Dear Healthcare Professional Letter of Rapid Safety Communication

September 2012

RANMARK SUBCUTANEOUS INJECTION 120mg (denosumab）

-Risk of severe hypocalcaemia, including fatal cases

11 September 2012

Dear Healthcare Professional,

DAIICHI SANKYO COMPANY, LIMITED would like to inform you of new important safety information related to hypocalcaemia associated with RANMARK (denosumab). There have been reported 32 cases of severe hypocalcaemia from 17 April 2012 to 31August 2012. Of them, there were 2 fatal cases for which the causality to the drug could not be ruled out. (The number of patients using this drug after launching the drug estimated by MAHs: approximately 7,300) In the light of this situation, package inserts of RANMARK has been revised to include WARNINGS to the section of Precautions.

Serum calcium should be measured before administration of RANMARK

Serum electrolyte levels such as serum calcium should be measured before administration of the drug. Corrected serum calcium levels* should be checked, and if hypocalcaemia is observed, pre-existing hypocalcaemia must be corrected prior to initiating therapy. Hypocalcaemia can occur at any time from within a few days after initiating the administration of this drug. Serum electrolyte levels such as serum calcium should be monitored frequently and patients should be carefully monitored after the start of the treatment.

Oral Supplementation of Calcium and vitamin D is required.

To reduce the risk of onset of hypocalcaemia, supplementation of calcium (at least 500mg/day) and natural vitamin D (at least 400 IU/day) is required in all patients every

day unless corrected serum calcium levels are high. For Patients with renal impairment, activated vitamin D should be used depending on the degree of renal impairment, due to the impaired activation of vitamin D. Calcium supplementation should be determined as needed and dosage of calcium should be adjusted appropriately.

Patients with severe renal impairment are at a greater risk of developing hypocalcaemia and therefore use the drug cautiously.

If hypocalcaemia is observed, calcium and vitamin D should be administered orally and when requiring emergency treatment, appropriate measures such as concomitant use of I.V. administration of calcium should be taken.

*In patients with hypoalbuminaemia, corrected serum calcium levels applying the following formula should be used due to false low calcium levels, when patients have serum albumin levels ＜4.0g/dL.
Corrected serum calcium levels (mg/dL) = serum calcium levels (mg/dL)＋4－serum albumin levels (g/dL)

Annex: revised copy of the RANMARK of package inserts

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Revision of the package insert of denosumab	Current
【Warnings】 1. Severe hypocalcaemia can occur at any time from within a few days after initiating the administration of denosumab and some fatal cases have been reported. When administrating this drug, blood test should be frequently performed and patients should be closely monitored. To reduce the risk of onset of hypocalcaemia, oral supplementation of calcium and vitamin D is required unless the corrected serum calcium levels are high (see also the section of “Precautions of dosage and administration”). 2. Patients with severe renal impairment are at a greater risk of developing hypocalcaemia and therefore use the drug cautiously (see also the section of “careful administration”). 3. If hypocalcaemia is observed after the initiation of the drug, when requiring emergency treatment, appropriate measures such as concomitant use of I.V. administration of calcium should be taken in addition to oral administration of calcium and vitamin D (see also the section of “Clinically significant adverse reactions”).	*None*
【 Precautions of dosage and administration】 *1. Same as current statement* 2. To reduce the risk of onset of hypocalcaemia, supplementation of calcium (at least 500mg/day) and natural vitamin D (at least 400 IU/day) is required in all patients every day unless the corrected serum calcium levels are high (see also the section of “clinical data”). For Patients with severe renal impairment, activated vitamin D should be used depending on the degree of renal impairment, due to the impaired activation of vitamin D. Calcium supplementation should be determined as needed and dosage of calcium should be adjusted appropriately.	**【 Precautions related to dosage and administration】** *Omission*

【Precautions】 1.Careful Administration： *1) Same as current statement* 2) Patients with severe renal impairment [Those patients are at greater risk of developing hypocalcaemia. In Phase III Clinical Trials of denosumab, patients with severe renal impairment (creatinine clearance < 30 mL/min) or patients with end stage renal failure requiring dialysis were excluded from the trials and there is only limited experience with the drug in those patients (see also the section of “clinical data”).]	**【Precautions】** 1.Careful Administration： *1) Omission* 2) Patients with severe renal impairment [There is only limited experience with the drug in those patients. Those patients are at greater risk of developing hypocalcaemia (see also the section of “clinical data”)].
2. Important precautions *1) ~2) same as current statement* 3) Hypocalcaemia may occur. Patients should be measured serum electrolyte levels such as serum calcium and phosphorus before the start of treatment. Check the level of corrected serum calcium, and if hypocalcaemia observed, pre-existing hypocalcaemia must be corrected prior to initiating therapy. 4) Hypocalcaemia can occur at any time from within a few days after initiating the administration of the drug. Serum electrolyte levels such as serum calcium should be monitored frequently and patients should be carefully monitored after the start of the treatment. *5) same as current statement of 6)* *6) same as current statement of 7)*	2. Important precautions *1) ~2) Omission* 3) Hypocalcaemia may occur. Patients should be measured serum electrolyte levels such as serum calcium and phosphorus before the start of treatment. If hypocalcaemia observed, pre-existing hypocalcaemia must be corrected prior to initiating therapy. 4) Hypocalcaemia can occur at any time from within a few days after initiating the administration of the drug. Patients should be carefully monitored and measured serum electrolyte levels such as serum calcium and phosphorus on a regular basis. To reduce the risk of onset of hypocalcaemia, oral supplementation of calcium and vitamin D is required in all patients every day unless the corrected serum calcium levels are high (see also the section of “clinical performance”). 5) If Hypocalcaemia with clinical symptoms such as tetany and numbness is observed, intravenous administration of calcium is effective. *6) Omission* *7) Omission*

3. Adverse reactions *Same as current statement* 1. Significantly Adverse reactions 1) Hypocalcaemia (5.8%) : Hypocalcaemia with symptoms including QT prolongation, seizures, tetany, numbness, disorientation may occur, and some cases leading to fatal cases have been reported. Patients should be carefully monitored, and if hypocalcaemia is observed after the initiation of the drug, when requiring emergency treatment, appropriate measures such as concomitant use of I.V. administration of calcium should be taken immediately in addition to oral administration of calcium and vitamin D. *2)~3) same as current statement* *2, 3 are same as current statement*	3 Adverse reactions *Omission* 1. Significantly Adverse reactions 1) Hypocalcaemia (5.8%): Hypocalcaemia with symptoms including seizures, tetany, numbness, disorientation and QT prolongation may occur. Patients should be carefully monitored, and If abnormalities are observed, appropriate measures such as intravenous administration of calcium should be taken. As well, some cases of severe hypocalcaemia leading to fatal cases are reported overseas. *2)~3) Omission* *2, 3 are same as current statement*

- (___) Revision recommended by MHLW, (_____) voluntary change by MAH, (_ _ _ _) deleted