



NCPE report on the cost effectiveness of nintedanib (Vargatef®) in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer of adenocarcinoma tumour histology after first line chemotherapy

The NCPE has issued a recommendation regarding the cost-effectiveness of nintedanib (Vargatef®). Following NCPE assessment of the applicant's submission, nintedanib is not considered cost-effective for the licensed indication and therefore is not recommended for reimbursement at the submitted price

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Boehringer Ingelheim Ltd) submission. The NCPE uses a decision framework to systematically assess whether a technology is cost effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Background

In June 2015, Boehringer Ingelheim Ltd submitted a dossier examining the cost effectiveness of nintedanib 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. Final data submitted by the Applicant was received on 16th December 2015.

The recommended dose is 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. In case of adverse events, dose reductions are permitted as outlined in the Summary of Product Characteristics. Patients continue treatment after discontinuation of docetaxel for as long as clinical benefit is observed or until unacceptable toxicity occurs.

In the submission, the comparator in the base case analysis was docetaxel monotherapy ($75\text{mg}/\text{m}^2$) given intravenously in 3 weekly cycles. Pemetrexed and erlotinib were considered as comparators in scenario analysis. This was considered appropriate by the NCPE, although it was noted that pemetrexed is generally used as a maintenance therapy following first line use with either carboplatin or cisplatin. As such, treating it as a second line monotherapy treatment may not be appropriate to the Irish setting.

1. Comparative effectiveness of nintedanib

Relative efficacy outcomes for the comparison with docetaxel monotherapy were derived from the LUME-Lung 1 study. This was a phase 3, multicentre, placebo-controlled, double-blind, randomised controlled trial comparing nintedanib plus docetaxel with docetaxel alone (1:1). Eligible patients were adults who had locally advanced, metastatic or locally recurrent NSCLC and whose disease had progressed on or after treatment with only one prior chemotherapy regimen. Patients in the nintedanib group received nintedanib (200 mg) twice daily, on day 2 to 21 of a 21-day cycle, plus docetaxel ($75\text{ mg}/\text{m}^2$) on day 1 of the 21-day cycle. If patients experienced adverse events, the trial design specified reducing the dose of nintedanib from 200 mg twice daily to 150 mg twice daily and then to 100 mg twice daily, and reducing the dose of docetaxel from $75\text{ mg}/\text{m}^2$ to $60\text{ mg}/\text{m}^2$. Treatment in both groups stopped when patients' disease progressed or if they experienced unacceptable adverse

events. The primary outcome was progression-free survival (PFS) and the main secondary outcome was overall survival (OS). Nintedanib is only licensed for the treatment of NSCLC patients with adenocarcinoma histology. Therefore, a retrospective subgroup analysis of the adenocarcinoma population was performed and resulted in a HR of 0.77 (95% CI 0.62, 0.96; p=0.0193) (4 months for nintedanib plus docetaxel vs. 2.8 months for docetaxel) for the primary analysis and a HR of 0.84 (95% CI 0.71, 1.00, p=0.0485) (4.2 months for nintedanib plus docetaxel vs. 2.8 months for docetaxel) for the follow up analysis (median follow-up 31.7 months, IQR 27.8 to 36.1 months). For the adenocarcinoma population, the median OS was 12.6 months vs 10.3 months in the nintedanib plus docetaxel vs docetaxel group respectively (HR 0.83 (95% CI 0.70, 0.99, p=0.0359)).

No direct evidence was available comparing nintedanib to pemetrexed or erlotinib. Therefore evidence synthesis in the form of a mixed treatment comparison was undertaken. A systematic review of the available evidence was provided by the applicant. Nine trials were identified from the search. The data was appropriately analysed in OpenBUGS. The cost-effectiveness model results for the comparisons with pemetrexed and erlotinib are presented as a scenario analysis. This was considered appropriate by the NCPE.

2. Safety of nintedanib

In general, there were more adverse events (AEs) reported in the nintedanib arm of the pivotal LUME-Lung 1 trial, which would be expected. Patients in the placebo arm had a higher frequency of Grade 1/2 AEs, while patients in the nintedanib arm were more likely to experience Grade ≥ 3 AEs, where the most common AEs were: liver enzyme elevations, decreased WBC and neutrophils, diarrhoea, vomiting, nausea and neutropenia. The decreased levels of WBC and neutrophils led to slightly more infections in the nintedanib arm. Slightly more cases of sepsis were also observed in the nintedanib arm. With regard to the Grade 1/2 AEs, more patients experienced diarrhoea, ALT elevations, AST elevations, nausea, decreased appetite, and vomiting in the nintedanib arm.

3. Cost effectiveness of nintedanib

For the cost-effectiveness analysis, the key effectiveness inputs in the model were PFS and OS. Inputs for the comparison of nintedanib in combination with docetaxel versus docetaxel monotherapy were derived from the LUME-Lung 1 trial. Inputs for the comparison of nintedanib with pemetrexed and erlotinib were derived from the mixed treatment comparison

conducted for the submission, and are presented as a scenario analysis. Cost-effectiveness was investigated using a Markov state transition model with a lifetime horizon. The model comprises three health states: Progression-Free (PF); Progressed Disease (PD); and death. This model type is used in most oncology submissions and is appropriate to the decision question.

The model uses the area under the curve to determine the proportion of patients in each of the three health states during each model cycle. The proportion of patients in the PD state is estimated as the difference between OS and PFS. Estimates of OS and PFS in the model are based on the data from LUME-Lung 1 and the corresponding parametric survival models. Survival data (Kaplan-Meier curves) in LUME-Lung 1 reached approximately 2% for PFS and 5% for OS. This data was then extrapolated over the lifetime horizon. Each health state in which patients are alive (PF and PD) is associated with a cost and a health-related quality-of-life utility.

Quality-adjusted life years (QALYs) were calculated for each treatment arm. The EQ-5D was collected in the LUME Lung-1 study. A systematic literature review was used to identify additional utility information for the three modelled states as well as data on disutility associated with adverse events.

Direct costs including drugs costs, drug administration costs and costs associated with adverse events were included. A dose intensity of 91.2% was assumed for nintedanib and 98.1% for docetaxel as per the LUME-Lung study. In the sensitivity analyses dose intensities of 100% and 92% were assumed for pemetrexed and erlotinib respectively. The review group consider that less than 100% dosing intensity for oral medications may not be appropriate in the Irish healthcare setting due to the manner in which drugs are reimbursed up front prior to the patient taking the drug.

The base case deterministic incremental cost-effectiveness ratio (ICER, cost per QALY) for docetaxel plus nintedanib versus docetaxel is €66,985/QALY. Nintedanib plus docetaxel dominates pemetrexed (i.e. is more effective and less costly) and the ICER for nintedanib plus docetaxel versus erlotinib is €27,512/QALY. The review group adjusted the dose intensity (to reflect use on the high tech drugs scheme) from 91.2% to 100% and the base case ICER increased to €72,751/QALY.

A probabilistic analysis was undertaken including the relevant parameters for the model. The probability of cost effectiveness for the base case of nintedanib plus docetaxel versus nintedanib at a threshold of €45,000/QALY was 9.9%. The probability of cost effectiveness

at this threshold for nintedanib plus docetaxel versus pemetrexed monotherapy and erlotinib was 92.3% and 89.7% respectively.

4. Budget impact of nintedanib

Nintedanib is targeted at the adenocarcinoma population which represents approximately 40% of NSCLC patients and a proportion of these patients will receive treatment after first line chemotherapy. It is estimated that the gross cumulative 5 year budget impact will be approximately €220,000.

5. Conclusion

Following NCPE assessment of the company submission, nintedanib (Vargatef®) is not considered cost-effective in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer of adenocarcinoma tumour histology after first line chemotherapy and therefore is not recommended for reimbursement at the submitted price.