The NCPE has issued a recommendation regarding the cost-effectiveness of ponatinib (Iclusig®). Following NCPE assessment of the applicant’s submission, ponatinib (Iclusig®) is not considered cost effective for its indication as stated and therefore is not recommended for reimbursement.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant’s (ARIAD Pharmaceuticals) economic dossier on the cost effectiveness of ponatinib (Iclusig®). 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 (NCCP) 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.

National Centre for Pharmacoeconomics  
**January 2016**
In June 2015, ARIAD Pharmaceuticals submitted a dossier for ponatinib (Iclusig®). Ponatinib is indicated for adult patients with: (i) CP-, AP-, or BP- chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation; and (ii) Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.

Ponatinib is a member of the tyrosine kinase inhibitor (TKI) drug class targeted against the Bcr-Abl protein; it is the first member of the third generation of drugs of this kind. The licensed dose of ponatinib is 45mg once daily. Treatment is recommended to continue as long as the patient does not experience disease progression or unacceptable toxicity. It is recommended that discontinuation of treatment be considered if the patient does not respond within three months.

1. Comparative effectiveness of ponatinib

- For the indication of CP-CML, drug comparators for ponatinib included the TKIs dasatinib, nilotinib and bosutinib. For advanced CML, i.e. AP- and BP- CML, the relevant drug comparators were bosutinib, or best supportive care, in the form of hydroxyurea. Within each CML model ponatinib was also compared to direct allogeneic stem cell transplantation (allo-SCT). For Ph+ ALL, the comparator treatment was best supportive care in the form of vincristine and prednisolone.

- Evidence submitted to support the efficacy of ponatinib was derived from a single-arm, phase II trial (‘PACE’) of ponatinib in 449 patients with CP-CML, AP-CML, BP-CML and Ph+ ALL. Patients within the trial were required to have disease resistant to, or intolerant of, treatment with nilotinib or dasatinib, or to have the Bcr-Abl T315I mutation. The primary trial outcome studied in patients with CP-CML was major cytogenetic response within the first 12 months of treatment, defined as complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR). Secondary outcomes in CP-CML included complete hematologic response (CHR). In patients
with AP- or BP-CML, or Ph+ ALL, the primary outcome was major haematologic response (MaHR) within the first 6 months, defined as complete haematologic response (CHR) or no evidence of leukaemia. Secondary outcomes for all patients included major molecular response, progression-free survival, overall survival and safety.

- Evidence used to determine the comparative effectiveness of ponatinib in CML was taken from the subset of patients within PACE who had failed two prior TKIs. For patients with Ph+ ALL, evidence was for patients resistant to or intolerant of dasatinib or nilotinib, or with the T315I mutation. Patients with CP-CML were assigned to mutually exclusive categories based on the best of the three responses as follows: CCyR (56% patients), PCyR (11% patients) and CHR (30% patients). Patients who did not respond comprised an additional category (3%). The rates of MaHR for AP-CML, BP-CML and Ph+ ALL were 62.5%, 43.5% and 41%, respectively.

- In the case of CP-CML, response rates for dasatinib and nilotinib were taken from subgroup analyses of an observational follow-up study. Response rates for bosutinib in CP-CML were taken from a phase I/II, open-label two-part study. The data for response rates for bosutinib in AP-CML and BP-CML were taken from the bosutinib NICE Single Technology Assessment submission.

- For CP-CML, progression-free survival and overall survival data were unavailable from the PACE study. Suitable data were also unavailable for its comparators. Instead, data were extrapolated from recent NICE appraisals of dasatinib and nilotinib which related to trials of patients receiving second-line treatment. For AP-CML and BP-CML, overall survival data for ponatinib were taken from PACE. Survival rates for bosutinib were assumed to equal those of ponatinib following MaHR. Progression-free survival, overall survival and duration of response data were extrapolated using best-fit parametric functions over a lifetime time horizon.

- The NCPE has a number of concerns regarding the validity of the effectiveness data used for the evaluation. Firstly, the effectiveness data is primarily based on response data which serve as surrogate outcomes for disease progression. As the PACE trial is non-comparative, it is difficult to make robust conclusions regarding the relative benefit of ponatinib. Due to the dearth of suitable data on comparators, data was
sourced from studies in different populations and different lines of treatment. A range of assumptions were necessary to derive progression-free survival and overall survival data and lengthy extrapolations were performed on data from studies of short duration.

2. Safety of ponatinib

- The most common non-haematological adverse events observed in the PACE trial included rash (24% patients), dry skin (32% patients) and abdominal pain (22% patients), though these were of low severity.

- Important serious adverse events associated with ponatinib include myelosuppression and vascular occlusion. Ponatinib was associated with severe (grade 3/4) thrombocytopenia, neutropenia and anaemia, the frequency of which was found to be greater in patients with AP- and BP-CML or Ph+ ALL.

- Within PACE, 23% of patients experienced vascular occlusive events, 18% experiencing serious events. These included fatal myocardial infarction, stroke, retinal vascular occlusions (which may result in permanent visual impairment), stenosis of large arterial vessels of the brain, severe peripheral vascular disease and the need for urgent revascularisation procedures. Venous occlusive events were more frequent with increasing patient age and in patients with a prior history of cardiovascular risk, and the risk is considered to be dose-related.

3. Cost effectiveness of ponatinib

Methods

- The economic evaluation comprised four cost utility models, considering patients initiating treatment while in (i) CP-CML; (ii) AP-CML; (iii) BP-CML; (iv) Ph+ ALL. The perspective of the HSE under the High Tech Drugs Arrangements was presented. A lifetime time horizon (up to 100 years of life) was applied with cycle lengths of three months.

- Each model took the form of a Markov cohort state transition model with varying health states, in addition to the death state.
  - Patients could enter the CP-CML model in one of four states (CCyR, PCyR, CHR and NR) following receipt of ponatinib or its comparators dasatinib,
nilotinib or bosutinib. Patients could transition from the CP-CML state to the progressed disease state, which included AP-CML and BP-CML as substates, or could transition to the state of ‘allo-SCT in progressed disease’. Alternatively, patients could enter the model and receive allo-SCT instead of a TKI drug.

- The AP-CML model included two substates representing the response categories of MaHR. Patients who responded to treatment could move to the state of ‘SCT with response’ and patients who progressed moved to the BP-CML state. Alternatively, patients entering the model could move directly to an allo-SCT state.
- The BP-CML model had a similar structure to the AP-CML model. Patients entered the BP-CML model in either the direct allo-SCT state or the BP-CML state. Patients who responded within the BP-CML state could move to the ‘SCT with response’ state.

- Health benefit was measured in quality adjusted life years (QALYs). Utility values were derived from literature estimates from various studies of CML patients. A single disutility value was applied for adverse events, regardless of type, in the first model cycle.
- Costs included pharmacologic therapy, allo-SCT, monitoring and follow-up care, adverse events and end-of-life care. Ponatinib costs were based on relative dose intensity, observed in the PACE study. As dose reductions and interruptions occurred frequently within PACE due to adverse events, dose intensity for ponatinib was lower than that observed in trials of its comparators. There is uncertainty regarding the dose intensity of ponatinib in the real-world setting, and the potential wastage of dispensed ponatinib where dose reductions occur. The applicant also provided cost effectiveness results using the full dose of ponatinib (45mg daily) in the submission.

**Results**

- For ponatinib use within CP-CML, assuming full dosing and dispensing, the ICERs ranged from €29,000 per QALY, versus dasatinib or nilotinib, to €38,000 per QALY versus bosutinib. The corresponding dose-adjusted ICERs ranged from €12,500 per
QALY to €20,000 per QALY.

- In AP-CML, the HSE threshold for cost effectiveness (€45,000 per QALY) was exceeded only for the comparison of ponatinib to allo-SCT (€58,000 per QALY, full-dose ICER; €43,100 per QALY, dose-adjusted). Ponatinib dominated bosutinib in the dose-adjusted model (i.e. less costly and more effective) and the corresponding ICER was approximately €3,600 per QALY in the full-dose model.

- In BP-CML, the ICER for the comparison of ponatinib to bosutinib was €10,600 per QALY for the dose-adjusted model and €20,000 per QALY in the full-dose model. Ponatinib dominated allo-SCT.

- In Ph+ ALL, the ICER compared with BSC was €44,000 per QALY in the full-dose model and €42,000 per QALY in the dose-adjusted model.

**Sensitivity analysis**

- The model results were particularly sensitive to uncertainty in the time horizon and the modelled estimates of survival. In the case of CP-CML, the model was particularly sensitive to the per-cycle cost of ponatinib.

- The NCPE requested that the applicant include a scenario without statistical extrapolation of treatment benefit beyond the period examined within the PACE trial. Following application of this scenario, model results were altered particularly in the case of the CP-CML model. In this case the assumption of faster progression to AP/BP -CML resulted in a much lower QALY gain due to higher mortality rates, and higher costs due to increased requirements for monitoring and follow-up. Results for the dose-adjusted model remained below the cost effectiveness threshold. No results were provided with the scenario assuming full dosing of ponatinib.

4. **Budget impact of ponatinib**

- The budget impact analysis was based on the assumption of reduced dose intensity. The CML treatment cost per patient per year of ponatinib was estimated to be similar to the corresponding costs associated with its TKI comparators (range €56,200 - €58,600). If the full dose of ponatinib were dispensed, the yearly costs would amount to approximately €76,000.

- The applicant predicted, the gross budget impact of ponatinib to rise from €451,600
in year one to €752,300 in year five.

- Cost offsets are expected due to the displacement of other TKIs. The applicant predicted the net budget impact of ponatinib to rise from €46,500 in year one to €77,500 in year five. However, there is uncertainty if significant displacement will occur in practice.

- As a scenario analysis, assuming 100% uptake of ponatinib within the eligible population, the gross budget impact was calculated as €1.48 million per year and the net budget impact was calculated as €114,800 per year. Estimates assuming full dosing of ponatinib were not supplied.

5. Conclusion

Following assessment of the company submission, the NCPE cannot conclude that overall cost effectiveness for ponatinib in CML and Ph+ ALL has been demonstrated due to the high level of uncertainty in the clinical effectiveness data. Ponatinib is therefore not recommended for reimbursement at the submitted price.