Exhibit 4

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

6 December 2012
EMA/COMP/595031/2012 [redacted]
Committee for Orphan Medicinal Products

EMA/COMP summary report

On an application for orphan medicinal product designation

Zoledronic acid

Treatment of complex regional pain syndrome

EMA/OD/125/12

Sponsor: Axsome Therapeutics Limited

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7040
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

[redacted]

pharmacological action by binding to the bone matrix, to osteoblasts and to osteoclasts. They directly inhibit osteoclast activity, formation and recruitment, and can cause osteoclast apoptosis. Nitrogren containing bisphosphonates, such as zoledronic acid, also inhibit the mevalonate pathway in the osteoclast thereby interrupting normal osteoclast function [12].

[redacted] Plausibility of the orphan condition; rationale for use of the medicinal product

The scientific rationale for the use of zoledronic acid in the treatment of CRPS is as follows:

a) A key feature of CRPS is patchy osteoporosis and bone marrow edema which are the result of osteoclast hyperactivity [1-4]. Zoledronic acid is a potent inhibitor of bone resorption and osteoclast activity [12-13, 31-32].

b) Pain is the primary symptom of CRPS [1-4]. Zoledronic acid has been shown to relieve pain in other disease settings both clinically as well as in animal models [14-19].

c) Zoledronic acid has been used to successfully treat CRPS patients in a controlled study and case report [21, 22].

CRPS is associated with localized bone resorption and bone marrow edema in the affected limb which are the result of osteoclastic hyperactivity. Consequently, investigators have theorized that bisphosphonates might be beneficial in the treatment of CRPS since these compounds inhibit bone resorption and have analgesic efficacy [20]. As will be discussed below, initial clinical reports are supportive of the potential efficacy of zoledronic acid in the treatment of CRPS [21, 22].

The analgesic efficacy of zoledronic acid has been demonstrated in patients with bone pain associated with both malignant and non-malignant disorders [14-19]. Animal studies, as reviewed by Yanow et al. [19] have demonstrated the antinociceptive effects of zoledronic acid and other bisphosphonates in non-bone-related pain. These clinical and preclinical observations support the potential analgesic activity of zoledronic acid in CRPS.

The mechanism by which bisphosphonates provide pain relief in CRPS is unknown but may involve inhibition of osteoclast activity as well as inhibition of prostaglandin E2, proteolytic enzymes, and lactic acid [7, 19]. Activated osteoclasts produce an acidic microenvironment in bone thereby activating acid-sensing nociceptors, and release nerve growth factor (NGF) which is also thought to contribute to hyperalgesia [19].

Clinical Experience with Zoledronic Acid in the Treatment of CRPS

Zoledronic acid has been successfully used to treat patients with CRPS as reported in a controlled study and case report [21, 22]. These reports are summarized in Table 4.

Zaspel et al. tested zoledronic acid in a prospective active control study of 24 patients with CRPS [21]. Patients in the treatment group received a 5 mg single infusion of zoledronic acid while those in the control group received methylprednisolone. Patients were followed for six months, and pain was measured using the VAS (visual analog pain scale). The zoledronic acid group experienced a 70% reduction in pain, an effect that was maintained over the entire six-month observation period. Furthermore this effect was statistically significant versus control ($p<0.001$). The control group, in contrast, showed only transient pain relief through month 1 versus baseline. No reduction in pain was seen in the control at other time points.

Trial and Case Report Investigating the Use of Zoledronic Acid for Complex Regional Pain Syndrome

Study	Dosage, administration	Outcomes	Patient(s) and follow-up duration	Results
Zaspel et al., 2007 [21]	5mg IV single infusion	VAS, dystrophic symptoms, edema, sudomotor activity	24 patients (10 zoledronic acid, 14 methylprednisolone), 6 months	70% pain reduction with zoledronic acid lasting 6 months, statist. signif. versus control. Tendency towards improvement of dystrophic symptoms.
de Castro et al., 2011 [22]	5mg IV single infusion	Pain, edema	31-year old patient with CRPS-I for 16 years refractory to multiple treatments, 6 months	Total regression of pain and edema with no recurrence for 6 months.

IV, intravenous; VAS, Visual Analog Pain Scale

de Castro et al. reported the successful use of zoledronic acid in a 31-year old patient who had suffered from CRPS for 16 years [22]. This patient presented with severe pain and had failed multiple therapeutic interventions including steroids, NSAIDs, amitriptyline, other antidepressants, carbamezapine, other anti-convulsants, sympathetic nerve blocks with lidocaine and bupivacaine, opioids, neuromuscular blockers, dexmedetomidine, magnesium sulfate and chlorpromazine over a two-year period. Given the lack of response to these measures, the patient was treated with a 5 mg infusion of zoledronic acid. The result was total regression of pain and edema lasting six months.

Corroborating the potential for zoledronic acid in this disease setting are the positive results from several randomized controlled studies using other bisphosphonates to treat CRPS [23-25]. These reports are summarized in Table 5.

Trials Investigating the Use of other Bisphosphonates for Complex Regional Pain Syndrome

Study	Drug studied	Type of study	Patients and follow-up duration	Results
Manicourt et al., 2004 [23]	Alendronate 40mg oral daily for 8 weeks	RCT, double-blind, placebo-controlled	39 patients (19 drug, 20 placebo), 12 weeks	Statist. signif. improvement in spontaneous pain, pressure tolerance, and joint mobility.
Robinson et al., 2004 [24]	Pamidronate 60mg IV, one time	RCT, double-blind, placebo-controlled	27 (14 drug, 13 placebo), 3 months	Statist. signif. improvement in pain score, global assessment of disease severity score, and physical function.
Varenna et al., 2000 [25]	Clodronate 300mg IV for 10 days	RCT, double-blind, placebo-controlled	32 patients (15 drug, 17 placebo), 40 days	Statist. signif. improvement in pain score and clinical global

Study	Drug studied	Type of study	Patients and follow-up duration	Results
				assessment.

Of all the bisphosphonate compounds available clinically, zoledronic acid has been shown to be the most potent inhibitor of osteoclast-mediated bone resorption [12]. For example, by some in vitro measures it is approximately 20 times as potent as alendronate (Fosamax) and over 60 times as potent as pamidronate (Aredia) [12]. This increased potency has translated into more rapid, more complete and more sustained clinically therapeutic effects than other bisphosphonates [13]. Therefore zoledronic acid may potentially provide greater efficacy, faster onset of action, and less frequent dosing than other bisphosphonates in the treatment of CRPS.

As a whole, we believe the signals of efficacy from these reports support the development of this potentially promising therapy for a debilitating, difficult-to-treat condition with few safe and effective treatment options, and for which there is currently no medicinal product authorized in the E.U.

Comment

Zoledronic acid (zoledronate) belongs to the class of bisphosphonates; molecules used for the treatment of osteoporosis and other osteoclastic conditions based on their inhibition of osteoclastic bone resorption. The sponsor is applying for orphan designation of zoledronic acid for oral use, and (as described in section E1) is developing zoledronic acid as disodium salt. The sponsor states that zoledronate is currently available as an intravenous formulation only. The company is in the process of completing the initial manufacture of the sodium salt.

The sponsor proposes the product for the treatment of CRPS base on the potentialto treat some of the clinical features of CRPS, namely patchy osteoporosis and bone marrow oedema. In addition, the sponsor claims that zoledronic acid has been able to reduce pain associated to different diseases, and the reduction of pain could be extrapolated to the proposed condition.

The sponsor provides only 2 citations directly related to the use of intravenous zoledronic acid in CRPS. The first of these references (Zaspel et al, 2007), is a meeting abstract that apparently has not been subsequently published as a full paper. As reported in this abstract, 24 patients with CRPS (type I, early stage) received treatment either with zoledronic acid (10 patients) or methylprednisolone (14 patients). The sponsor reports that zoledronic acid seemed to induce reduction of pain as compared to methylprednisolone. However the authors stated also that *"over the entire period, compared to the bisphosphonate, cortisone showed a significant ($p < 0.001$) impact on the improvement of dystrophic symptoms such as oedema and sudomotor activity"*. From this study it seems that the product would be active on pain but not necessarily on oedema. In addition, being the the study reported as a short communication and not published in a peer-reviewed journal, it lacks relevant information that would be necessary for an in-depth assessment of the results

The other reference is a single case report published in Revista Dor (Brasil), which is a regional peer-reviewed pain journal. The description of the case is lacking details that would be useful for the evaluation of the efficacy of the product, e.g. there is no mentioning of any initiating noxious event, which is a typical criterion for CRPS.

Even though there are more relevant references to published studies on other bisphosphonates in CRPS, the sponsor provides no specific data or discussion as to whether such data can be extrapolated to their product.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.