

**SB TITCK 26.09.2023 AMOKSISILIN İÇEREN İLAÇLAR ACIL GÜVENLİLİK KISITLAMASI GÖRÜŞ
KATKI_EN**

Turkish Ministry of Health Turkish Medicines and Medical Devices Agency
Number: E-24931227-510.01.04-1234586 26.09.2023 Subject: Amoxicillin-Containing
Products / Urgent Safety Restriction / Call for Opinions/Suggestions

FILE

The Agency has given consideration to the scientific conclusions reached, and the rationale therefor, issued by the Pharmacovigilance Risk Assessment Committee (PRAC) of European Medicines Agency (EMA) based on the conclusions drawn from Periodic Benefit/Risk Assessment Reports, literature data and spontaneous reports, and requires that the specific wording provided in the attachment be incorporated in the local summary of product characteristics (KÜB) and package leaflet (KT). You are invited to forward any opinions, suggestions or other input related to this decision to the Pharmacovigilance Risk Management Unit of the Pharmacovigilance and Controlled Substances Department by 10.10.2023, and in the meantime to refrain from making any submissions to the Pharmacovigilance Assessment Unit.

Dr. Asım Hocaoglu Agency President

Annex 1: Announcement to Associations/Unions (5 pages) Annex 2:
https://www.ema.europa.eu/en/documents/psusa/amoxicillin-cmdh-scientific-conclusions-grounds-variation-amendments-product-information-timetable/00000187/202203_en.pdf Annex 3: https://www.ema.europa.eu/en/documents/psusa/amoxicillin/clavulanate-cmdh-scientific-conclusions-grounds-variation-amendments-product-information-timetable/00000188/202203_en.pdf

Distribution for Appropriate Action: Association of Research-Based Pharmaceutical Companies Turkish Pharmaceutical Manufacturers Association Association of Turkish Pharmaceutical Manufacturers Health Products Association

Bears a secure electronic signature. Verification code:
ZW56ZW56ak1URG83ZmxXRG83ak1UZW56 Document Tracking Address:
<https://www.turkiye.gov.tr/saglik-titck-ebys.1> | 6

Turkish Ministry of Health Turkish Medicines and Medical Devices Agency

Amendments to be included in the relevant sections of the product information (new text underlined and in bold, deleted text strike through) for products containing amoxicillin

Local Summary of Product Characteristics (KÜB)

4.4 Special warnings and precautions for use

The existing warning should be revised as follows: Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid non- allergic hypersensitivity and severe cutaneous reactions) have been reported in patients on penicillin therapy. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin therapy must be discontinued and appropriate alternative therapy instituted.

A warning should be added as follows: Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin (see Section 4.8). DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after drug <intake> <administration> <use>) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, diarrhea, hypotension or leukocytosis with neutrophilia. There have been severe cases including progression to shock.

The existing warning should be revised as follows: In patients with reduced urine output, crystalluria (including acute renal injury) has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to

maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see Sections 4.8 and 4.9).

4.5 Interaction with other medicinal products and other forms of interaction

Methotrexate Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Probenecid Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin.

Bears a secure electronic signature. Verification code:
ZW56ZW56ak1URG83ZmxXRG83ak1UZW56 Document Tracking Address:
<https://www.turkiye.gov.tr/saglik-titck-ebys>. 2 | 6

Turkish Ministry of Health Turkish Medicines and Medical Devices Agency

4.8 Undesirable effects

The following adverse reactions should be added to appropriate sections: Skin and subcutaneous tissue disorders Not known: Linear IgA disease Nervous system disorders Not known: Aseptic meningitis Cardiac disorders Not known: Kounis syndrome Gastrointestinal disorders Not known: Drug-induced enterocolitis syndrome (DIES) Renal and urinary tract disorders Not known: Crystalluria (including acute renal injury)

4.9 Overdose

The following information should be added: Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see Section 4.4).

Local Package Leaflet (KT)

Section 2 What you need to know before you are given Amoxicillin DO NOT TAKE <X> in the following cases

Methotrexate (used to treat cancer and severe psoriasis), penicillins may reduce the excretion of methotrexate causing a potential increase in side effects.

Probenecid (used to treat gout), concomitant use of probenecid may reduce the excretion of amoxicillin and is not recommended.

Section 4 Possible side effects

Like all medicines <X> can cause some side effects in persons who are sensitive to its ingredients. You may experience some of the following side effects when taking this medicine. Stop taking <X> and see a doctor IMMEDIATELY or visit the emergency room at the nearest hospital if you experience any of the following: Conditions you need to look out for

Allergic reactions: Chest pain in the context of allergic reactions, which may be a symptom of allergy triggered cardiac infarction (Kounis syndrome)

Bears a secure electronic signature. Verification code:
ZW56ZW56ak1URG83ZmxXRG83ak1UZW56 Document Tracking Address:
<https://www.turkiye.gov.tr/saglik-titck-ebys>. 3 | 6

Turkish Ministry of Health Turkish Medicines and Medical Devices Agency

Drug-induced enterocolitis syndrome (DIES): Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin. It is a certain kind of allergic reaction with the leading symptom of repetitive vomiting (1-4 hours after drug <intake> <administration> <use>). Further symptoms could comprise abdominal pain, lethargy (constant state of sleepiness), diarrhea, and low blood pressure. Crystals in urine leading to acute renal injury Rash with blisters arranged in a circle with central crusting or like a string of pearls (linear IgA disease) Inflammation of the membranes that surround the brain and spinal cord (aseptic meningitis)

Amendments to be included in the relevant sections of the product information (new text underlined and in bold, deleted text strike through) for products containing a combination of

amoxicillin and clavulanate.

Local Summary of Product Characteristics (KÜB)

4.4 Special warnings and precautions for use

The existing warning should be revised as follows: Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous reactions) have been reported in patients on penicillin therapy. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted.

A warning should be added as follows: Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin/clavulanate (see Section 4.8). DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after drug <intake> <administration> <use>) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, diarrhea, hypotension or leukocytosis with neutrophilia. There have been severe cases including progression to shock.

The existing warning should be revised as follows: In patients with reduced urine output, crystalluria (including acute renal injury) has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see Sections 4.8 and 4.9).

Bears a secure electronic signature. Verification code:
ZW56ZW56ak1URG83ZmxXRG83ak1UZW56 Document Tracking Address:
<https://www.turkiye.gov.tr/saglik-titck-ebys>. 4 | 6
Turkish Ministry of Health Turkish Medicines and Medical Devices Agency

4.8 Undesirable effects

The following adverse reactions should be added to appropriate sections: Skin and subcutaneous tissue disorders Not known: Linear IgA disease Nervous system disorders Not known: Aseptic meningitis Cardiac disorders Not known: Kounis syndrome Gastrointestinal disorders Not known: Drug-induced enterocolitis syndrome (DIES) Renal and urinary tract disorders Not known: Crystalluria (including acute renal injury)

Local Package Leaflet (KT)

Section 4 Possible side effects

Like all medicines <X> can cause some side effects in persons who are sensitive to its ingredients. You may experience some of the following side effects when taking this medicine. Stop taking <X> and see a doctor IMMEDIATELY or visit the emergency room at the nearest hospital if you notice any of the following: Be alert for the following conditions Allergic reactions: skin rash inflammation of blood vessels (vasculitis) which may be visible as red or purple raised spots on the skin, but can affect other parts of the body fever, joint pain, swollen glands in the neck, armpit or groin swelling, sometimes of the face or throat (angioedema), causing difficulty in breathing collapse (a severe decline induced by dilation of peripheral blood vessels causing local accumulation of blood, a sudden breakdown) Chest pain in the context of allergic reactions, which may be a symptom of allergy triggered cardiac infarction (Kounis syndrome)

Contact a doctor immediately if you get any of these symptoms. Stop taking <X>.

Inflammation of large intestine: Inflammation of the large intestine, causing watery diarrhea usually with blood and mucus, stomach pain and/or fever.

Bears a secure electronic signature. Verification code:
ZW56ZW56ak1URG83ZmxXRG83ak1UZW56 Document Tracking Address:

<https://www.turkiye.gov.tr/saglik-titck-ebys>. 5 | 6

Turkish Ministry of Health Turkish Medicines and Medical Devices Agency

Acute inflammation of the pancreas (acute pancreatitis): If you have severe and on-going pain in the stomach area this could be a sign of acute pancreatitis.

Drug-induced enterocolitis syndrome (DIES): Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin. It is a certain kind of allergic reaction with the leading symptom of repetitive vomiting (1-4 hours after drug <intake> <administration> <use>). Further symptoms could comprise abdominal pain, lethargy (constant state of sleepiness), diarrhea, and low blood pressure.

Contact your doctor as soon as possible for advice if you get these symptoms.

Side effects are defined as shown in the following categories:

Unknown:

Crystalluria (including acute renal injury)

Rash with blisters arranged in a circle with central crusting or like a string of pearls (linear IgA disease)

Inflammation of the membranes that surround the brain and spinal cord (aseptic meningitis)

Bears a secure electronic signature. Verification code:
ZW56ZW56ak1URG83ZmxXRG83ak1UZW56 Document Tracking Address:

<https://www.turkiye.gov.tr/saglik-titck-ebys>. 6 | 6