March 2010

Updated safety information on reports of renal impairment and renal failure with Aclasta (zoledronic acid, 5 mg solution for infusion)

Dear Healthcare Professional

Summary

- **Renal impairment and renal failure have been observed following the administration of Aclasta, especially in patients with pre-existing renal dysfunction or other risks, including advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy, or dehydration occurring after Aclasta administration.**
- **Renal impairment has been observed in patients after the first administration.**
- **Renal failure requiring dialysis or with a fatal outcome has occurred rarely.**
- **It is important that Aclasta is not administered to patients with creatinine clearance < 35 ml/min, that the patient is appropriately hydrated and that monitoring of serum creatinine is considered for patients at risk.**

Further information on the safety concern

Novartis has received spontaneous reports of renal impairment following administration of Aclasta (18 cases per 100,000 patient years). In the majority of cases the following risk factors were observed: advanced age, concomitant medicinal products with known renal toxicity (e.g. NSAIDs and diuretics) and/or pre-existing co-morbidities such as cardiovascular and metabolic diseases, infection, renal impairment, concurrent or preceding dehydration. Rare cases of renal failure requiring dialysis and rare cases with a fatal outcome have been reported in patients with pre-existing renal dysfunction or other risk factors. As of 14 August 2009, the cumulative worldwide patient exposure of Aclasta was estimated to be 777,607 patient-treatment-years.

Advice for health care professionals

The following precautions should be taken into account to minimise the risk of renal adverse reactions:

- Creatinine clearance should be measured before each Aclasta dose.
- Aclasta should not be used in patients with creatinine clearance < 35 ml/min.
- Transient increase in serum creatinine may be greater in patients with underlying impaired renal function.
- Monitoring of serum creatinine should be considered in at-risk patients.
- Aclasta should be used with caution when concomitantly used with other medicinal products that could impact renal function.
- Patients, especially elderly patients and those receiving diuretic therapy, should be appropriately hydrated prior to administration of Aclasta.
- A single dose of Aclasta should not exceed 5 mg and the duration of infusion should be at least 15 minutes.

Changes of Summary of Product Characteristics (SmPC)
Precautions to minimise the risk of renal adverse reactions have been amended to the SmPC Section 4.4 (Special warnings and precautions for use) and Section 4.8 (Undesirable effects), the "Renal and urinary disorders" section of Table 1 has been amended with information on the risk of renal impairment (See ANNEX 1).

The content of this letter has been agreed with European Medicines Agency and the National Competent Authorities.

Call for reporting
Healthcare professionals should report any suspected adverse reactions associated with the use of Aclasta (see below).

Suspected adverse drug reactions with the use of Aclasta should be reported to the Irish Medicines Board by use of the IMB web-site (www.imb.ie). Adverse events should also be reported to Novartis by phone to 01-2080612 or by email to drugsafety.dublin@novartis.com.

Communication information
Should you have any questions or require additional information regarding the use of Aclasta (zoledronic acid), please contact Novartis Ireland at 01 2601255**.**

Dr. Greg Hays
Medical Director, Novartis Ireland

ANNEX 1

Information in the SmPC concerning the risk of renal impairment

Section 4.2

Patients with renal impairment
Aclasta should not be used in patients with creatinine clearance < 35 ml/min (see section 4.4).

Section 4.4 Special warnings and precautions for use

Renal impairment has been observed following the administration of Aclasta (see section 4.8), especially in patients with pre-existing renal dysfunction or other risks including advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy (see section 4.5), or dehydration occurring after Aclasta administration. Renal failure requiring dialysis or with fatal outcome has rarely occurred in patients with underlying renal impairment or with any of the risk factors described above.

The following precautions should be taken into account to minimise the risk of renal adverse reactions:
- Creatinine clearance should be measured before each Aclasta dose.
- Aclasta should not be used in patients with creatinine clearance < 35 ml/min (see section 5.2).
- Transient increase in serum creatinine may be greater in patients with underlying impaired renal function.
- Monitoring of serum creatinine should be considered in at-risk patients.
- Aclasta should be used with caution when concomitantly used with other medicinal products that could impact renal function (see section 4.5).
- Patients, especially elderly patients and those receiving diuretic therapy, should be appropriately hydrated prior to administration of Aclasta.
- A single dose of Aclasta should not exceed 5 mg and the duration of infusion should be at least 15 minutes (see section 4.2).

Section 4.5 Interaction with other medicinal products and other forms of interaction

Zoledronic acid is eliminated by renal excretion. Caution is indicated when Aclasta is administered in conjunction with medicinal products that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration) (see section 4.4).

In patients with renal impairment, the systemic exposure to concomitant medicinal products that are primarily excreted via the kidney may increase.

Section 4.8 Undesirable effects

Uncommon	Blood creatinine increased, pollakiuria, proteinuria
*Not known***	Renal impairment. Rare cases of renal failure requiring dialysis and rare cases with fatal outcome have been reported in patients with pre-existing renal dysfunction or other risk factors such as advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy, or dehydration in the post infusion period have been reported (see sections 4.4 and 4.8 Class

effects)

****** Based on post-marketing reports. Frequency cannot be estimated from available data.