FERRING
PHARMACEUTICALS

October 11, 2018

To the NCCN Committee on Prostate Cancer,

On behalf of Ferring, we respectfully request the NCCN Guidelines Committee on Prostate Cancer to review the enclosed data for: 1) re-inclusion in the 2018 guidelines under section PROS-F and 2) for consideration of additional published data in the area of cardiovascular safety differences between GnRH antagonists compared to GnRH agonists (Section MS-35).

Specific Changes:

1. Recommend the re-inclusion of the option for use of the GnRH antagonist degarelix in the areas of regional disease, adjuvant treatment of lymph node metastases, or patients on observation who require treatment and neoadjuvant, concurrent, and/or adjuvant ADT as part of radiation therapy for clinically localized disease (PROS-F).
2. Recommend the inclusion of additional data concerning observed differences in cardiovascular events between GnRH agonists and GnRH antagonists as noted in published work below – see references (MS-35 – section entitled Diabetes and Cardiovascular Disease).

FDA Clearance:

1. Both GnRH agonists and antagonists are similarly approved in the advanced prostate cancer setting which is a very broad therapeutic category. Furthermore, while neither the GnRH antagonist degarelix nor any of the GnRH agonists are explicitly approved by the FDA in the neoadjuvant setting, Androgen Deprivation Therapy (ADT) has been widely used in clinical practice and both GnRH agonists and the GnRH antagonist degarelix have all been included as therapeutic options on the NCCN guidelines in the PROS-F section in previous years.
2. Currently no ADT therapies have specific approval in the sub-population of patients with existing cardiovascular disease. However, GnRH agonists have been mandated by the FDA to include a warning for cardiovascular safety in their label, while the GnRH antagonist degarelix does not have this same requirement. This difference in requirements is not reflected in the recently updated guidelines (section MS-35 – Diabetes and Cardiovascular Disease)

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Rationale:

1. We are unaware of any recent scientific data that would support the exclusion of degarelix from the list of GnRH analogue options included in the recently update 2018 NCCN Guidelines (section PROS-F).
2. In addition to the Scailteux 2017 publication as the only reference noted in the updated 2018 Guidelines showing similarity in cardiovascular event rates, our pooled analysis (analyzed and published independently by Albertsen et al 2014), showed important differences in rates of subsequent cardiovascular events amongst patients whom have pre-existing cardiovascular disease (HR =0.44; 95% CI, 0.26-0.74; p-0.002).

References:

The following articles are submitted in support of these proposed change. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

Cardiovascular Literature:

1. Albertsen PC et al. Cardiovascular Morbidity Associated with Gonadotropin Releasing Hormone Agonists and an Antagonist. *EAU*. 2014; 565-573. *This paper aggregated data from 6 RCT's of nearly 2328 showed important differences in rates of subsequent cardiovascular events amongst patients whom have pre-existing cardiovascular disease (HR =0.44; 95% CI, 0.26-0.74; p-0.002).*
2. Margel D et al. Cardiovascular Events and Biomarkers in a Randomized Trial Comparing LHRH Agonist and Antagonist among Patients with AAdvanced Prostate Cancer. AUA. 2018; MP52-17 Abst. *This study showed prospectively (n=80), with a median follow up of 10 months; 28% (n=11) of patients randomized to LHRH agonist had a cardiovascular event compared to 7% (n=3) of those randomized to antagonists (log rank p=0.008).*

Sincerely,

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