nintedanib 100mg and 150mg soft capsules (Vargatef®)  SMC No. (1027/15)

Boehringer Ingelheim International GmbH

6 March 2015

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 NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission under the end of life and orphan equivalent process

nintedanib (Vargatef®) is accepted for use within NHS Scotland.

**Indication under review:** in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.

Addition of nintedanib to second-line treatment of stage IIIb/IV NSCLC with docetaxel significantly increased overall survival in the subgroup patients with adenocarcinoma tumour histology.

This advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost effectiveness of nintedanib and is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

**Chairman,**

Scottish Medicines Consortium
### Indication

In combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.

### Dosing Information

200mg twice daily administered approximately 12 hours apart, on days 2 to 21 of a standard 21 day docetaxel treatment cycle.

Nintedanib must not be taken on the same day of docetaxel chemotherapy administration (= day 1).

Treatment with nintedanib should be initiated and supervised by a physician experienced in the use of anticancer therapies.

### Product availability date

January 2015 Nintedanib meets SMC orphan equivalent and end of life criteria in this treatment setting.

### Summary of evidence on comparative efficacy

Nintedanib is a triple angiokinase inhibitor. Tumour angiogenesis contributes to tumour growth, progression and formation of metastases. Nintedanib blocks vascular endothelial growth factor receptors, platelet-derived growth factor receptors and fibroblast growth factor receptors kinase activity, preventing endothelial and perivascular cell proliferation and survival.¹

LUME-Lung 1 was a phase III, randomised, double-blind, placebo-controlled study comparing the efficacy and safety of docetaxel plus nintedanib with docetaxel alone in 1,314 adult patients with histologically or cytologically confirmed stage IIIb/IV recurrent NSCLC (all histologies) who had received one previous first-line chemotherapy regimen.² Patients were permitted one additional previous chemotherapy regimen to allow for adjuvant, neoadjuvant or neoadjuvant plus adjuvant therapy. Male and female patients aged ≥18 years with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and at least one target lesion measurable according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0 were included in the study. Patients were randomised equally and stratified by ECOG performance status (0 versus 1), previous bevacizumab treatment (yes versus no), histology (squamous versus non-squamous) and presence of brain metastases (yes versus no). Patients received docetaxel 75mg/m² body surface area intravenously (iv) on day 1 plus nintedanib 200mg or placebo orally twice daily on days 2 to 21, every three weeks until disease progression or unacceptable toxicity. Nintedanib and docetaxel dose reductions were permitted in response to adverse events. There was no crossover and similar numbers of patients received subsequent anticancer therapies in each group.²

The primary outcome was progression free survival (PFS), defined as time from randomisation to progression or death, assessed by central independent review. At the time of the primary analysis, median PFS (central independent review) was 3.4 months in the docetaxel plus nintedanib group and 2.7 months in the docetaxel plus placebo group, hazard ratio (HR) 0.79 (95% confidence interval [CI]: 0.68 to 0.92), p=0.0019.² In a post hoc analysis of the subgroup of patients with adenocarcinoma histology, making up approximately half the study population, median PFS (central independent...
review) was 4.0 months in the docetaxel plus nintedanib group and 2.8 months in the docetaxel plus placebo group, HR 0.77 (95% CI: 0.62 to 0.96), p=0.0193.\(^3\)

Overall survival (OS) was a key secondary outcome. At the time of final OS analysis, there had been 1,121 deaths. In a pre-specified analysis of 658 patients with adenocarcinoma histology, median OS was 2.3 months longer in the docetaxel plus nintedanib group compared with the docetaxel plus placebo group: 12.6 months and 10.3 months respectively, HR 0.83 (95% CI: 0.70 to 0.99), p=0.0359. In the overall study population, there was no significant difference in OS between the two treatment groups, median overall survival was 10.1 months in the docetaxel plus nintedanib group and 9.1 months in the docetaxel plus placebo group, HR 0.94 (95% CI: 0.83 to 1.05), p=0.2720.\(^2\)

Investigator assessed PFS was similar to centrally assessed PFS. An objective response (assessed by independent review) was achieved by a low number of patients in each group.\(^2\)

There was no significant difference in the time to deterioration of the pre-specified symptoms of cough, dyspnoea and pain in the two treatment groups. There was a significant deterioration in the diarrhoea symptom scale in the docetaxel plus nintedanib group compared with the docetaxel plus placebo group. Self-reported quality of life was not improved or adversely affected by nintedanib treatment.\(^1\)

### Summary of evidence on comparative safety

Adverse events affecting the gastrointestinal tract, including diarrhoea, nausea, decreased appetite and vomiting, and increased liver enzyme test results were more common in the docetaxel plus nintedanib group compared with the docetaxel plus placebo group. These were managed with dose reductions and supportive treatments, 19% of patients in the docetaxel plus nintedanib group and 6.3% of patients in the docetaxel plus placebo group required at least one dose reduction of nintedanib or placebo. Increases in liver enzymes were reversible. Approximately one fifth of patients in each group discontinued study treatment permanently because of adverse events.\(^2\)

The proportion of patients experiencing adverse events associated with anti-angiogenic medicines were similar; bleeding (14% versus 12%), thrombotic events (5.1% versus 4.6%), hypertension (3.5% versus 0.9%), and gastrointestinal perforation (0.5% versus 0.5%) were reported in the full study population (docetaxel plus nintedanib versus docetaxel plus placebo).\(^2\)

An adverse event leading to death possibly unrelated to disease progression was reported in 5.4% of patients in the docetaxel plus nintedanib group and 3.8% of patients in the docetaxel plus placebo group. These included sepsis (five versus one), pneumonia (two versus seven), respiratory failure (four versus none) and pulmonary embolism (none versus three).\(^2\)

### Summary of clinical effectiveness issues

Nintedanib is the first triple angiokinase inhibitor to be licensed for the treatment of lung cancer. The prognosis for patients with locally advanced, metastatic or locally recurrent NSCLC is poor with median survival being less than a year.\(^2\) Docetaxel, erlotinib, pemetrexed and gefitinib are licensed for use as second-line treatment for locally advanced, metastatic or locally recurrent NSCLC. Erlotinib can also be used in the first-line setting for patients with EGFR mutations, and pemetrexed in combination with cisplatin is licensed for the first-line treatment of patients with non-squamous histology. Gefitinib is not recommended for use by SMC. Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area due to the lack of effective treatment options. Nintedanib meets SMC orphan equivalent and end of life criteria in this treatment setting.
Addition of nintedanib to docetaxel second line treatment of stage IIIb/IV NSCLC significantly improved PFS and OS in the subgroup of patients with adenocarcinoma histology (~50% of patients in each treatment group) in a large phase III study. The PFS analysis in the adenocarcinoma subgroup was post hoc; however, the OS analysis was specified prior to the database lock. Patients were required to have an ECOG performance status of 0 or 1; there is no information about the efficacy or tolerability in patients with a performance status lower than this. Patients treated in clinical practice may also be older than those treated in the pivotal study.

Patients in LUME-Lung 1 were not tested for mutations such as epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) as it was not standard practice at the time of the study design. It is unknown how the presence of these mutations would affect response to treatment.

The submitting company presented a Bayesian mixed treatment comparison (MTC) using fixed and random effects to provide an evaluation of the efficacy and safety of nintedanib plus docetaxel with all possible comparators in adults with stage IIIb/IV NSCLC or recurrent NSCLC. Each study included had to report data for the adenocarcinoma subgroup or at least 75% of included patients had to have adenocarcinoma. The comparators included in the base case and scenario analyses were docetaxel, pemetrexed and erlotinib. The scenario analysis assumed equivalence of pemetrexed and docetaxel. The sensitivity analysis included studies that specifically or indirectly selected patients with epidermal growth factor receptor (EGFR) mutations and therefore provided a comparison with gefitinib. The results suggest that nintedanib plus docetaxel has the greatest probability of prolonging OS and PFS compared with docetaxel, pemetrexed and erlotinib. Clinical experts consulted by SMC considered that nintedanib plus docetaxel would be an alternative to single agent docetaxel in patients with good performance status so the MTC results have limited relevance.

Clinical experts consulted by SMC considered that nintedanib is a therapeutic advancement due to the associated survival benefit. They noted that the introduction of this medicine may impact on the patient and/or service delivery due to the management of toxicities, though the adverse event profile is as expected for this class of medicine and can be managed by supportive care, dose interruptions and dose reductions.

### Summary of patient and clinician engagement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of nintedanib, as an orphan equivalent and end of life medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Advanced lung cancer has a devastating impact on patients and their families. The prognosis for patients relapsing after first-line chemotherapy is very poor with most having less than a year to live.

- There have been no new second-line treatments for unselected adenocarcinoma patients for over 10 years so there is an unmet need in this area.

- Second-line chemotherapy has modest effects at best. Nintedanib in combination with docetaxel offers an additional survival benefit of 2.3 months, which is small but significant for this group of patients in the context of limited remaining months.

- There are also limited data suggesting that nintedanib may improve some aspects of quality of life.
Clinicians stressed that use of nintedanib should only be considered as an option in very fit patients (ECOG performance status of 0 or 1) as per the eligibility criteria within the LUME-Lung 1 study. They indicated that benefit may be greater in patients who progress soon after first-line therapy but that this required further testing.

It was suggested that treatment would require careful monitoring for drug-related toxicities.

**Summary of comparative health economic evidence**

The company submitted a cost-utility analysis comparing nintedanib plus docetaxel to docetaxel, erlotinib or pemetrexed. The patient group was adults with non-small cell lung cancer of adenocarcinoma tumour histology, after first-line chemotherapy, who were performance status 0 or 1. A 15-year time horizon and NHS perspective were adopted.

The analysis used a Markov model with a three-week cycle length and three health states: progression free, with progressive disease and death. Progression free survival and overall survival rates for the docetaxel arms came from the randomised clinical study,2 data for the comparators were from a mixed treatment comparison. Several curves were fitted to extrapolate data beyond the end of the studies. Adverse events came from a range of sources including the clinical study2 and submissions to NICE. Resource use was primarily the opinion of one expert, with validation by a clinical Advisory Board and reference to published sources. Unit costs were from national datasets or literature. Utility values were from the clinical study. The cost for erlotinib included an estimate of the patient access scheme (PAS) in place for this medicine and docetaxel was included according to the list price of the medicine.

A patient access scheme was submitted for nintedanib following the New Drugs Committee meeting and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The PAS offered a confidential discount on the list price of the medicine. With the PAS, the incremental cost effectiveness ratio (ICER) was £33,412 compared to docetaxel. In the comparisons with erlotinib and pemetrexed, the ICERS were £31,732 and £19,575 respectively. It is SMC policy to include the estimated QALY gain and incremental cost in the detailed advice document for all submissions. However, the submitting company has advised that these figures should remain confidential.

Sensitivity analyses show that base case ICER was sensitive to the utility value after progression, discontinuation risk and best supportive care cost for the comparison with docetaxel monotherapy. For example, a sensitivity analysis using alternative post-progression utility values that were more conservative increased the ICER versus docetaxel to £43,040. The hazard ratio for overall survival was the key parameter impacting on the base case for the comparison against erlotinib and pemetrexed; these results were also sensitive to the utility value after progression, discontinuation risk and best supportive care costs.

Probabilistic sensitivity analyses reported there was a 37% and 82% probability that the combination was cost-effective compared to docetaxel at a £30,000 and £50,000 threshold respectively. The equivalent values for erlotinib were 54% and 92% at the £30,000 and £50,000 thresholds.

There were a number of uncertainties associated with the analysis:

- The modelled increase in mean overall survival is 3.96 months compared to 2.87 months from the study, ie about 40% higher. The company notes that the study means are restricted means and underestimate the true difference between treatment arms but nevertheless the model may
overstate the survival benefit. At the end of the study, actual survival was known for 85% of patients. The company provided some additional analysis using alternative survival modelling methods to give lower predicted survival gains. In the comparison with docetaxel, this had the impact of increasing the ICERs to between £37k and £45k, with the latter figure noted by the company as resulting from a potentially underestimated survival gain.

- Utility value for disease progression lacks face validity, being too high compared to values reported by three other sources. As noted above, the use of alternative values increased the ICER.

Clinical experts advised that the most relevant comparator to nintedanib plus docetaxel is single agent docetaxel.

The Committee also considered the benefits of nintedanib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as nintedanib is an orphan-equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted nintedanib for use in NHS Scotland.

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

### Summary of patient and public involvement

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

- A submission was received from the Roy Castle Lung Cancer Foundation (RCLCF), which is a registered charity.

- The RCLCF has received pharmaceutical company funding in the past two years including from the submitting company.

- Due to the absence of symptoms until the later stages, non small cell lung cancer (NSCLC) is most commonly diagnosed at stage 4 where treatment options are palliative and limited. Patients and families are affected by both the diagnosis and poor prognosis simultaneously. This has a devastating impact emotionally. Late stage lung cancer will result in distressing symptoms such as breathlessness, pain, multiple clinical appointments and other significant physiological distress.

- In this patient group with advanced NSCLC where life expectancy is very limited, and if patients do not present with a mutation, the current treatment options are chemotherapy and radiotherapy which involve multiple hospital appointments, invasive procedures and significant levels of toxicity which have an adverse effect on quality of life.

- Nintedanib would provide a treatment option for these patients which may increase their life expectancy and quality of life and give them hope. As it is taken orally it is easier for patients to manage than other treatments.
Additional information: guidelines and protocols

The Scottish Intercollegiate Guideline Network (SIGN) guideline on the management of lung cancer published in February 2014 recommends single agent docetaxel or erlotinib be considered as second line therapy in patients with performance level 0-2 recurrent NSCLC. Pemetrexed has been shown to be equivalent to docetaxel in terms of clinical efficiency but with lower toxicity and should be considered for second line therapy in non-squamous cell NSCLC.

The 2011 National Institute for Health and Care Excellence (NICE) guidance on the diagnosis and management of lung cancer recommends docetaxel monotherapy as second line treatment in advanced or metastatic NSCLC. The guideline refers readers to the single technology appraisal (STA) of erlotinib. The guideline does not make any specific recommendations for second line treatment of adenocarcinoma patients.

The European Society for Medical Oncology published guidance on metastatic NSCLC in 2014. Pemetrexed (non-squamous histology only) and docetaxel are recommended as equivalent choices in second line therapy with erlotinib as an additional potential option in patients with unknown EGFR status or EGFR WT patients.

NICE is currently undertaking a multiple technology assessment (MTA) of erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed following prior chemotherapy (review of NICE technology appraisals 162 and 175). The date of publication is to be confirmed.

Additional information: comparators

Docetaxel, erlotinib and pemetrexed. Gefitinib is not recommended by SMC.

Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose regimen</th>
<th>Cost per cycle (£)</th>
<th>Cost per course (£)</th>
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<tbody>
<tr>
<td>nintedanib plus docetaxel</td>
<td>200mg orally twice daily on days 2 to 21 75mg/m² iv on day 1 every three weeks</td>
<td>2,154</td>
<td>10,771</td>
</tr>
<tr>
<td>pemetrexed</td>
<td>500mg/m² iv on day 1 every three weeks</td>
<td>1,440</td>
<td>7,200</td>
</tr>
<tr>
<td>erlotinib</td>
<td>150mg orally once daily continuously</td>
<td>1,142</td>
<td>5,710</td>
</tr>
<tr>
<td>docetaxel</td>
<td>75mg/m² iv on day 1 every three weeks</td>
<td>720</td>
<td>3,601</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Costs for nintedanib from the company submission and from Monthly Index of Medical Specialities 20 November 2014 for all other medicines, and based on 1.8m² body surface area. For nintedanib plus docetaxel the cost per course assumes 5 cycles, all containing docetaxel. Cost per course assumes five 21 day cycles of docetaxel, pemetrexed and erlotinib for comparison. Costs do not take any patient access schemes into consideration.
Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 125 patients. This assumes 83% of patients with lung cancer have NSCLC, of whom 25% are stage III/IV NSCLC and performance status 0 or 1, with 40% having an adenocarcinoma subtype. This is equivalent to 409 patients, of whom 68% are estimated to be treated first line and 45% of these receive second line therapy.

Without PAS
Based on an estimated uptake of 10% in year 2 and 45% in year 5, the gross impact on the medicines budget was estimated at £123k in year 2 and £552k in year 5. The company assumed erlotinib, permetrexed and single agent docetaxel would be displaced in equal proportion and the list price of erlotinib was used. The net medicines budget impact was estimated at £121k and £472k in years 2 and 5 respectively.

Clinical experts advise that single agent docetaxel is most likely to be replaced by the combination and thus the estimated savings are overstated.

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

The undernoted references were supplied with the submission.

1. Nintedanib soft capsules (Vargatef®) Summary of product characteristics. Boehringer Ingelheim International GmbH.


This assessment is based on data submitted by the applicant company up to and including 2 March 2015.

*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_Statements/Policy_Statements

Drug 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 drug 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 NHS Scotland 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 NHS Scotland 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.