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.

Summary of Investigation Results

Ritodrine hydrochloride, magnesium sulfate hydrate/glucose, magnesium sulfate hydrate (indicated for eclampsia)

March 30, 2021

Non-proprietary name

a. Ritodrine hydrochloride (injection)
b. Ritodrine hydrochloride (oral dosage form)
c. Magnesium sulfate hydrate/glucose
d. Magnesium sulfate hydrate

Branded name (Marketing authorization holder)

a. Utemerin Injection 50 mg (Kissei Pharmaceutical Co., Ltd.), and the others
b. Utemerin Tablets 5 mg (Kissei Pharmaceutical Co., Ltd.), and the others
c. Magsent Injection 100 mL, Magsent Injection Syringe 40 mL, Magnesol for Intravenous Injection 20 mL (Aska Pharmaceutical. Co., Ltd.)
d. Magnesium Sulfate Hydrate "NikP" (Nichi-Iko Pharmaceutical Co., Ltd.)

Indications

a. Threatened abortion/premature labour that requires emergency treatment
b. Threatened abortion/premature labour
c. Magsent Injection 100 mL, Magsent Injection Syringe 40 mL:
   1. Inhibition of uterine contractions in threatened premature labour
   2. Prophylaxis and treatment of eclampsia in severe hypertensive disorders of pregnancy

   Magnesol for Intravenous Injection 20 mL:

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Prophylaxis and treatment of eclampsia in severe hypertensive disorders of pregnancy

d. Constipation (oral dosage form)
Cholelithiasis (infusion via duodenal tube)
Hypomagnesaemia (injection)
Eclampsia (injection)
Tachyarrhythmia (injection)

Summary of revisions

a.

1. A cautionary statement should be added to the IMPORTANT PRECAUTIONS section concerning hypoglycaemia in infants born to mothers who were administered ritodrine hydrochloride (injection).
2. A cautionary statement should be added to the IMPORTANT PRECAUTIONS section concerning hyperkalaemia in infants born to mothers who were co-administered ritodrine hydrochloride (injection) with magnesium sulfate hydrate (injection).
3. Increased risks of hyperkalaemia that have been reported in infants born preterm should be added to the language concerning magnesium sulfate hydrate (injection) in the Precautions for Co-administration section.
4. “Neonatal hyperkalaemia” should be added to the Clinically Significant Adverse Reactions section.

b.

<Old instructions>

“Neonatal hyperkalaemia” should be added to the language concerning events reported with ritodrine hydrochloride (injection) in the Clinically Significant Adverse Reactions section.

<New instructions>

“Neonatal hyperkalaemia” should be added to the language concerning events reported with ritodrine hydrochloride (injection) in the OTHER PRECAUTIONS section.

c.

1. A cautionary statement should be added to the IMPORTANT PRECAUTIONS section concerning hyperkalaemia in infants born to mothers who were co-administered magnesium sulfate hydrate/glucose with ritodrine hydrochloride (injection).
2. Ritodrine hydrochloride (injection) should be added to the Precautions for Co-

administration section followed by language concerning increased risks of hyperkalaemia that have been reported in infants born preterm.

d.

1. A cautionary statement should be added to the IMPORTANT PRECAUTIONS section concerning hyperkalaemia in infants born to mothers who were co-administered magnesium sulfate hydrate for eclampsia during administration of ritodrine hydrochloride (injection).
2. Ritodrine hydrochloride (injection) should be added to the Precautions for Co-administration section followed by language concerning increased risks of hyperkalaemia that have been reported in infants born preterm.

Investigation results and background of the revision

Based on the results of the investigation conducted by the Japan Society of Perinatal and Neonatal Medicine (Scientific Reports. 2020;10:7804) on hypoglycaemia and hyperkalaemia in infants born to mothers who were administered ritodrine or magnesium sulfate, as well as cases of neonates involving hypoglycaemia and hyperkalaemia with the use of ritodrine hydrochloride, magnesium sulfate hydrate/glucose, and magnesium sulfate hydrate (indicated for eclampsia) reported in Japan, MHLW/PMDA in consultation with expert advisors concluded that revision of the package inserts was necessary.

Number of cases and patient mortalities* reported in Japan during the previous 3 fiscal years

Cases involving neonatal hyperkalaemia

a. A total of 8 cases have been reported to date (including 4 cases for which a causal relationship between the drug and event was reasonably possible). 1 instance of patient mortality has been reported to date (A causal relationship could not be established for this case.)
b. No cases have been reported to date.

c.

· Magsent Injection 100 mL, Magsent Injection Syringe 40 mL

Not investigated ‡

· Magnesol for Intravenous Injection 20 mL

No cases have been reported to date.

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d. No cases have been reported to date.

Cases involving neonatal hypoglycaemia

a. Not investigated ‡

b., c., d. No cases have been reported to date.

*: Cases were retrieved if it could be determined:

That the combination of ritodrine hydrochloride and magnesium sulfate hydrate or magnesium sulfate hydrate/glucose intended for threatened premature labour or eclampsia was not administered, and that neonates (younger than 28 days old) were reported judging from their age.

‡: Predictable from precautions in the package insert

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).