manner across the population body surface area range to achieve an estimate of overall mean cost per dose of £35.79 in place of the manufacturer's estimate of £58.36 per dose.
- updating the dacarbazine administration cost using the most recent NHS Reference Costs 2012/13, resulting in an increase from £203.16 to £214.16 per dose.

6.20 The ERG applied equal costs for post-study anti-cancer treatment to the dabrafenib and dacarbazine groups given that the difference between the post-study treatments received in BREAK-3 were not statistically

significant. This amendment increased the ICER by £3,047 per QALY gained for dabrafenib compared with dacarbazine. Combining all the ERG's exploratory analyses and model amendments together resulted in an ICER of £112,727 per QALY gained.

7 End-of-life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	In the BRIM-3 trial (February 2012 data-cut) the median overall survival was of 13.6 and 9.7 months for patients treated with vemurafenib and dacarbazine respectively. In the BREAK-3 trial, the median overall survival was 15.6 months for dacarbazine.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	In the BREAK-3 trial, the median overall survival was 18.2 and 15.6 months respectively for dabrafenib and dacarbazine, a difference of 2.6 month.
The treatment is licensed or otherwise indicated for small patient populations	The population with unresectable or metastatic melanoma with a BRAFV600 mutation in England and Wales is estimated to be 990 per annum based on 2013 Cancer Research UK data based on the manufacturer's submission.

7.1 The manufacturer stated that dabrafenib met the NICE end-of-life criteria because updated analysis from BRIM-3 (February 2012) confirmed that median overall survival was 13.6 months with vemurafenib and 9.7 months with dacarbazine. The manufacturer also estimated a maximum of 990 patients would be eligible for treatment with dabrafenib per annum in England and Wales and this figure was consistent with the estimate provided by the manufacturer of vemurafenib in the same indication. The manufacturer stated that the estimated log-normal and AJCC survival extrapolations employed in the economic evaluation confirmed that dabrafenib gave an extension to life of at least 3 months in comparison with dacarbazine (incremental median overall survival was 7.5 months).

7.2 The ERG noted that the manufacturer's base-case economic model used a mean survival in the dacarbazine arm of [redacted]. It stated that the results of the BREAK-3 trial indicate the median overall survival to be 18.2 and 15.6 months with a difference of only 2.6 months. The ERG therefore indicated that using the figures from the clinical data in the manufacturer's submission shows that the criteria for end-of-life treatment has not been met.

8 Equality issues

8.1 No potential equality issue were raised at the scoping workshop, or in the evidence submitted.

9 Innovation

9.1 The manufacturer stated that that dabrafenib was innovative because it is a step-change in the management of metastatic melanoma as until very recently, the standard first-line management of metastatic melanoma irrespective of BRAF mutation status was with dacarbazine, an intravenously administered cytotoxic agent, associated with poor response rates and no survival benefit. The manufacturer stated that like vemurafenib, dabrafenib achieves high response rates and prolongs progression free survival compared with dacarbazine and is more convenient to administer due to its oral formulation.

10 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. NICE technology appraisal guidance 319 (2014).
- Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. NICE technology appraisal guidance 269 (2012).

NICE pathways

- There is a NICE pathway on dabrafenib, which is available from http://pathways.nice.org.uk/pathways/melanoma

Appendix B: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002604/WC500149673.pdf