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Health Canada Authorizes AKEEGA™ (niraparib and abiraterone acetate) Dual Action Tablets for Targeted Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) with BRCA (1/2) Gene Mutations

Approval for AKEEGA™ is based on results from the Phase 3 MAGNITUDE study, a prospectively designed precision medicine study that includes the largest cohort to date of BRCA1/2-positive patients with untreated metastatic castration-resistant prostate cancer (mCRPC)[1,2]

Niraparib in combination with abiraterone acetate plus prednisone or prednisolone (AAP), showed significant improvement in radiographic progression-free survival (rPFS) compared to AAP in mCRPC patients with BRCA1/2 mutations[3]

Toronto, June 14, 2023/CNW/ - The Janssen Pharmaceutical Companies of Johnson & Johnson announced today that Health Canada has issued a Notice of Compliance with conditions (NOC/c) for AKEEGA™ (niraparib and abiraterone acetate) tablets, plus prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious BRCA mutated (germline and/or somatic) metastatic castration resistant prostate cancer (mCRPC), who are asymptomatic/mildly symptomatic, and in whom chemotherapy is not clinically indicated. Patients must have confirmation of BRCA mutation before AKEEGA™ treatment is initiated.[4] The approval with conditions is based on a clinically meaningful radiographic progression-free survival (rPFS), time to symptomatic progression

(TSP) and time to cytotoxic chemotherapy (TCC) with continued approval contingent upon the verification and description of clinical benefit from the final OS analyses.[4]

"Patients with BRCA-altered prostate cancer face an aggressive disease that can have a worse prognosis than patients whose cancers do not have these mutations," says Dr. Kim Chi*, Medical Oncologist, BC Cancer. "Thankfully, years of research have led to the development of novel targeted therapies like the combination of niraparib with abiraterone plus prednisone that can significantly improve outcomes for the right patients. Early biomarker identification paired with targeted treatment can set a new standard of care for patients and enable physicians to take a more personalized and precision medicine approach to treating this unique subset of prostate cancers."

Prostate cancer is the most common cancer (excluding non-melanoma skin cancers) and third leading cause of cancer death among Canadian men, with an estimated 4,600 deaths in 2022.[5] Approximately 10 to 50 per cent of prostate cancer patients progress to mCRPC within three years of a diagnosis[6] of whom an estimated 10 to 15 per cent harbour a BRCA mutation.[7] Despite advancements in available therapies, the five-year survival rate for men with metastatic prostate cancer remains at 30 per cent.[8]

The presence of mutations in homologous recombination repair (HRR) genes, which include *BRCA1/2* genes, is associated with potentially an early onset of disease, a more aggressive form of the disease, a higher rate of recurrence, and poor prognosis, demonstrating the importance of biomarker testing for timely identification of these mutations.[6]

"There is a significant need among those diagnosed with this form of prostate cancer who, until now, have had no treatment options targeting their disease. It is critical for these patients to get the right treatment at the right time, underscoring the importance of early genetic testing for these biomarkers," says Jackie Manthorne**, President & CEO, Canadian Cancer Survivor Network. "The approval of this new therapy represents a clear path toward better outcomes and gives patients the hope that they can have more meaningful time with those they love."

The Health Canada NOC/c is based on positive results from the randomized, double-blind, placebo-controlled multicenter Phase 3 MAGNITUDE study.[4] The trial assessed whether the addition of niraparib to abiraterone acetate plus prednisone or prednisolone (AAP) compared with placebo plus AAP improved outcomes in those with mCRPC, with or without alterations

in HRR- associated genes, including *BRCA1/2*.[4,9] A total of 423 patients with HRR gene alterations were enrolled, 225 of whom had BRCA mutations, making this the largest cohort of *BRCA1/2*-positive patients with first line mCRPC in any clinical study to date.[1,4] At the primary analysis with a median follow-up of 18.6 months, patients with BRCA mutations who received niraparib and AAP treatment experienced an improvement in rPFS, with a 47 per cent reduction in the risk of radiographic progression or death compared with the placebo group (HR = 0.533; 95% CI: [0.361, 0.789], two-sided p = 0.0014).[3,4] Improvements in TCC and TSP were also observed although the significance boundary of 0.0001 was not met by either endpoint at the first interim analysis for these secondary endpoints.[3]

The observed safety profile of the combination of niraparib and AAP was consistent with the known safety profile of each agent, with no new safety signals identified.[4] Serious adverse events occurred in 36 per cent of patients treated with niraparib plus AAP and 25 per cent of patients treated with placebo plus AAP.[4] Permanent discontinuation due to an adverse event occurred in 10.8 per cent of patients treated with niraparib plus AAP and 6.2 per cent of patients treated with placebo plus AAP.[4] The combination of niraparib and AAP also maintained overall quality of life in comparison with placebo and AAP.[3]

AKEEGA™ will be available as regular strength tablets containing 100 mg niraparib / 500 mg abiraterone (recommended starting dose) and low-strength tablets of 50 mg niraparib / 500 mg abiraterone acetate respectively.[4]

"For the past 30 years, Janssen has been dedicated to improving patient outcomes through delivering transformational therapies where they are needed most, especially where people face devastating forms of cancer with limited treatment options," says Berkeley Vincent, President, Janssen Inc. "The approval of AKEEGA™ further strengthens our portfolio of prostate cancer therapies and enables us to take another step toward changing the trajectory of this disease."

Janssen's legacy of innovation in prostate cancer has significantly contributed to the evolution of treatment approaches for over a decade. From the first approval for ZYTIGA® (abiraterone acetate) in 2011 followed by ERLEADA® (apalutamide tablets) in 2018, Janssen has continued to build on insights from clinical research, leading to four approved indications in prostate cancer.[10,11] The authorization of AKEEGA™ marks Janssen's fifth indication for the treatment of prostate cancer across the continuum of the disease.

About AKEEGA™

AKEEGA™ (niraparib and abiraterone acetate) is an orally administered, tablets of niraparib, a highly selective poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor, and abiraterone prodrug, an androgen biosynthesis inhibitor which blocks enzyme 17a-hydroxylase/C17,20-lyase (CYP17).[4] This combination targets two oncogenic drivers in patients with mCRPC and HRR gene alterations.[4] AKEEGA™ is indicated with prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious BRCA mutated (germline and/or somatic) mCRPC, who are asymptomatic/mildly symptomatic, and in whom chemotherapy is not clinically indicated. Patients must have confirmation of BRCA mutation before AKEEGA™ treatment is initiated.[4]

The overall safety profile of AKEEGA™ is based on MAGNITUDE cohort 1, which consisted of HRR positive patients who received niraparib 200 mg once daily plus AAP (n=212) or placebo plus AAP (n=211).[4] The median duration of exposure to niraparib plus AAP was 13.8 months.[4] Serious adverse events occurred in 36 per cent of patients treated with niraparib plus AAP and 25 per cent of patients treated with placebo plus AAP.[4] Fatal adverse events occurred in 5.7 per cent of those treated with niraparib plus AAP and 3.3 per cent of patients treated with placebo plus AAP.[4] The most common adverse events (all grades) in patients treated with niraparib plus AAP were anemia, hypertension, constipation, fatigue, nausea and thrombocytopenia.[4] The most frequently observed adverse events greater or equal to grade 3 were anemia, hypertension, thrombocytopenia, neutropenia and blood alkaline phosphatase increased.[4]

Additional ongoing studies include the Phase 3 AMPLITUDE study, evaluating the combination of niraparib and AAP in a biomarker-selected patient population with metastatic castration-sensitive prostate cancer (mCSPC).[12]

About MAGNITUDE

MAGNITUDE (NCT03748641) is a Phase 3 randomized, double-blind, placebo-controlled, multicenter clinical study evaluating the safety and efficacy of the combination of niraparib and AAP for patients with mCRPC (n=765), with or without certain HRR gene alterations and who have not received prior therapy for mCRPC, and for patients with mCSPC who have only received standard of care, next-generation androgen receptor inhibitors and up to four months of AAP.[3,4] The study includes patients with (HRR biomarker [BM] positive; ATM,

BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2) and without specified gene alterations (HRR BM negative), who were randomized 1:1 to receive niraparib 200 mg once daily plus AAP or placebo plus AAP.[3] A total of 423 patients with HRR gene alterations were enrolled, 225 (53.2 per cent) of whom had BRCA mutations.[1,4] The primary endpoint of the MAGNITUDE trial is rPFS assessed by blinded independent central review.[4] Secondary endpoints include TCC, TSP and overall survival (OS).[4]

About single agents (abiraterone acetate and niraparib)

Abiraterone acetate, marketed by Janssen in Canada as ZYTIGA®, is an orally administered androgen biosynthesis inhibitor. In Canada, abiraterone acetate is indicated in combination with prednisone for the treatment of mCRPC in patients who are asymptomatic or mildly symptomatic or have received prior chemotherapy containing docetaxel after failure of androgen deprivation.[10] It is also indicated in combination with prednisone and androgen deprivation therapy (ADT) for the treatment of patients with newly diagnosed hormone-sensitive high-risk metastatic prostate cancer who may have received up to 3 months of prior ADT.[10]

In April 2016, Janssen Biotech, Inc. entered a worldwide (except Japan) collaboration and license agreement with TESARO, Inc. (acquired by GlaxoSmithKline [GSK] in 2019) for exclusive rights to niraparib in prostate cancer.

In Canada, niraparib is currently marketed by GSK as ZEJULA®, as a monotherapy for the maintenance treatment of female adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy; and for the maintenance treatment of female adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.[13]

About the Janssen Pharmaceutical Companies of Johnson & Johnson

At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity, and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular, Metabolism & Retina; Immunology; Infectious Diseases & Vaccines; Neuroscience; Oncology; and Pulmonary Hypertension.

Learn more at www.janssen.com/canada. Follow us at www.twitter.com/JanssenCanada. Janssen Inc. is one of the Janssen Pharmaceutical Companies of Johnson & Johnson.

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Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding AKEEGA™ (niraparib/abiraterone acetate). The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Inc., any of the other Janssen Pharmaceutical Companies, and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended January 1, 2023, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in Johnson & Johnson's subsequent Quarterly Reports on Form 10-Q and other filings with the Securities and Exchange Commission. Copies of these filings are available online at http://www.sec.gov/, http://www.jnj.com/ or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

*Dr. Kim Chi was not compensated for this media work. He has been compensated previously by Janssen for other professional engagements.

**Jackie Manthorne was not compensated for this media work. Canadian Cancer Survivor Network has been compensated previously by Janssen for an advisory board that Jackie Manthorne participated in.

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