



Summary of investigation results

Bisphosphonates

Etidronate Disodium, Pamidronate Disodium Hydrate, Alendronate Sodium Hydrate, Risedronate Sodium Hydrate, Zoledronic Acid Hydrate, Minodronic Acid Hydrate, Ibandronate Sodium Hydrate

May 31, 2016

Non-proprietary name

- a. Etidronate disodium
- b. Pamidronate disodium hydrate
- c. Alendronate sodium hydrate
- d. Risedronate sodium hydrate
- e. Zoledronic acid hydrate
- f. Minodronic acid hydrate
- g. Ibandronate sodium hydrate

Brand name (Marketing authorization holder)

- a. Didronel Tablets 200 mg (Sumitomo Dainippon Pharma Co., Ltd.)
- b. Aredia for I.V. Infusion 15 mg, 30 mg (Novartis Pharma K.K.), and the others
- c. Teiroc Injection 5 mg, 10 mg, Bonalon Tablets 5 mg, 35 mg, Bonalon Oral Jelly 35 mg, Bonalon Bag for I.V. Infusion 900 µg (Teijin Pharma Limited.), Fosamac Tablets 5 mg, 35 mg (MSD K.K.), and the others
- d. Actonel Tablets 2.5 mg, 17.5 mg, 75 mg, Benet Tablets 2.5 mg, 17.5 mg, 75 mg (EA Pharma Co., Ltd., Takeda Pharmaceutical Company Limited.), and the others
- e. Zometa for I.V. Infusion 4 mg/5 mL, 4 mg/100 mL (Novartis Pharma K.K.), and the others
- f. Bonoteo Tablets 1 mg, 50 mg (Astellas Pharma Inc.), Recalbon Tablets 1 mg, 50 mg (Ono Pharmaceutical Co., Ltd.)
- g. Bonviva Injection 1 mg Syringe, Bonviva Tablets 100 mg (Chugai Pharmaceutical Co., Ltd.)

Pharmaceuticals and Medical Devices Agency

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Indications

Refer to the attachment below.

Summary of revision

1. Precautions regarding osteonecrosis of external auditory canal should be newly added in the Important Precautions section.
2. "Osteonecrosis of external auditory canal" should be newly added in the Clinically significant adverse reaction section.

Background of the revision and investigation results

There have been reports of safety measures overseas that osteonecrosis of external auditory canal was added in the summary of product characteristics for bisphosphonates in Europe. In addition, cases of osteonecrosis of external auditory canal have been reported in patients treated with bisphosphonates in Japan and overseas. Following an investigation result based on the opinions of expert advisors and the available evidence, the MHLW/PMDA concluded that revision of the package insert was necessary.

The number of reported adverse reactions and fatal cases in the last 3 fiscal years in Japan

No cases associated with osteonecrosis of external auditory canal has been reported.

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.

Attachment

	Active ingredients	Applicable brand names	Launch in Japan	Indications	Name of company
a.	Etidronate disodium	Didronel Tablet 200	November 1990	Osteoporosis, prevention of heterotopic ossification in the early or advanced stages after the following conditions (spinal cord injury, hip replacement), Paget's disease of bone	Dainippon Sumitomo Pharma Co., Ltd.
b.	Pamidronate disodium hydrate	Aredia for I.V. Infusion 15 mg Aredia for I.V. Infusion 30 mg	September 1994	Hypercalcaemia of malignancy, osteolytic bone metastases of breast cancer (to be used concomitantly with chemotherapy, endocrine therapy, or radiotherapy), osteogenesis imperfecta	Novartis Pharma K.K.
c.	Alendronate sodium hydrate	Teiroc Injection 5 mg	July 1997	Hypercalcaemia of malignancy	Teijin Pharma Limited
		Teiroc Injection 10 mg			
		Bonalon Tablets 5 mg	August 2001	Osteoporosis	
		Bonalon Tablets 35 mg	September 2006		
		Bonalon Oral Jelly 35 mg	March 2013		
		Bonalon Bag for I.V. Infusion 900µg	May 2012		
		Fosamac Tablets 5 mg	August 2001	Osteoporosis	
Fosamac Tablets 35 mg	September 2006				

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	Active ingredients	Applicable brand names	Launch in Japan	Indications	Name of company
d.	Risedronate sodium hydrate	Actonel Tablets 2.5 mg	May 2002	Osteoporosis	EA Pharma Co., Ltd.
		Actonel Tablets 17.5 mg	July 2007	Osteoporosis, Paget's disease of bone	
		Actonel Tablets 75 mg	February 2013	Osteoporosis	
		Benet Tablets 2.5 mg	May 2002	Osteoporosis	Takeda
		Benet Tablets 17.5 mg	June 2007	Osteoporosis, Paget's disease of bone	Pharmaceutical
		Benet Tablets 75 mg	December 2013	Osteoporosis	Company Limited
e.	Zoledronic acid hydrate	Zometa for I.V. Infusion 4 mg/5 mL	January 2005	Hypercalcaemia of malignancy, bone lesion associated with multiple myeloma or bone metastases from solid tumors	Novartis Pharma K.K.
		Zometa for I.V. Infusion 4 mg/100mL	February 2013		
f.	Minodronic acid hydrate	Bonoteo Tablets 1 mg	April 2009	Osteoporosis	Astellas Pharma Inc.
		Bonoteo Tablets 50 mg	September 2011		
		Recalbon Tablets 1 mg	April 2009	Osteoporosis	Ono Pharmaceutical Co., Ltd.
		Recalbon Tablets 50 mg	September 2011		
g.	Ibandronate sodium hydrate	Bonviva Injection 1 mg Syringe	August 2013	Osteoporosis	Chugai Pharmaceutical Co., Ltd.
		Bonviva Tablets 100 mg	April 2016		