ZURAMPIC (LESINURAD) APPROVED IN THE EUROPEAN UNION FOR PATIENTS WITH GOUT

AstraZeneca today announced that the European Commission (EC) has granted marketing authorisation for *Zurampic*™ (lesinurad) 200mg in combination with a xanthine oxidase inhibitor (XOI) for the adjunctive treatment of hyperuricemia in adult gout patients (with or without tophi) who have not achieved target serum uric acid (sUA) levels with an adequate dose of an XOI alone.

Zurampic is a selective uric acid reabsorption inhibitor (SURI) that inhibits the urate transporter, URAT1, which is responsible for the majority of the renal reabsorption of uric acid. By inhibiting URAT1, *Zurampic* increases uric acid excretion and thereby lowers sUA.

In combination with the current standard of care, XOIs allopurinol or febuxostat, *Zurampic* provides a dual mechanism of action to increase excretion and decrease production of uric acid, enabling more patients with inadequately controlled gout to achieve target treatment goals.

Sean Bohen, Executive Vice President, Global Medicines Development and Chief Medical Officer at AstraZeneca, said: "There has been limited therapy innovation in gout over the last 50 years. With the approval of *Zurampic*, we are pleased to offer a new treatment option for the many patients who are suffering from the effects of gout and who are not reaching the recommended serum uric acid treatment targets with the current standard of care."

As part of the European Union (EU) approval, AstraZeneca will conduct a Non-Interventional Post-Authorisation Safety Study (PASS) to investigate the cardiovascular safety profile (mainly in patients with history of cardiovascular disorder) exposed to *Zurampic*. In addition to the PASS, we have agreed to conduct an EU renal study to assess efficacy and safety in patients with creatinine clearance of 30-45mL/min.

The EU approval of *Zurampic* was based on data from three pivotal Phase III studies, CLEAR1, CLEAR2 and CRYSTAL, which represent the largest clinical trial data set of gout patients (n=1,537 total) treated with combination urate lowering therapy.

Gout is a serious and debilitating form of inflammatory arthritis caused by hyperuricemia (elevated sUA). It affects millions of patients, many of whom do not reach recommended sUA treatment goals on the current standard of care (XOIs), which decrease production of uric acid. For those inadequately controlled patients, the addition of a urate lowering therapy to increase excretion of uric acid, may help them achieve treatment goals.

The EC marketing authorisation applies to all member states of the EU, Iceland, Norway and Lichtenstein. Today's announcement follows the approval on 22 December 2015 by the US Food and Drug Administration of *Zurampic*® (lesinurad) 200mg tablets in combination with an XOI for the treatment of hyperuricemia associated with gout in patients who have not achieved target sUA levels with an XOI alone.

About *Zurampic*™ (lesinurad) 200mg tablets

Zurampic™ (lesinurad) 200mg tablets inhibit the urate transporter, URAT1, which is responsible for the majority of the renal reabsorption of uric acid. By inhibiting URAT1, *Zurampic* increases uric acid excretion and thereby lowers serum uric acid (sUA). *Zurampic* also inhibits organic anion transporter (OAT) 4 a uric acid transporter involved in diuretic-induced hyperuricemia. In addition, in people, *Zurampic* does not inhibit OAT1 and OAT3, which are drug transporters in the kidney associated with drug-drug interactions.

About the *Zurampic* Development Programme

CLEAR1 and CLEAR2 (see prior release on this topic here) were pivotal Phase III studies that evaluated the efficacy and safety of a once daily dose of *Zurampic* in combination with allopurinol compared to allopurinol alone. In CLEAR1 and CLEAR2, *Zurampic* when used in combination with allopurinol met

the primary endpoint in both studies with approximately twice as many patients achieving the serum uric acid (sUA) goal of <6.0mg/dL (360 µmol/L) by month 6, compared to those treated with allopurinol alone.

CRYSTAL (see prior release on this topic here) was a pivotal Phase III study that evaluated the efficacy and safety of a once daily dose of *Zurampic* in combination with febuxostat 80mg compared to febuxostat 80mg alone in gout patients with tophi (visible deposits of urate crystals in joints and skin). Patients were administered febuxostat 80mg orally once daily for 3 weeks before randomisation. In CRYSTAL, results showed *Zurampic* 200mg in combination with febuxostat demonstrated greater (nominal p<0.05) sUA lowering to the target for tophaceous gout of <5.0mg/dL (300 µmol/L) compared to febuxostat alone at all months except at the time of the primary endpoint, month 6 (56.6% vs. 46.8%, non significant). In the subgroup of patients with baseline sUA ≥5.0mg/dL (300 µmol/L) (i.e. those above recommended sUA treatment target for tophaceous gout on febuxostat alone), *Zurampic* 200mg in combination with febuxostat resulted in more subjects reaching target sUA of <5.0mg/dL (300 µmol/L) compared to febuxostat alone at month 6.

In a pooled analysis of the three clinical trials, the safety profile was similar for *Zurampic* 200mg in combination with an XOI to that of an XOI alone, with the exception of an increased incidence of predominantly reversible serum creatinine (sCr) elevations.

About Hyperuricemia and Gout
Gout is a serious, chronic, progressive, and debilitating form of inflammatory arthritis that affects more than 16.3 million people in major markets.* The underlying cause of gout is hyperuricemia (elevated sUA), which leads to the deposition of crystals primarily in the joints and in other tissues. This can result in recurrent attacks of inflammatory arthritis and, if left uncontrolled, could lead to chronic, progressive arthritis, and tophus (visible deposits of urate crystals) formation.

The goal of sUA lowering treatment is to reduce sUA levels to the target level of <6.0mg/dL (360 µmol/L) as recommended by both the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR). In those with greater disease severity and urate burden, such as those with tophi, guidelines recommend lowering sUA to <5.0mg/dL (300 µmol/L) to achieve better disease control.

Among patients treated in clinical trials, less than 50% of patients on allopurinol 300mg reached sUA target levels <6.0mg/dL (360 µmol/L). For patients who cannot reach target on an XOI alone, the current ACR and EULAR guidelines recommend adding an agent that increases uric acid excretion.

**Major markets include the United States, France, Germany, Italy, Spain, the United Kingdom and Japan*

About Ardea Biosciences
Ardea Biosciences is a member of the AstraZeneca Group, located in San Diego, California. Ardea is leading the development of AstraZeneca's gout portfolio, including *Zurampic* and RDEA3170. RDEA3170 is a potent selective uric acid reabsorption inhibitor (SURI), also intended for use as a combination urate lowering therapy with xanthine oxidase inhibitors (XOIs). RDEA3170 is our lead investigational urate lowering therapy (ULT) in Asia and is currently entering a Phase IIb trial worldwide.

About AstraZeneca
AstraZeneca is a global, innovation-driven biopharmaceutical business that focuses on the discovery, development and commercialisation of prescription medicines, primarily for the treatment of diseases in three main therapy areas - respiratory, inflammation, autoimmune disease (RIA), cardiovascular and metabolic disease (CVMD) and oncology - as well as in infection and neuroscience. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. For more information please visit: www.astrazeneca.com

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Key: RIA - Respiratory, Inflammation and Autoimmunity, CVMD - Cardiovascular and Metabolic Disease, ING - Infection, Neuroscience and Gastrointestinal

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