Cost-effectiveness of ixazomib (Ninlaro®) for the Treatment of Adult Patients with Multiple Myeloma who have Received at Least One Prior Therapy

The NCPE has issued a recommendation regarding the cost-effectiveness of ixazomib (Ninlaro®). Following NCPE assessment of the applicant's submission, ixazomib (Ninlaro®) is not considered cost-effective for the treatment of multiple myeloma 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 (Takeda) economic dossier on the cost-effectiveness of ixazomib (Ninlaro®). 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 **December 2017**

Summary

In June 2017, Takeda submitted a dossier for ixazomib (Ninlaro®). Ixazomib in combination with lenalidomide and dexamethasone (IXA+LEN+DEX) is indicated for the treatment of adult patients with multiple myeloma (MM) who have received at least one prior therapy. Ixazomib is a proteasome inhibitor (PI). IXA was granted orphan status for the treatment of MM by the European Commission in September 2011. A conditional marketing authorisation was granted by the EMA on 21st November 2016. The recommended starting dose is 4mg to be taken orally on days 1, 8 and 15 of a 28-day treatment cycle. Treatment should be continued until disease progression or unacceptable toxicity. Treatment for longer than 24 cycles should be on an individual benefit risk assessment, as the data on the tolerability and toxicity beyond 24 cycles are limited. The Applicant is seeking reimbursement in the community setting under the High Tech Drugs Scheme. IXA+LEN+DEX is the first all oral triple therapy regimen for this indication.

1. **Comparative effectiveness of IXA+LEN+DEX**

- The pharmacoeconomic evaluation included several comparators. To provide evidence for a 2nd line positioning (1+ line), in line with IXA's indication and marketing authorisation, the evaluation compares IXA+LEN+DEX with LEN+DEX, bortezomib (BOR) +DEX, carfilzomib (CAR) +LEN+DEX, CAR+DEX and BOR+LEN+DEX. However, patients may also potentially receive IXA+LEN+DEX as 3rd line therapy (2+ line) and in this patient group the evaluation considered LEN+DEX and pomalidomide (POM) +DEX as the most relevant comparators. The NCPE review team considered that daratumumab may also be a potential comparator in a 3rd line positioning.
- The only direct evidence available for the efficacy of IXA+LEN+DEX is from the on-going global, Phase III, randomised, double-blind, multicentre TMM-1 clinical trial comparing IXA+LEN+DEX to LEN+DEX in patients with RRMM who have received 1-3 prior therapies. RRMM was defined as relapsed, relapsed and refractory or primary refractory MM. Patients refractory to prior LEN or PI-based therapy were not eligible. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), overall response rate (ORR), duration of response (DoR), time to progression (TTP), safety and health-related quality of life (HRQoL) measures. In addition, health resource utilisation data was collected. Three

sequential interim analyses plus a final analysis were planned. The first-interim analysis (IA1) was planned when approximately 36% of patients experienced a PFS event and was considered as the final statistical analysis of the PFS endpoint.

- At the IA1 data cut-off the median PFS was 20.6 months (95% CI 17.0, NE) for IXA+LEN+DEX versus 14.7 months (95% CI 12.9, 17.6) for LEN+DEX; HR = 0.74 (95% CI 0.59, 0.94). At IA2 the median PFS was 20.0 months (95% CI 18.0, 23.4) for IXA+LEN+DEX versus 15.9 months (95% CI 13.2, 18.8) for LEN+DEX; HR = 0.82 (95% CI 0.67, 1.0). Median OS was not reached in either of the study arms at the IA2 data cut-off, mean OS was 27.05 months in the IXA+LEN+DEX arm and 26.22 months in the LEN+DEX arm; HR = 0.87 (95% CI 0.64, 1.18). The ORR (IA2) was 78.6% in the IXA+LEN+DEX arm compared with 73.2% in the LEN+DEX arm (OR = 1.35; 95% CI 0.96, 1.91). The median DoR (IA2), was 26.0 months (95% CI 22.5, NE) in the IXA+LEN+DEX arm compared with 21.7 months (95% CI 17.8, NE) in the LEN+DEX arm. TTP (IA2) was 22.4 months (95% CI 18.7, 27.7) in the IXA+LEN+DEX arm compared with 17.6 months (95% CI 14.5, 20.3) in the LEN+DEX arm. HRQoL scores indicated similar patient reported QoL in both treatment arms.
- The NCPE review team identified a number of key issues and uncertainties with the available clinical-effectiveness data from the TMM-1 trial comparing IXA+LEN+DEX with LEN+DEX. The main issue being the immaturity of the OS data, with median OS not being reached. Definitive conclusions regarding the effect of treatment with IXA+LEN+DEX on OS cannot be drawn. In addition, the NCPE review team has some concerns that the IA2 analysis appears to indicate a reduced treatment effect between treatment arms compared to IA1 with regards to PFS (4.1 months vs 5.9 months). The worsening of the results suggests that the data may not yet have reached maturity and the potential remains that it could worsen further on extended follow-up. Therefore there is a high level of uncertainty in the clinical benefit of IXA+LEN+DEX vs LEN+DEX especially in relation to OS and PFS.
- A range of network meta-analyses (NMAs) were conducted to establish estimates of relative effectiveness for use in the economic model. Insufficient RCT evidence was available to form a connected network of evidence. Some comparisons therefore rely on non-RCT evidence. Comparisons based on RCT evidence could be established with CAR+LEN+DEX. For other comparisons, the network was enriched with non-RCT

evidence. Comparisons with CAR+DEX and BOR+DEX rely on a matched pairs analysis. Comparison with BOR+LEN+DEX relies on a non-randomised study and simulated treatment comparison (STC). In the 2+ prior lines population, the comparison with POM+DEX also relies on a matched pairs analysis. To investigate the reliability of the BOR+LEN+DEX comparison several matching adjusted indirect comparisons (MAICs) and simulated treatment comparisons (STCs) were presented the results of which were highly variable indicating that any conclusions for this comparison should be interpreted with great care.

2. Safety of IXA+LEN+DEX

- Adverse events occurring more frequently in the IXA+LEN+DEX treatment arm in the TMM-1 trial included diarrhoea, constipation, rash, thrombocytopenia, peripheral neuropathy, nausea, peripheral oedema, vomiting and back pain. Cases of neutropenia and anaemia although high occurred at a similar rate between the two regimens.
- There were no substantial differences between the IXA+LEN+DEX and LEN+DEX groups with respect to heart failure, arrhythmias, hypertension, myocardial infarction, new primary malignancy, acute renal failure or pneumonia.

3. **Cost effectiveness of IXA+LEN+DEX**

Methods

- Cost-utility analyses comparing IXA+LEN+DEX with LEN+DEX, BOR+DEX, CAR+LEN+DEX, CAR+DEX and BOR+LEN+DEX, in patients who had received 1+ prior lines of therapy, were submitted by the applicant. In addition, cost-utility analyses comparing IXA+LEN+DEX with LEN+DEX and POM+DEX in patients who had received 2+ prior lines of therapy were also presented. The perspective of the HSE (payer) was presented as the base case.
- The model was a multi-state cost-utility Markov model, incorporating three health states: pre-progression, post-progression and death.
- The base case considered a lifetime perspective based on 99% of patients predicted to have died within the IXA+LEN+DEX arm, this equated to 33.02 years in the 1+ prior lines base case population and 25 years in the 2+ prior lines population. Cycle

lengths of 1 week were used and a half-cycle correction was applied.

- Health benefit was measured in quality adjusted life years (QALYs). EQ-5D-3L data collected in the TMM-1 trial were transformed into utility values using the EQ-5D UK tariff values. A regression was fitted to predict utility based on response, hospitalisations, adverse events, age, gender, race, death within 3-months and new malignancies.
- Costs included treatment administration and monitoring, adverse events, concomitant medications, hospitalisations, post-progression therapies and terminal care costs.
- Survival curves modelling OS and PFS were used to inform treatment effectiveness in the model. The main efficacy outcomes used in the model were PFS, OS and time on treatment (ToT). For the IXA+LEN+DEX versus LEN+DEX comparison, treatment efficacy was based on multivariate parametric survival curves fitted to data from the TMM-1 trial. For the IXA+LEN+DEX versus BOR+DEX, CAR+LEN+DEX, CAR+DEX and POM+DEX comparisons, comparative efficacy was based on estimates from a network meta-analysis (NMA). For the IXA+LEN+DEX versus BOR+LEN+DEX comparison, comparative efficacy was based on a STC. HRs for PFS and OS were applied to parametric curves fit to the LEN+DEX data from the TMM-1 trial for all of these comparisons.
- The NCPE review team identified a number of key issues and uncertainties with the economic model including the assumption that relative treatment effects last for the duration of the model, when this assumption is not supported by the immature TMM-1 data. In addition, the review team had concerns that ToT may be overestimated in the model. Median ToT for LEN+DEX in the TMM-1 trial was 14.7 months. In contrast, median ToT observed in clinical practice for LEN-based regimens using real-world data from the IMS MM tracker for Ireland was 21-weeks. The parametric curve fit to the ToT data was shown to have a considerable impact on the final ICER. There was also uncertainty regarding the approach to modelling treatment costs in the model and using ToT may lead to an underestimation of treatment costs due to it being shorter than PFS. Furthermore, the model appears to be especially sensitive to parameters related to OS.

Results

1+ prior lines of treatment (Applicant base case)

- The incremental cost due to treatment with IXA+LEN+DEX versus LEN+DEX was €195,494 for a QALY gain of 0.29 resulting in an ICER of €668,357 per QALY.
- The incremental cost due to treatment with IXA+LEN+DEX versus BOR+DEX was €331,218 for a QALY gain of 0.85 resulting in an ICER of €387,742 per QALY.
- The comparison of IXA+LEN+DEX with CAR+LEN+DEX resulted in lower costs and lower QALYs for IXA+LEN+DEX. The net monetary benefit in this case equates to €52,763, based on a willingness-to-pay threshold of €45,000.
- IXA+LEN+DEX dominated CAR+DEX with lower costs and higher QALYs.
- The incremental cost due to treatment with IXA+LEN+DEX versus BOR+LEN+DEX was €240,193 for a QALY gain of 1.23 resulting in an ICER of €195,486 per QALY.

2+ prior lines of treatment (Applicant base case)

- The incremental cost due to treatment with IXA+LEN+DEX versus LEN+DEX was €251,100 for a QALY gain of 0.97 resulting in an ICER of €260,328 per QALY.
- The incremental cost due to treatment with IXA+LEN+DEX versus POM+DEX was €242,743 for a QALY gain of 1.68 resulting in an ICER of €144,535 per QALY.

Sensitivity analysis

- A series of one-way sensitivity analyses were performed. The results were most sensitive to the treatment coefficients for OS and ToT associated with IXA+LEN+DEX relative to LEN+DEX and the HRs for OS and PFS relative to LEN+DEX.

  Several alternative scenarios were also considered. The choice of parametric curve fit to the OS data had the greatest impact on results demonstrating the uncertainty in the OS estimates. This was further supported by an alternative scenario estimating OS based on a study by Felix *et al* (2013) which also resulted in varying results compared to the base cases. Furthermore, the parametric curve fit to the ToT data also had a considerable impact on the results. As there were concerns that the duration of LEN treatment in the model was overestimated, scenario analyses were performed capping treatment at a

median of 21-weeks and 24 treatment cycles. This also had an impact on the final results as did differing assumptions on the duration of relative treatment effect for IXA+LEN+DEX. The probability of cost-effectiveness at €45,000 per QALY ranged from 3.71%-39.5% versus 1+ line comparators and from 1.39% to 2.35% versus 2+ line comparators.

Additional analysis requested by NCPE

- A number of changes were implemented in the model for the preferred base case including applying a cap on treatment effect rather than assuming a treatment effect for the entire modelling period and using PFS to model treatment costs rather than ToT. These changes resulted in higher final ICERs. Assuming the treatment benefit associated with both IXA+LEN+DEX and LEN+DEX declines from 32-months over a 5-year time horizon, resulted in an ICER €703,426 per QALY. Assuming that treatment benefit associated with both IXA+LEN+DEX and LEN+DEX declines from 32-months over a 5-year time horizon and using PFS to model treatment costs in preference to ToT resulted in an ICER of €986,235 per QALY. The Review Group note that there is a high level of uncertainty with the cost-effectiveness estimates which can only be addressed when further clinical evidence becomes available.

4. Budget impact of IXA+LEN+DEX

- The price to wholesaler of ixazomib is €7,500 for 3 X 4mg capsules, equating to one 28-day treatment cycle. The annual cost per patient, including all relevant fees, mark-ups and rebates, is estimated as €145,280 for IXA+LEN+DEX and €82,375 for IXA alone.
- Predicted patient numbers applied in the budget impact analysis were: 19 (year 1), 42 (year 2), 61 (year 3), and 75 (years 4 & 5).
- The projected gross drug budget impact including drug acquisition costs only and based on company estimates of market share was estimated as €2,708,399 (year 1), €6,093,897 (year 2), €8,802,296 (year 3), and €10,833,595 (years 4 & 5), resulting in a cumulative budget impact of €39.3 million over 5-years.
- The company also presented a net drug budget impact representing the gross

budget impact when IXA is introduced minus the gross budget impact of continuing the current treatment pathway assuming IXA is not introduced. The cumulative net drug budget impact over 5-years is estimated as €15.7 million .

- An additional net budget impact was presented including costs associated with administration, resource use, adverse events, disease management and terminal care. The cumulative net budget impact over 5-years is estimated as €14.7 million.

5. Patient Submissions

- No patient submissions were received in support of the application.

6. Conclusion

Following NCPE assessment of the Applicant's submission, cost-effectiveness of ixazomib (Ninlaro®) for this indication has not been demonstrated and therefore is not recommended for reimbursement.