Translated by **Pharmaceuticals and Medical Devices Agency**

Office of Safety I

July 22, 2015

Office of Safety I, Medical Device Safety Division

Partial Modifications to "Relative Contraindications Based on Notifications Issued for Revision of Precautions"

Based on "Regarding Amendments to the Notes on Compilation of Package Inserts for Medical Device" (Pharmaceutical and Food Safety Bureau [PFSB]/Safety Division [SD] Notification No. 1002-8 issued by the Director of PFSB, Ministry of Health, Labour and Welfare [MHLW] dated October 2, 2014), "Regarding the Notes on Compilation of Package Inserts for Medical Device (Bylaws)" (PFSB/SD Notification No. 1002-1 of the SD, PFSB, MHLW dated October 2, 2014), and "Regarding the Notes on Compilation of Precaution of Package Inserts for Medical Device" (PFSB/SD Notification No. 1002-5 of the SD, PFSB, MHLW dated October 2, 2014), the "Relative Contraindications" subsection of the Contraindications section has been deleted from package inserts. In association with this modification to the notes of compilation in the package insert, consultations on the revisions to the package insert are being provided to marketing authorization holders who have already established the "Relative Contraindications" subsection in the package inserts for their products, and the relevant information included in this subsection is being transferred to other sections appropriately. Similarly, for products in which revisions to precautions were instructed to include descriptions in the "Relative Contraindications" subsection, the revised descriptions must be transferred to other sections; therefore, the following 2 notifications issued have been reviewed. Results of this review are as shown in Attachment 1 and 2.

<Relevant Notifications>

Title of Notification
"Regarding Self-checks for Electrosurgical Devices, etc." (Joint Pharmaceutical and Food Safety Bureau (PFSB)/Evaluation and Licensing Division (ELD) Notification No. 1201001 of the ELD, PFSB, Ministry of Health, Labour and Welfare (MHLW) and PFSB/Safety Division (SD) Notification No. 1201001 of the SD, PFSB, MHLW dated December 1, 2003)
"Regarding Revisions of Precautions in the Package Insert for Intraocular Lens (IOL)" (Joint Pharmaceutical and Food Safety Bureau (PFSB)/Evaluation and Licensing Division (ELD)/Office of Medical Devices Evaluation (OMDE) Notification No. 0720-4 of the OMDE, ELD, PFSB, Ministry of Health, Labour and Welfare (MHLW) and PFSB/Safety Division (SD) Notification No. 0720-5 of the SD, PFSB, MHLW dated July 20, 2011)

Self-checks for Electrosurgical Devices, etc.

Of the electrosurgical devices, etc. available, products used for the purpose of necrotizing liver parenchyma cells through ablation therapy, etc. are instructed to include the following description in the “Relative Contraindications” subsection in “Regarding Self-checks for Electrosurgical Devices, etc.” (PFSB/ELD Notification No. 1201001 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW and PFSB/SD Notification No. 1201001 of the Safety Division, Pharmaceutical and Food Safety Bureau, MHLW dated December 1, 2003). This description was included for patients who have a history of undergoing biliary tract reconstruction associated with pancreaticoduodenectomy, etc. as these patients may suffer from decreased or complete loss of sphincter function in the duodenal papilla. As a result, these products are reported to possibly cause severe complications such as liver abscess or sepsis associated with bacteria proliferation due to retrogradation of intestinal bacteria in necrotic sites of the liver after undergoing ablation of liver parenchyma cells, etc.

“RELATIVE CONTRAINDICATIONS (As a general rule, this device is contraindicated in the following patients. If the use of this device is considered essential, it should be used carefully.)”

Patients who have a history of undergoing surgery related to the biliary tract.
[There are risks of severe complications such as liver abscess or sepsis associated with bacteria proliferation due to retrogradation of intestinal bacteria in necrotic sites of the liver after undergoing ablation of liver parenchyma cells, etc.]

Currently, the positioning and candidate sections to transfer the above description to in the package insert have been discussed with the Japanese Society of Interventional Radiology (JSIR), the Japan Society of Hepatology, and Liver Cancer Study Group of Japan.

All these relevant medical societies believe that patients who have a history of undergoing surgery related to the biliary tract should not be included in the Contraindications section as there are cases where ablation therapy, etc. can be conducted in a safe manner as long as decisions regarding eligibility are made cautiously and appropriate measures such as post-operative administration of antibiotics are adopted. However, they think it is important for physicians carrying out the procedure to be sufficiently aware of possible risks of severe complications such as liver abscess or sepsis associated with bacteria proliferation due to retrogradation of intestinal bacteria in necrotic sites of the liver after undergoing ablation of liver parenchyma cells, etc. when using such products for patients who have a history of undergoing surgery related to the biliary tract. As a result, they consider that the description should be moved to the “Precautions” section, which includes information regarding cases with high risk of malfunctions or adverse events compared to other patient types. Through continuous provision of information in such a manner, they believe physicians carrying out such procedures will be made aware of the associated risks.

Based on the above opinion, it should be appropriate to revise the descriptions as follows:

“PRECAUTIONS (The device should be used carefully in the following patients.)”
Patients who have a history of undergoing surgery related to the biliary tract. [There are risks of severe complications such as liver abscess or sepsis associated with bacteria proliferation due to retrogradation of intestinal bacteria in necrotic sites of the liver after undergoing ablation of liver parenchyma cells, etc.] (See “Important Precautions.”)

“IMPORTANT PRECAUTIONS”
If the patient has a history of undergoing biliary tract reconstruction associated with pancreaticoduodenectomy, the patient may suffer from decreased or complete loss of sphincter function in the duodenal papilla. As a result, there may be risk of severe complications such as liver abscess or sepsis associated with bacteria proliferation due to retrogradation of intestinal bacteria in necrotic sites of the liver after undergoing ablation of liver parenchyma cells, etc. Therefore, the product should be used carefully after reviewing the sphincter function of the duodenal papilla and ablation site, etc.

"Revisions of Precautions for Intraocular Lens (IOL)"

At the Subcommittee on Medical Device Safety, Committee on Medical Device Safety, Pharmaceutical Affairs and Food Sanitation Council held on June 22, 2011, use of intraocular lens (IOL) in children was discussed. As a result, it was agreed that the use of IOL for children aged 2 or older should be included in "Precautions" while the use for children under 2 years of age should be included in "Relative Contraindications." For the latter group, considering the benefits for early prevention of irreversible cataract-related amblyopia caused by impaired development of the optic nerves and visual cortex, IOL should be used carefully when considered necessary based on the risks and benefits while the observed risks of additional surgeries due to axial length growth were acknowledged. Based on the agreements, the following description is instructed in "Regarding Revisions of Precautions in the Package Insert for Intraocular Lens (IOL)" (PFSB/ELD/OMDE Notification No. 0720-4 of the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW and PFSB/SD Notification No. 0720-5 of the Safety Division, Pharmaceutical and Food Safety Bureau, MHLW dated July 20, 2011) to be included in the "Relative Contraindications" subsection, etc.

"RELATIVE CONTRAINDICATIONS (As a general rule, IOL is contraindicated in the following patients. If the use of IOL is considered essential, it should be used carefully.)"
Children under 2 years of age (See "Important Precautions")

"PRECAUTIONS (IOL should be used carefully in the following patients.)"
Children aged 2 or older

"IMPORTANT PRECAUTIONS"
IOL implantation should be performed in children under the supervision of ophthalmologists with adequate knowledge and experience of characteristics of children. Especially, IOL implantation and manipulation could be difficult in the small eyes of children under 2 years of age, and it has been reported that additional surgery may be required due to axial length growth. The child's guardian should be thoroughly informed of these possible risks in advance.

Currently, the positioning and candidate sections to transfer the above descriptions to in the package insert have been discussed with experts from Japanese Ophthalmological Society who participated in the Subcommittee of Medical Device Safety as witnesses.

Japanese Ophthalmological Society expressed their opinion as follows:
While risks of additional surgery associated with axial length growth etc. are observed to be higher among children under 2 years of age, IOL should not be contraindicated for such patients. However, it is particularly important for physicians carrying out the procedure to sufficiently understand that, in children under 2 years of age, IOL implantation and manipulation could be difficult in their small eyes and there is an increased risk of additional surgery due to axial length growth. Therefore, current alert for caution in the "Important Precautions" section should be maintained and children can be included collectively in the "Precautions" section without differentiating those aged 2 or older and those under 2 years of age.

Based on the above opinion, it should be appropriate to revise the descriptions as follows:

"PRECAUTIONS (IOL should be used carefully in the following patients.)"
Pediatrics (See "Important Precautions".)

"IMPORTANT PRECAUTIONS"
IOL implantation should be performed in children under the supervision of ophthalmologists with adequate knowledge and experience of characteristics of children. Especially, IOL implantation and manipulation could be difficult in the small eyes of children under 2 years of age, and it has been reported that additional surgery may be required due to axial length growth. The child's guardian should be thoroughly informed of these possible risks in advance, and IOL should be used carefully after considering the risks and benefits.