Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2184

dacomitinib 15mg, 30mg and 45mg film-coated tablets (Vizimpro®)

Pfizer Ltd

9 August 2019

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and orphan medicine process

dacomitinib (Vizimpro®) is accepted for use within NHSScotland.

Indication under review: as monotherapy, for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations.

In an open-label, randomised, phase III study, dacomitinib significantly improved progression-free survival compared with another EGFR tyrosine kinase inhibitor in adults with locally advanced or metastatic NSCLC with EGFR-activating mutations.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of dacomitinib. This advice is contingent upon the continuing availability of the PAS in NHSScotland or a list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

As monotherapy, for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations.[1]

Dosing Information

EGFR mutation status should be established prior to initiation of dacomitinib therapy.

The recommended dose of dacomitinib is 45mg taken orally once daily, until disease progression or unacceptable toxicity occurs. Patients should be encouraged to take their dose at approximately the same time each day. Dose modifications may be required based on individual safety and tolerability. The Summary of Product Characteristics (SPC) contains advice regarding dose modification and management for specific adverse reactions.

Treatment with dacomitinib should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.[1]

Product availability date

May 2019. Dacomitinib meets SMC orphan equivalent and end of life criteria.

Summary of evidence on comparative efficacy

Dacomitinib is a second generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor. It is a human EGFR (HER) (EGFR/HER1, HER2, and HER4) inhibitor, with activity against mutated EGFR with Ex19del or L858R. It binds selectively and irreversibly to HER family targets thereby providing prolonged inhibition.[1, 2]

The key evidence comes from a randomised, open-label, phase III study (ARCHER 1050) which compared dacomitinib with gefitinib. Eligible patients were aged ≥18 years (≥20 years in Japan and Korea) with newly diagnosed stage IIIB/IV or recurrent NSCLC, confirmed as adenocarcinoma. Those with recurrent disease were required to have a disease-free interval of ≥12-months between completing adjuvant or neoadjuvant therapy and recurrence. Patients also had at least one confirmed EGFR mutation (Ex19del or L858R mutation with or without T790M mutation) and at least one measurable target lesion (according to Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1) that had not previously been irradiated. They also had Eastern Co-operative Oncology Group (ECOG) performance status 0 or 1 and adequate renal, hepatic and haematological function.[2]

Eligible patients were randomised equally to receive dacomitinib 45mg orally daily or gefitinib 250mg orally daily until disease progression, starting a new anticancer treatment, unacceptable toxicity, non-compliance, withdrawal of consent or death. Treatment could be continued after

radiological progression if the investigator considered there was evidence of clinical benefit. The dose of dacomitinib could be reduced to 30mg daily and then 15mg daily if necessary for toxicity. In the gefitinib group, treatment could be interrupted for toxicity and restarted at daily or alternate day dosing. Randomisation was stratified by race (Japanese versus Chinese versus other east Asian versus non-Asian) and type of EGFR mutation (Ex19del versus L858R).

The primary outcome was progression-free survival (PFS) defined as the time from randomisation to disease progression according to RECIST version 1.1 assessed by an independent radiological central (IRC) review, or death due to any cause. At the primary analysis (data cut-off July 2016), after a median duration of follow-up of 22.1 months, PFS events had occurred in 60% (136/227) of dacomitinib and 80% (179/225) of gefitinib patients. Median IRC-assessed PFS was statistically significantly longer in the dacomitinib group compared with the gefitinib group; 14.7 months versus 9.2 months, hazard ratio (HR) 0.59 (95% confidence interval [CI]: 0.47 to 0.74), p<0.0001.[2]

Pre-specified subgroup analyses of the primary outcome found that the treatment effect was generally consistent across subgroups, including by mutation type, with the exception of non-Asian patients. In the non-Asian subgroup, 68% (39/57) of dacomitinib and 80% (39/49) of gefitinib patients had a PFS event; HR 0.89 (95% CI: 0.57 to 1.39); while in the Asian subgroup, 57% (97/170) of dacomitinib and 80% (140/176) of gefitinib patients had a PFS event; HR 0.51 (95% CI: 0.39 to 0.66).[2]

A hierarchical statistical testing strategy was used for primary and secondary outcomes of IRC-assessed PFS, IRC-assessed overall response rate (ORR) and overall survival to control the type I error rate. ORR assessed by the IRC (defined as best overall response of complete or partial response according to RECIST version 1.1) was achieved by 75% (170/227) of dacomitinib patients and 72% (161/225) of gefitinib patients (p=0.388). A complete response was achieved by 5.3% (12/227) and 1.8% (4/225) of patients respectively. Since the comparison of ORR was not statistically significant, no formal testing of overall survival was conducted and results reported are descriptive only and not inferential (no p-values reported).[1, 2]

Overall survival data were immature at the time of the primary PFS analysis as there had only been 167 deaths. A final overall survival analysis (data cut-off February 2017) was performed after a median follow-up of 31.1 months in the dacomitinib group and 31.4 months in the gefitinib group based on 220 deaths (45% [103/227] and 52% [117/225] respectively). Median overall survival was 34.1 months in dacomitinib patients compared with 26.8 months in gefitinib patients; HR 0.76 (95% CI:0.58 to 0.99) but this was considered exploratory due to the pre-specified statistical testing procedure.[2, 3]

Other secondary outcomes at the July 2016 data cut-off included PFS assessed by investigator and this was longer in the dacomitinib group compared with the gefitinib group; 16.6 months versus 11.0 months, HR 0.62 (95% CI: 0.50 to 0.78). The median duration of response as assessed by the IRC was 14.8 months in dacomitinib patients and 8.3 months in gefitinib patients; HR 0.40 (95% CI: 0.31 to 0.53). Time to treatment failure (TTF; defined as the time from randomisation to

documented disease progression, death from any cause or discontinuation of study treatment due to any cause) was longer in the dacomitinib group than the gefitinib group: median TTF assessed by IRC was 11.1 months versus 9.2 months (HR 0.67 [95% CI: 0.54 to 0.83]).[2]

Quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the lung cancer module (EORTC QLQ-LC13). At the time of the primary PFS analysis, changes from baseline in symptoms scores found greater improvements in pain in chest with dacomitinib compared with gefitinib (-10.24 versus -7.44). Improvements in cough, dyspnoea, pain in arm or shoulder or in other parts and fatigue were similar in both treatment groups. There was greater worsening in diarrhoea (19.88 versus 7.32) and sore mouth (15.09 versus 3.51) with dacomitinib compared with gefitinib and the improvement in global quality of life was greater with gefitinib (4.94) compared with dacomitinib (0.20). Changes of ≥ 10 points were considered clinically meaningfully.[2]

The Euro-Qol 5-dimension visual analogue scale (EQ-5D VAS) remained similar to baseline (73.1) at the time of analysis (73.4) in the dacomitinib group. In the gefitinib group there was a small improvement from baseline (74.7 to 77.7).[2, 4]

The submitting company presented an indirect treatment comparison (ITC) of dacomitinib with afatinib and erlotinib/gefitinib for the first line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR mutations. The company assumed that erlotinib was equivalent to gefitinib and this assumption was supported by the CTONG 0901 study which found no significant difference between erlotinib and gefitinib in a subgroup analysis of first-line use.[5] The network meta-analysis (NMA) included two studies (ARCHER 1050 and LUX-Lung 7) and compared treatments on two outcomes: progression free survival (PFS) and overall survival.[2, 6, 7] Since proportional hazards in the included studies were considered to have been violated, a fractional polynomial NMA was undertaken to compare the medicines. The company concluded that the results of the NMA suggested dacomitinib is the superior treatment in both PFS and overall survival compared to all comparator therapies (afatinib, erlotinib and gefitinib).

Summary of evidence on comparative safety

The median duration of treatment was longer in the dacomitinib group (15.3 months) compared with the gefitinib group (12.0 months) and the reported adverse events rates do not take account of this difference. An adverse event was reported by the majority of patients: 99.6% (226/227) of dacomitinib and 98% (220/224) of gefitinib patients. Serious adverse events were reported in 27% of dacomitinib and 22% of gefitinib patients respectively and were considered treatment-related in 9.3% and 4.5% of patients respectively. Adverse events led to discontinuation of study medicine in 9.7% of dacomitinib and 6.7% of gefitinib patients. Dosing interruptions occurred in 78% and 54% of patients respectively. Toxicity led to dose reductions in 66% of dacomitinib patients (38% to 30mg daily and 28% to 15mg daily) and 8.0% of gefitinib patients (to dosing every other day).[2]

Common adverse events were generally more frequently reported in the dacomitinib compared with the gefitinib group and respectively included: diarrhoea (87% versus 56%), paronychia (nail disorder; 62% versus 20%), dermatitis acneiform (49% versus 29%), stomatitis (44% versus 18%), decreased appetite (31% versus 25%), dry skin (28% versus 17%), decreased weight (26% versus 17%), alopecia (23% versus 13%), cough (21% versus 19%), pruritus (20% versus 14%), increased alanine aminotransferase (19% versus 39%), conjunctivitis (19% versus 4.0%), nausea (19% versus 22%) and increased aspartate aminotransferase (19% versus 36%). The most frequently reported serious adverse events in the dacomitinib and gefitinib groups respectively were: disease progression (3.5% versus 4.9%), diarrhoea (2.2% versus 0%), pleural effusion (2.2% versus 0.9%), pneumonia (2.2% versus 0.9%) and dyspnoea (0.4% versus 1.8%).[2]

Three deaths were considered to be related to study treatment toxicity. Two patients treated with dacomitinib died: one related to untreated diarrhoea and one to untreated cholelithiasis/liver disease. One patient treated with gefitinib died related to sigmoid colon diverticulitis/rupture which was complicated by pneumonia.[2]

Summary of clinical effectiveness issues

EGFR tyrosine kinase inhibitors are recommended by current guidelines for the first-line treatment of locally advanced or metastatic NSCLC with EGFR mutations. Three EGFR tyrosine kinase inhibitors are currently available and accepted for first-line use by SMC (afatinib, gefitinib and erlotinib). Another EGFR tyrosine kinase inhibitor, osimertinib, has also recently received marketing authorisation for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations and is currently being reviewed by SMC.[8] Dacomitinib is a second generation EGFR tyrosine kinase inhibitor. It meets SMC orphan equivalent and end of life criteria.

The key study, ARCHER 1050, directly compared dacomitinib with gefitinib and found statistically significantly longer IRC-assessed PFS in the dacomitinib group compared with the gefitinib group (14.7 months versus 9.2 months); a PFS benefit of 5.5 months. The secondary outcome of overall survival was approximately 7 months longer in the dacomitinib group than the gefitinib group but due to the hierarchical statistical testing, and the non-significant difference in the earlier ORR outcome, there was no formal testing of survival.[1-3]

The study had a number of limitations. It was of open-label design but the primary outcome of PFS was assessed by IRC which minimised potential bias. However the potential for bias in subjective outcomes, including quality of life and safety, remains. The final analysis of overall survival may be confounded by post-study treatments which had been received by 50% (113/227) of the dacomitinib group and 62% (140/225) of the gefitinib group. The majority of study patients were Asian (77%) and only 23% of patients were white and this may affect the generalisability of the study results to the Scottish population. Subgroup analysis also suggested that the relative treatment effect may be less in non-Asian patients than Asian patients but the number of non-

Asian patients was small and the study was not powered for subgroup analysis. The study included patients with common EGFR mutations only (Ex19del and L858R) and there is no evidence of efficacy for those with rarer EGFR mutations. The study excluded patients with brain or leptomeningeal metastases and with ECOG performance status of ≥2 and therefore the treatment effect of dacomitinib in these patients is unknown.[2]

There were no directly comparative data with afatinib and erlotinib which may be more commonly used than gefitinib in clinical practice. The company performed a fractional polynomial NMA and suggested that dacomitinib was superior to afatinib and gefitinib/erlotinib in PFS and overall survival. However a number of limitations affect the validity of these conclusions. The NMA results of HRs and credible intervals (CrI) for PFS and overall survival varied over the different time-points analysed, at times the HR favoured the comparator and at times the CrI included the value one, suggesting no evidence of a difference. There were differences between the design of the studies (LUX-Lung 7 was an exploratory phase IIB study) and in their duration of follow-up. There were differences between the study populations, particularly the proportions of Asian patients, and LUX-Lung 7 included a small proportion of patients with brain metastases. There were also differences between the studies in the proportions of patients receiving subsequent post-study anticancer treatment and this may have confounded the overall survival results. The NMA did not assess safety and health-related quality of life, which may be clinically relevant when considering the risk/benefit of treatments. A scenario analysis and an additional analysis using a first order fractional polynomial for PFS also indicated no evidence of a difference between dacomitinib and afatinib or erlotinib/gefitinib. The superiority of dacomitinib over gefitinib has been demonstrated through the ARCHER 1050 study, but there are too many weaknesses and uncertainties in the indirect treatment comparison to make a similar conclusion for dacomitinib and afatinib.

The introduction of dacomitinib would offer another option for the first-line treatment of patients with advanced NSCLC with EGFR mutations. Dacomitinib improved PFS compared with gefitinib but was associated with a higher incidence of the most frequently reported adverse events.

While dacomitinib meets SMC orphan equivalent and end of life criteria in this indication, the company did not request a Patient and Clinician Engagement (PACE) meeting to consider the added value of dacomitinib in the context of treatments currently available in NHS Scotland.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis to evaluate dacomitinib versus gefitinib, afatinib and erlotinib for the first-line treatment of adults with locally advanced or metastatic NSCLC with EGFR activating mutations. The time horizon for the analysis was 15 years, which may be long given the study population. It was reduced in a scenario analysis to 10 years.

A cohort-level partitioned survival model was used, with three states including end of life and death, along with PFS and post-progression survival. The cycle length was 28 days.

Clinical data were taken from the ARCHER 1050 study for overall survival and PFS for dacomitinib versus gefitinib.[2] An NMA was used to incorporate afatinib via the LUX-Lung 7 study that compared this medicine against gefitinib .[6, 7] Erlotinib was considered clinically equivalent to gefitinib on the basis of data from the CTONG 0901 study. Data were modelled beyond the median study follow up period from ARCHER 1050 of 31.3 months by applying an extrapolation distribution to the gefitinib arm for both PFS and overall survival (generalised gamma in each case).Fractional polynomial models were then fitted to each for these outcomes in order to simulate hazard ratios over time as the assumption of proportional hazards was not met. Various fractional polynomial models were tried in order to find the most suitable fit for the NMA data. This was done by varying the first and second order power values (P1 and P2 respectively). The power values selected for the base case (second order P1=0.5, P2=1.5 in the base case for PFS and first order P1=-0.5 in the base case for OS) were also varied in scenario analysis.

Utility data were modelled based on EQ-5D-3L data collected in the ARCHER 1050 study until progression (there was only one data collection point for this outcome measure beyond progression). Of note, utility values were lower for dacomitinib and afatinib than for gefitinib and erlotinib. For progressive disease, utility values came from published literature for this population. The range of values used and the effect of using treatment specific utility values for the progression-free state were tested in scenario analysis. Disutilities associated with adverse events in the base case were assumed to be incorporated in the elicited utilities from the ARCHER 1050 study. However, a scenario analysis considered the impact of applying these disutilities separately.

Aside from medicines costs and their administration, costs included GP visits, outpatient visits, cancer nurse hours as well as complete blood count, biochemistry, CT scans and chest x-rays for both the progression-free and post-progression states. The costs of treating treatment-related grade 3 and 4 adverse events were included and the cost of end-of-life care was applied when patients reached this state.

The costs associated with second and third-line treatments were incorporated in the base case. For second line this was based on the proportion of participants who would likely be eligible to receive osimertinib (56%) rather than platinum doublet chemotherapy. Third line treatment was docetaxel for those receiving platinum doublet chemotherapy at second line and platinum doublet chemotherapy for those who received osimertinib at second line.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. PASs are in place for gefitinib, afatinib and erlotinib and these were included in the analysis by using an estimate of the PAS prices for these comparator treatments.

SMC would wish to present the cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS and the comparator PAS estimates, SMC is unable to publish these results.

The main limitations with the analysis were:

- Direct comparative study data were only available for one of the three comparators (gefitinib) using the ARCHER 1050 study. For the other comparisons an NMA was conducted which has limitations as noted above.
- The choice of base-case extrapolations for the gefitinib arm PFS and OS estimates (generalised gamma) were not fully tested in scenario analysis (only a log logistic alternative for overall survival was undertaken). However, additional information was subsequently provided from the submitting company showing the results were not overly sensitive to alternative extrapolation approaches.

The Committee considered the benefits of dacomitinib in the context of the SMC decision modifiers that can be applied and agreed that as dacomitinib is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the Committee accepted dacomitinib for use in NHSScotland.

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from the Roy Castle Lung Cancer Foundation and the Scottish Lung Cancer Nurses Forum. The Roy Castle Lung Cancer Foundation is a registered charity and the Scottish Lung Cancer Nurses Forum is an unincorporated organisation.

- The Roy Castle Lung Cancer Foundation has received 7.5% pharmaceutical company funding in the past two years, including from the submitting company. The Scottish Lung Cancer Nurses Forum has received 80% pharmaceutical company funding in the past two years, including from the submitting company.

- Lung Cancer is a leading cause of cancer related mortality in the UK. Patients with EGFR mutations tend to be diagnosed later, as they do not fit the ‘typical’ lung cancer patient profile. They tend to be younger and more likely to be light/non-smokers. In addition to the psychological impact of diagnosis, late stage lung cancer may be accompanied by symptoms (such as breathlessness, fatigue, weight loss and chest pain) that can reduce patient's ability to carry out personal care, cook for themselves and contribute actively to family or business activities.

- The addition of targeted therapies and immunotherapy, in the treatment of NSCLC, has ensured active therapy options for many. However, overall outcomes for many of this patient population remain poor. Therefore the availability of new therapy choices is of key importance.

- Dacomitinib represents a new therapy option, which may extend survival for this patient group. It appears to be generally well tolerated with manageable side effects. It is also convenient for patients and their carers, as it can be taken with or without food at the same time each day. Patients with access to dacomitinib report being able to return to activities they enjoyed before their diagnosis.

Additional information: guidelines and protocols

The European Society for Medical Oncology (ESMO) published an updated clinical practice guideline on the diagnosis, treatment and follow-up of metastatic NSCLC in September 2018.[9] The guidance makes the following recommendations:

- EGFR tyrosine kinase inhibitors represent the standard of care as first-line treatment for advanced EGFR-mutated NSCLC.
- Patients who have benefited from EGFR tyrosine kinase inhibitor treatment may continue to receive the same therapy beyond initial radiological progression as long as they are clinically stable.
- Patients with localised distant progression and ongoing systemic control, continuation of treatment with EGFR tyrosine kinase inhibitors in combination with local treatment of progressing metastatic sites may be considered.
- Continuous use of EGFR tyrosine kinase inhibitors in combination with chemotherapy is not recommended as it was not associated with PFS improvement and showed a detrimental effect on overall survival.
- Erlotinib, gefitinib and afatinib are recommended as first-line therapy in patients with advanced NSCLC who have active sensitising EGFR mutations, regardless of their performance status.
- There is no consensus preferring any of the three currently available first-line EGFR tyrosine kinase inhibitors over others.
- Dacomitinib will be added to the list when it is approved by regulatory agencies, the United States FDA and the EMA.
- First-line osimertinib is now considered one of the options for NSCLC patients with sensitising EGFR mutations.[9]

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 137, Management of lung cancer in February 2014.[10]The guidance recommends that first-line single agent tyrosine kinase inhibitors should be offered to patients with advanced NSCLC who have a sensitising EGFR mutation. Adding combination systemic anticancer therapy to a TKI confers no benefit and should not be used.[10]

Additional information: comparators

Afatinib, erlotinib and gefitinib. Osimertinib has recently received marketing authorisation for this indication and is currently being reviewed by SMC.

Cost of relevant comparators

Medicine	Dose Regimen	Cost year (£)
Dacomitinib	**45mg orally daily**	**32,796**
Osimertinib	80mg orally daily	70,009
Afatinib	40mg orally daily	26,303
Gefitinib	250mg orally daily	26,302
Erlotinib	150mg orally daily	19,796

Doses are for general comparison and do not imply therapeutic equivalence. Costs for dacomitinib from MIMS online on 31 July 2019, osimertinib and gefitinib from MIMS online on 6 May 2019 and costs for afatinib and erlotinib from eVadis on 3 May 2019. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The number of patients assumed to be eligible was for treatment is estimated to be 200 per year.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

References

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This assessment is based on data submitted by the applicant company up to and including 14 June 2019.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.