4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2018-N-4627]

Intent to Consider the Appropriate Classification of Hyaluronic Acid Intra-articular Products Intended for the Treatment of Pain in Osteoarthritis of the Knee Based on Scientific Evidence

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing our intent to consider the appropriate classification of hyaluronic acid (HA) intra-articular products intended for the treatment of pain in osteoarthritis (OA) of the knee. Although HA products intended for this use have been regulated as devices (Procode MOZ; acid, hyaluronic, intra-articular), the current published scientific literature supports that HA achieves its primary intended purpose of treatment of pain in OA of the knee through chemical action within the body. Because HA for this use may not meet the definition of a device, sponsors of HA products who intend to submit a premarket approval application (PMA) or a supplement to a PMA for a change in indications for use, formulation, or route of administration are encouraged to obtain an informal or formal classification and jurisdiction determination through a Pre-Request for Designation (Pre-RFD) or Request for Designation (RFD), respectively, from FDA prior to submission. If a sponsor believes their product meets the device definition, they may provide relevant evidence in the Pre-RFD or RFD.

FOR FURTHER INFORMATION CONTACT: Leigh Hayes, Office of Combination Products, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 32, Rm. 5129, Silver Spring, MD 20993, 301-796-8938, Fax: 301-847-8619, combination@fda.gov.

SUPPLEMENTARY INFORMATION:

I. Background

HA is a linear polysaccharide formed by repeating disaccharide units of D-glucuronic acid and N-acetylglucosamine linked by β (1, 4) and β (1, 3) glycoside bonds (Ref. 1). HA is present throughout the body and in joints where it acts as a structural element (Ref. 2). It is also found in the cavities of synovial joints and plays a role in promoting the viscoelastic properties of the synovial fluid and in joint lubrication (Refs. 3 and 4).

Intra-articular administration of exogenous HA has been used to treat pain in OA of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and to certain analgesics (e.g., acetaminophen). Although HA for this use has been regulated as a Class III device (Procode MOZ; acid, hyaluronic, intra-articular), as discussed further below, the current published scientific literature supports that HA achieves its primary intended purpose of the treatment of pain in OA of the knee through chemical action within the body.

Under section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321(h)) a device "does not achieve its primary intended purposes through chemical action within or on the body," among other things. Under FDA's interpretation of this device definition, products exhibit "chemical action" if they interact at the molecular level with bodily components (e.g., cells or tissues) to mediate (including promoting or inhibiting) a bodily response, or with foreign entities (e.g., organisms or chemicals) to alter that entity's interaction

with the body; and interaction at the molecular level occurs through either chemical reaction (i.e., formation or breaking of covalent bonds), intermolecular forces (e.g., electrostatic interactions), or both (see, e.g., FDA Guidance, "Classification of Products as Drugs and Devices and Additional Product Classification Issues", available at https://www.fda.gov/RegulatoryInformation/Guidances/ucm258946.htm).

OA pain has a complex pathophysiology and has several components, including: (1) neuropathic pain (related to a lesion or disease of the somatosensory nervous system); (2) local inflammation; and (3) joint degradation (Ref. 5). During the intra-articular injection, HA is introduced to the synovial fluid of the affected joint. Previously, it was suggested that mechanical or physical actions at the joint (e.g., shock absorption) are responsible for achieving the primary intended purpose of the treatment of pain in OA of the knee; however, the current scientific literature supports that the mechanisms of action of HA also include chemical actions (e.g., chondroprotection, anti-inflammatory effects and cartilage matrix alterations) (Refs. 6 to 9). Published scientific literature supports that intra-articular injection of HA achieves its primary intended purpose of the treatment of pain in OA of the knee through multiple mechanisms (we note that the published scientific literature discussed in this notice is not exhaustive). These include, but are not limited to:

(1) *Anti-inflammatory effects*: Local inflammation is an important part of the pathophysiology of OA joint pain (Ref. 5). As such, the mitigation of inflammation can result in pain relief (Ref. 10). The scientific literature supports that HA acts though chemical action to achieve its anti-inflammatory effects. These effects are mediated through the binding of HA to cellular receptors that include the Cluster of Differentiation 44 Receptor (CD44), Receptor for Hyaluronan Mediated Motility (RHAMM), and Toll-Like Receptor (TLR)2 and TLR4, which

alter numerous downstream cell signaling activities and/or pathways resulting in anti-inflammatory effects (Refs. 9, 11, and 12). Some of the downstream anti-inflammatory effects discussed in the scientific literature include alteration of cytokines (e.g., Interleukin (IL)-1β) and inducible nitric oxide synthase (iNOS), which all have regulatory roles in inflammatory processes (Ref. 9).

(2) *Analgesic effects*: Joint inflammation is usually characterized by mechanical hyperalgesia, likely caused by an increased mechanosensitivity of joint nociceptors (Ref. 13). The scientific literature supports that HA interacts with cellular receptors (e.g., nociceptors, CD44) to reduce pain (Refs. 2, 8, 9, and 11). For instance, binding of HA to CD44 has been reported to act via signaling pathways to reduce pain, such as by downregulating Prostaglandin E2 (PGE_2) and Cyclooxygenase (COX-2) production (Refs. 2 and 11). The literature also reports that HA may also act to relieve pain by activating opioid receptors (Ref. 11). In other words, the literature explains that HA binds to cellular receptors that act to alleviate pain through modification of cellular pain pathways.

(3) *Chondroprotective effects*: Pain intensity in OA is positively associated with the degree of joint degradation (Ref. 5). HA has been reported to have chondroprotective effects by reducing the degradation and/or restoration of cartilage (Refs. 11 and 14). According to the scientific literature, much of the mechanisms responsible for these effects are through molecular pathways (e.g., CD44-initiated pathways) that have downstream biological effects that act to alter the disease state of the joint by the synthesis of extracellular matrix (ECM) proteins (e.g., collagen type II) and joint components (e.g., increased proteoglycan and glycosaminoglycan) (Refs. 2, 9, 11, and 14). Collectively, these binding interactions of HA may act on molecular pathways that serve to protect and restore cartilage.

Taken together, most of the effects described above (i.e., anti-inflammatory, analgesic, and chondroprotective) are achieved through various molecular pathways that depend on the direct interaction of HA with bodily components (e.g., cellular receptors) and downstream activation of specific signaling pathways.

Additionally, although injection of HA provides mechanical effects (e.g., shock absorption), it is believed that such effects are limited due to the short half-life of HA (Refs. 2 and 15). Exogenous-introduced HA has been reported to have a half-life of a few days or up to 30 days for cross-linked versions (Refs. 2 and 15). Nevertheless, treatment with HA has been reported to result in clinical therapeutic effect for up to 6 months following injection (Ref. 9). In other words, treatment with HA has been reported to continue reduction in pain long after it is cleared from the knee joint. This further supports that HA achieves its primary intended purpose of the treatment of pain in OA of the knee through chemical action within the body (e.g., through its anti-inflammatory and chondroprotective effects that act to mitigate the underlying OA condition).

Because the current published scientific literature supports that HA achieves its primary intended purpose of the treatment of pain in OA of the knee through chemical action, and therefore, HA for this use may not meet the definition of a device, sponsors of HA products who intend to submit a PMA or a supplement to a PMA for a change in indications for use, formulation, or route of administration are encouraged to obtain an informal or formal classification and jurisdictional determination through a Pre-RFD or RFD, respectively, from FDA prior to submission. If a sponsor believes their product meets the device definition, they may provide relevant evidence in the pre-RFD or RFD.

II. References

The following references are on display with the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; these are not available electronically at https://www.regulations.gov as these references are copyright protected. Some may be available at the website address, if listed. FDA has verified the website addresses, as of the date this document publishes in the Federal Register, but websites are subject to change over time.

1. Vasi, A.M., M. Popa, M. Butnaru, et al., "Chemical Functionalization of Hyaluronic Acid for Drug Delivery Applications." *Materials Science and Engineering*, 38: 177-185, 2014.

2. Altman, R.D., V. Dasa, and J. Takeuchi, "Review of the Mechanism of Action for Supartz FX in Knee Osteoarthritis." *Cartilage*, 9: 11-20, 2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5724672/

3. Greenberg, D.D., A. Stoker, S. Kane, et al., "Biochemical Effects of Two Different Hyaluronic Acid Products in a Co-Culture Model of Osteoarthritis." *OsteoArthritis and Cartilage*, 14: 814-822, 2006. https://www.sciencedirect.com/science/article/pii/S1063458406000367?via%3Dihub

4. Jahn, S., J. Seror, and J. Klein, "Lubrication of Articular Cartilage." *Annual Review of Biomedical Engineering*, 18: 235-258, 2016.

5. Trouvin, A.-P. and S. Perrot, "Pain in Osteoarthritis. Implications for Optimal Management." *Joint Bone Spine*, 85: 429-434, 2018.

6. Balazs, E.A., "The Physical Properties of Synovial Fluid and the Special Role of Hyaluronic Acid." In *Disorders of the Knee*, A. Helfet, pp. 63-75. Philadelphia: Lippincott Company, 1974.

7. Liao, Y.-H, S.A. Jones, B. Forbes, et al., "Hyaluronan: Pharmaceutical Characterization and Drug Delivery." *Drug Delivery*, 12: 327-342, 2005. https://www.tandfonline.com/doi/full/10.1080/10717540590952555%20

8. Moreland, L.W. "Intra-Articular Hyaluronan (hyaluronic acid) and Hylans for the Treatment of Osteoarthritis: Mechanisms of Action." *Arthritis Research and Therapy*, 5: 54-67, 2003. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC165033/

9. Altman, R.D., A. Manjoo, A. Fierlinger, et al., "The Mechanism of Action for Hyaluronic Acid Treatment in the Osteoarthritic Knee: A Systematic Review." *BMC Musculoskeletal Disorders*, 16: 321, 2015. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4621876/

10. Richards, M., J. Maxwell, L. Weng, et al., "Intra-Articular Treatment of Knee Osteoarthritis: From Anti-inflammatories to Products of Regenerative Medicine." *The Physician and Sportsmedicine*, 44: 101-108, 2016. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4932822/

11. Nicholls, M., A. Fierlinger, F. Zaizi, et al., "The Disease Modifying Effects of Hyaluronan in the Osteoarthritic Disease State." *Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders*, 10: 1-10, 2017. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5555499/

12. Migliore, A. and S. Procopio, "Effectiveness and Utility of Hyaluronic Acid in Osteoarthritis." *Clinical Cases in Mineral and Bone Metabolism*, 12: 31-33, 2015. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4469223/

13. Schaible, H.-G., F. Richter, A. Ebersberge, et al., "Joint Pain." *Experimental Brain Research*, 196: 153-162, 2009.

14. Chen, L., J. Xue, Z. Zheng, et al., "Hyaluronic Acid, an Efficient Biomacromolecule for Treatment of Inflammatory Skin and Joint Diseases: A Review of Recent Developments and Critical Appraisal of Preclinical and Clinical Investigations." *International Journal of Biological Macromolecules*, 116: 572-584, 2018.

15. Strauss, E., J. Hart, M. Miller, et al., "Hyaluronic Acid Viscosupplementation and Osteoarthritis: Current Uses and Future Directions." *The American Journal of Sports Medicine*, 37: 1636-1644, 2009.

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Leslie Kux,

Associate Commissioner for Policy.

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