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NCCN Guidelines Panel: Multiple Myeloma

On behalf of Takeda Pharmaceutical Company Limited, I respectfully request the NCCN Multiple Myeloma Panel to review the enclosed data on the use of NINLARO (ixazomib) in combination with lenalidomide and dexamethasone as therapy for patients with previously treated multiple myeloma. NINLARO is a registered trademark of Millennium Pharmaceuticals, Inc. Millennium Pharmaceuticals, Inc. is a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

Specific Changes:
Inclusion of new phase 3 data on the use of ixazomib plus lenalidomide-dexamethasone in the NCCN Clinical Practice Guidelines (NCCN Guidelines™) for Multiple Myeloma (version V2.2016); specifically, the inclusion of:

- Ixazomib/lenalidomide/dexamethasone as a suggested Preferred Regimen (Category 1) for Previously Treated Multiple Myeloma, on slide MYEL-D (2 of 2)

In addition, we suggest the inclusion of the new data and associated references within the narrative section of the Guidelines, specifically on pages MS-29–35 of version V2.2016, where the current data on Preferred Regimens for Previously Treated Multiple Myeloma are included.

FDA Clearance: NINLARO in combination with lenalidomide and dexamethasone is approved by the US FDA for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Rationale: Data from the double-blind, randomized, placebo-controlled phase 3 TOURMALINE-MM1 (NCT01564537) clinical trial of the combination of ixazomib plus lenalidomide-dexamethasone (ixazomib regimen) versus placebo plus lenalidomide-dexamethasone (placebo regimen), in 722 patients with relapsed and/or refractory multiple myeloma, demonstrated significantly improved progression-free survival (PFS) with the ixazomib regimen. Data from the study are included in the United States prescribing information and will be presented at the 2015 Annual Meeting of the American Society of Hematology (ASH).

Supportive data:

- After a median follow-up of 14.8 and 14.6 months in the ixazomib and placebo groups, there was a 35% improvement in the primary end-point of PFS with ixazomib regimen versus placebo regimen (hazard ratio [HR] 0.742, p=0.012); median PFS was 20.6 vs 14.7 months in the ixazomib vs placebo groups, respectively.
    - In patients with high-risk cytogenetics, the HR for PFS for ixazomib vs placebo regimen was 0.543, with the median PFS in the ixazomib group similar to the

median PFS in the overall ixazomib group

- A non-inferential PFS analysis was conducted at a median follow up of 23 months with 372 PFS events. PFS HR was 0.82 (95% confidence interval [0.67, 1.0]) for ixazomib regimen versus placebo regimen, and estimated median PFS was 20 months in the ixazomib regimen and 15.9 months in the placebo regimen.
    - At the same time, a planned interim OS analysis was conducted with 35% of the required number of deaths for final OS analysis; there were 81 deaths in the ixazomib regimen and 90 deaths in the placebo regimen. An OS benefit was not demonstrated.
- Overall response rates were 78.3% in the ixazomib group and 71.5% in the placebo group (p=0.035), including 48.1% vs 39.0% very good partial response or better (≥VGPR; p=0.014) and 11.7% vs 6.6% complete response (p=0.019).
- Grade ≥3 adverse events (AEs) were reported in 68% and 61% of patients in the ixazomib and placebo groups, respectively.
    - The rate of grade 3–4 thrombocytopenia was 26% and 11% in the ixazomib and placebo groups, respectively, and the rate of grade 3-4 neutropenia was 26% and 30% in the ixazomib and placebo groups, respectively.
- The incidence of peripheral neuropathies was 28% vs 21% in the ixazomib and placebo groups (including 2% grade 3 in each group).
- Serious AEs were reported in 40% and 44% of patients in the ixazomib and placebo groups, respectively.

The following enclosures are submitted in support of the above proposed changes:

- Moreau P et al. Ixazomib, an Investigational Oral Proteasome Inhibitor (PI), in Combination with Lenalidomide and Dexamethasone (IRd), Significantly Extends Progression-Free Survival (PFS) for Patients (Pts) with Relapsed and/or Refractory Multiple Myeloma (RRMM): The Phase 3 TOURMALINE-MM1 Study (NCT01564537). Blood 2015;126(21):abstract 727; data from ASH 2015 Annual Meeting abstract.
- NINLARO® (ixazomib) capsules, for oral use. United States prescribing information, issued November 2015.

Yours sincerely,

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