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# Summary of Investigation Results

## Bisphosphonates, denosumab (genetical recombination), and romosozumab (genetical recombination)

July 20, 2021

**Non-proprietary name**

See Attachment

**Branded name (Marketing authorization holder)**

See Attachment

**Indications**

See Attachment

**Summary of revisions**

a.-h.

1. A statement should be added to the IMPORTANT PRECAUITIONS section that occurrence of atypical fracture in nonfemur sites (such as proximal ulnar shaft) has been reported.
2. “Atypical fracture of subtrochanteric femur and proximal femoral shaft” in the Clinically Significant Adverse Reactions section should be revised to “atypical fracture of subtrochanteric femur, proximal femoral shaft, proximal ulnar shaft, or other sites.”

i.

A statement that occurrence of atypical fracture in nonfemur sites (such as proximal ulnar shaft) has been reported should be added to the precaution in the IMPORTANT PRECAUTIONS section concerning atypical fracture of femur in patients on long-term treatment with bisphosphonates.



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**Investigation results and background of the revision**

Adverse reaction reports of atypical fracture in ulna, etc. following administration of bisphosphonates (hereinafter referred to as “BP preparations”) or denosumab (genetical recombination) (hereinafter referred to as “denosumab”) have been identified. Necessity and scope of revision of Japanese package inserts were discussed.

Taking the following into account and in consultation with expert advisors, MHLW/PMDA concluded that revision of the IMPORTANT PRECAUTIONS section and the Clinically Significant Adverse Reactions section was necessary for the package inserts of all BP preparations and denosumab.

- Findings similar to those in atypical femur fracture have been identified among the reported atypical fractures in nonfemur sites (such as ulna or tibia) that occurred following administration of BP preparations or denosumab such as a traverse fracture image and thickened bone lateral cortex, being induced by mild external force, bilaterally occurring, or delayed healing observed.
- Cases involving nonfemur atypical fracture reported in Japan have been identified for which a causal relationship with BP preparations or denosumab was reasonably possible.
- It has been reported that an involvement of suppression of bone turnover induced by long-term administration of BP preparations or denosumab is indicated in the occurrence of atypical femoral fracture (J Bone Miner Res 2010; 25(11): 2267-94, etc.). The risk of atypical fracture on nonfemur sites could not be ruled out depending on the sites subjected to external load.

Regarding romosozumab (genetical recombination) (hereinafter referred to as romosozumab), MHLW/PMDA considered the following and in consultation with expert advisors concluded that revision of the IMPORTANT PRECAUTIONS section alone was appropriate at this time.

- Given the effect to increase bone formation that romosozumab also has, the risk of atypical fracture caused by its effect to suppress bone turnover is presumably lower compared with BP preparations and denosumab.
- No information is currently available on the safety associated with long-term administration of romosozumab.



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・ No cases involving nonfemur atypical fracture have been reported in Japan to date.

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

Cases involving nonfemur atypical fracture

a. A total of 9 cases have been reported to date. (A causal relationship between the drug and event was reasonably possible for these cases.)
No patient mortalities have been reported to date.

b. A total of 4 cases have been reported to date (including 2 cases for which a causal relationship between the drug and event was reasonably possible).
No patient mortalities have been reported to date.

c. No cases have been reported to date.

d. A total of 2 cases have been reported to date. (A causal relationship between the drug and event was reasonably possible for these cases.)
No patient mortalities have been reported to date.
By branded name,
(1) A total of 2 cases have been reported. (A causal relationship between the drug and event was reasonably possible for these cases.)
(2) No cases have been reported.

e. No cases have been reported to date.

f. A total of 2 cases have been reported to date. (A causal relationship between the drug and event was reasonably possible for these cases.)
No patient mortalities have been reported to date.

g. A total of 6 cases have been reported to date (including 5 cases for which a causal relationship between the drug and event was reasonably possible).
No patient mortalities have been reported to date.

h. A total of 5 cases have been reported to date (including 3 cases for which a causal relationship between the drug and event was reasonably possible).
No patient mortalities have been reported to date.
By branded name,
(1) A total of 2 cases have been reported (including 1 case for which a causal relationship between the drug and event was reasonably possible).
(2) A total of 2 cases have been reported (including 1 case for which a causal relationship between the drug and event was reasonably possible).

1 case has been reported with the branded name unknown. (A causal relationship between the drug and event was reasonably possible for this case.)

i. No cases have been reported to date.
(Japanese market launch: March 2019)

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).

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Attachment

| | Nonproprietary name | Branded name | Approval holder | Indications |
|---|---|---|---|---|
| a | Alendronate sodium hydrate | (1) Bonalon Tablet 5 mg, 35 mg, Bonalon Oral Jelly 35mg, Bonalon Bag for I.V. Infusion 900 μg<br>(2) Fosamac Tablets 5, 35 mg<br>and the others | (1) Teijin Pharma Limited.<br>(2) MSD K.K.<br>and the others | Osteoporosis |
| b | Ibandronate sodium hydrate | Bonviva Tablets 100 mg, Bonviva Syringes for Intravenous Injection 1 mg | Chugai Pharmaceutical Co., Ltd. | Osteoporosis |
| c | Etidronate disodium | Didronel Tablets 200 | Sumitomo Dainippon Pharma Co., Ltd. | ・Osteoporosis<br>・Prevention of ectopic ossification in the early or advanced stages in the following conditions<br>Post-spinal cord injury or post-hip arthroplasty<br>・Paget's disease of bone |
| d | Zoledronic acid hydrate | (1) ZOMETA for i.v. infusion 4 mg/5 mL, 4 mg/100 mL, and the | (1) Novartis Pharma K.K., and the others | (1)<br>・Hypercalcaemia of malignancy |



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| | Nonproprietary name | Branded name | Approval holder | Indications |
|---|---|---|---|---|
| | | others<br>(2) Reclast for I.V. Injection 5 mg | (2) Asahi Kasei Pharma Corporation | ・Bone lesion associated with multiple myeloma or bone metastasis of solid carcinoma<br>(2)<br>Osteoporosis |
| e | Pamidronate disodium hydrate | Pamidronate Disodium intravenous for drip use 15 mg "F", 30 mg "F", and the others | Fuji Pharma Co., Ltd., and the others | 1. Hypercalcaemia of malignancy<br>2. Osteolytic bone metastases of breast cancer (to be used in combination with chemotherapy, endocrine therapy or radiotherapy)<br>3. Osteogenesis Imperfecta |
| f | Minodronic acid hydrate | (1) Bonoteo Tablets 1 mg, 50 mg<br>(2) Recalbon Tablets 1 mg, 50 mg<br>and the others | (1) Astellas Pharma Inc.<br>(2) ONO Pharmaceutical Co., Ltd.<br>and the others | Osteoporosis |



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| | Nonproprietary name | Branded name | Approval holder | Indications |
|---|---|---|---|---|
| g | Sodium risedronate hydrate | (1) Actonel Tablets 2.5 mg, 17.5 mg, 75 mg<br>(2) Benet Tablets 2.5 mg, 17.5 mg, 75 mg<br>and the others | (1)EA Pharma Co., Ltd.<br>(2) Takeda Pharmaceutical Company Limited.<br>and the others | ・2.5mg, 75 mg Tablets<br>Osteoporosis<br>・17.5 mg Tablets<br>Osteoporosis<br>Paget's disease of bone |
| h | Denosumab (genetical recombination) | (1) Ranmark Subcutaneous Injection 120 mg<br>(2) Pralia Subcutaneous Injection 60 mg Syringe | (1), (2) Daiichi Sankyo Co., Ltd. | (1)<br>・Bone lesion associated with multiple myeloma or bone metastasis of solid carcinoma<br>・Bone giant cell tumor<br>(2)<br>・Osteoporosis<br>・Suppressing progression of bone erosion associated with rheumatoid arthritis |
| i | Romosozumab (genetical recombination) | Evenity Subcutaneous Injection 105 mg Syringes | Amgen K.K. | Osteoporosis with high risk of bone fracture |



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