June 1, 2021
Pharmaceuticals and Medical Devices Agency

Investigation Results on Diclofenac Etalhyaluronate Sodium

I. Summary of drug

[Branded name]	Joyclu 30mg intra-articular injection
[Non-proprietary name]	Diclofenac etalhyaluronate sodium
[Approval holder]	Seikagaku Corporation
[Indications]	Osteoarthritis (in the knee and hip joints)
[Estimated number of users]	Approximately 5 500 (March 23-May 28, 2021)

Outline of Investigation

Diclofenac etalhyaluronate sodium (hereinafter referred to “this drug”) is a drug substance in which diclofenac is covalently bonded to hyaluronate sodium. This drug is used for osteoarthritis treatment. This drug is administered to intra-articular space and improve clinical symptoms by anti-inflammatory and analgesic activity of diclofenac which are continuously released, as well as by stimulating production of high molecular weight hyaluronate in synoviocytes and inhibiting production of matrix metalloprotease in chondrocytes. Marketing of this drug was started in May 19, 2021.

Since its marketing approval in March 2021, a precaution for shock and anaphylaxis has been in place under the Clinically Significant Adverse Reactions section of the package insert. However, during the period from the marketing approval on March 23, 2021 to May 28, 2021, a total of 10 cases of serious shock, anaphylaxis were reported in Japan and that included 1 case that resulted in death, although the causal relationship with this drug is unknown. PMDA in consultation with expert advisors concluded that revision of precautions in the package insert was necessary.

Results of Investigation

PMDA concludes that this revision of the package insert is an emergency matter based on the following and opinions of expert advisors:

- Adverse reactions involving serious shock, anaphylaxis have been reported including a case that resulted in death.
- Multiple cases have been reported in a short period of time since the Japanese

market launch of this drug on May 19, 2021.

- A causal relationship between this drug and the serious adverse events was reasonably possible in 7 of the 10 serious cases.
- Although a precaution regarding shock, anaphylaxis has been in place since its marketing approval in March 2021 under the Clinically Significant Adverse Reactions section in the package insert of this drug, cases of an onset after the patient went back home following administration of this drug were identified in addition to cases in which the adverse reactions occurred immediately following administration. Besides healthcare professionals, precaution is also considered necessary for patients or their caregivers, etc.

In addition to the fact that serious cases of shock, anaphylaxis have been reported including a case that resulted in death, the following measures should be communicated in an attempt to ensure early detection and treatment in order to prevent serious outcomes.

1. Adequate arrangement for emergency responses should be ensured prior to administration of this drug.
2. Patients should be carefully monitored for their conditions during and after administration of this drug.
3. Patients or their caregivers, etc., should be informed adequately of the risk of shock, anaphylaxis with its signs and symptoms and should be instructed to seek medical attention immediately if any abnormalities are observed in patients.

The expert advisors present at the Expert Discussion regarding the current investigation were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the “Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Appendix 1

Diclofenac Etalhyaluronate Sodium

Revised language is underlined.

Current	Revision
(N/A)	1. WARNINGS Serious shock and anaphylaxis may occur following administration of this drug. Sufficient preparation for emergency responses should be ensured prior to administration. Patients should be carefully monitored after administration of this drug.
8. IMPORTANT PRECAUTIONS (N/A)	8. IMPORTANT PRECAUTIONS Serious shock and anaphylaxis may occur following administration of this drug. Sufficient preparation for emergency responses should be ensured prior to administration. Patients should be carefully monitored during and after administration of this drug. Patients and their caregivers, etc., should be adequately informed that shock and anaphylaxis may occur, with signs and symptoms, and that patients should seek medical attention immediately if any abnormalities are observed.

N/A: Not Applicable, because the section is not included in the current package insert or no corresponding language is included in the section.