# Summary of risk management plan for Duzallo (allopurinol/lesinurad)

This is a summary of the risk management plan (RMP) for allopurinol/lesinurad fixed dose combination (FDC). The RMP details important risks of allopurinol/lesinurad FDC, how these risks can be minimised, and how more information will be obtained about allopurinol/lesinurad FDC's risks and uncertainties (missing information).

Allopurinol/lesinurad FDC's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how allopurinol/lesinurad FDC should be used.

This summary of the RMP for allopurinol/lesinurad FDC should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current one will be included in updates of allopurinol/lesinurad FDC's RMP.



## I. The medicine and what it is used for

Allopurinol/lesinurad FDC is authorised in adults for the treatment of hyperuricaemia in gout patients who have not achieved target serum uric acid levels with an adequate dose of allopurinol alone (see SmPC for the full indication). It contains allopurinol and lesinurad as the active substances and it is given by oral route of administration.

Further information about the evaluation of allopurinol/lesinurad FDC's benefits can be found in allopurinol/lesinurad FDC's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

## II. Risks associated with the medicine and activities to minimise or further characterize the risks

Important risks of allopurinol/lesinurad FDC, together with measures to minimise such risks and the proposed studies for learning more about allopurinol/lesinurad FDC's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of allopurinol/lesinurad FDC, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report (PSUR) assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of allopurinol/lesinurad FDC is not yet available, it is listed under 'missing information' below.

## II.A List of important risks and missing information

Important risks of allopurinol/lesinurad FDC are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of allopurinol/lesinurad FDC. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

| List of important risks and missing information | |
|---|---|
| Important identified risks | – Renal impairment<br>– Serious hypersensitivity (allergic) reactions and increased risk for certain serious skin reactions particularly in people of Han Chinese or Thai origin |
| Important potential risks | – Major Adverse Cardiovascular Events (MACE) (mainly in patients with history of cardiovascular disorders)<br>– Concomitant administration of ampicillin/amoxicillin |
| Missing information | – Use in children<br>– Use in pregnant or lactating women<br>– Use in pre-existing hepatic impairment<br>– Use in subjects ≥75 years of age<br>– Use in patients with moderate renal impairment with CrCl 30-45 ml/min) |

## II.B Summary of important risks

| Important identified risk < Renal impairment > | |
|---|---|
| Evidence for linking the risk to the medicine | Based on clinical trial data, there were more patients who experienced kidney related events when they were treated with lesinurad alone or when they were treated with lesinurad in combination with a xanthine oxidase inhibitor (XOI) compared to placebo or XOI alone. Renal-related adverse reactions were reported in patients treated with lesinurad 200 mg in combination with an XOI (5.7%) compared to XOI alone (4.5%). The most frequent renal-related adverse reaction was blood creatinine increased (4.3% with lesinurad 200 mg in combination with an XOI compared to 2.3% with XOI alone). The majority of the patients recovered, many while continuing to take lesinurad. Based on the safety profile the recommended dose of lesinurad is 200 mg daily taken together with an XOI. |
| Risk factors and risk groups | In a study of male veterans in the US, Krishnan demonstrated that hyperuricemia (defined as sUA >7 mg/dL) was associated with an increased risk of kidney disease (Krishnan et al. 2013). Even after controlling for other risk factors, the prevalence of gout and hyperuricemia increases as renal function decreases, as demonstrated in a cross-sectional analysis in NHANES (Krishnan et al. 2012).<br>Renal impairment is extremely common in patients with gout. Analysis of 2007-2008 NHANES data found that 71% of patients with gout had stage ≥2 chronic kidney disease (CKD) (defined as GFR <60 mL/min) and 19.9% had CKD stage ≥3 (glomerular filtration rate [GFR] <30 mL/min) (using Modification of Diet in Renal Disease [MDRD] study equation), compared to |

| Important identified risk < Renal impairment > | |
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| | 42.1% and 5.2% in the non-gout population, respectively (Zhu et al. 2012). These findings are similar to those of an analysis of 2007-2010 NHANES data which demonstrated that the prevalence of gout increased with increasing stage of CKD (adjusted prevalence ratio 3.20 [95% confidence interval (CI): 1.96, 5.24]) comparing those with CKD Stage 4 to those without CKD (Juraschek et al. 2013). In the CACTUS study, renal failure, as defined by GFR <60 mL/min, was present in 9% of the studied gout population (Richette et al. 2013).<br>Renal impairment was assessed as part of the ICARUS study. In this study, the baseline prevalence of renal disease (defined as a diagnosis for CKD or renal failure) was: in the US 6.5% (adjusted 4.7%); in the UK 24.1% (adjusted, 10.9%); in Germany 12.1% (adjusted 6.7%); and in France 1.9% (adjusted 1.0%). When defined as new or worsening renal impairment during follow-up in the study, the incidence in the US was 5.65 per 100 person-years (PY) (95% CI: 5.56-5.74), (adjusted 4.34; 95% CI: 4.26, 4.43). The incidence in the UK was 5.14 per 100 PY (95% CI: 5.02, 5.26), (adjusted 3.38; 95% CI: 3.22, 3.56). The incidence in Germany was 3.14 per 100 PY (95% CI: 3.06, 3.22), (adjusted 1.67, 95% CI: 1.57, 1.78). The incidence in France was 3.93. per 100 PY (95% CI: 3.79, 4.07) (adjusted 2.76, 95% CI: 2.50, 3.05). |
| Risk minimisation measures | *Routine risk minimisation measures:*<br>Routine risk communication:<br>– Statements within Sections 4.2, 4.4 and 4.8 of the SmPC<br>– Statements within Sections 2, 3 and 4 of the PL<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>– Recommendations for healthcare professionals regarding renal function monitoring are included in SmPC Section 4.4<br>– Recommendations for patients to stay well hydrated to reduce the risk of kidney stones are included in in Section 3 of the PL |

| Important identified risk < Serious hypersensitivity (allergic) reactions and increased risk for certain serious skin reactions particularly in people of Han Chinese or Thai origin > | |
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| Evidence for linking the risk to the medicine | Serious hypersensitivity reactions involving fever, skin rash, joint pain, and abnormalities in blood and liver function tests (these may be signs of a multiorgan sensitivity disorder) are rare possible adverse reactions. Serious skin rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis) have been reported with the use of allopurinol. Frequently, the rash can involve ulcers of the mouth, throat, nose, genitals and conjunctivitis (red and swollen eyes). These serious skin rashes are often preceded by influenza-like symptoms fever, headache, body ache (flu-like symptoms). The rash may progress to widespread blistering and peeling of the skin. These serious skin reactions can be more common in people of Han Chinese or Thai origin. Very rarely acute anaphylactic shock has been reported. It is a severe disorder that can be life-threatening without prompt treatment. |
| Risk factors and risk groups | Population-based data on the incidence and mortality of rare severe cutaneous adverse reactions (sCARs) are infrequent.<br>In the a population-based cohort study conducted by Kim and colleagues, it was reported that the crude incidence rate (IR) of sCARs in non-allopurinol users was 0.04 (95% CI 0.02-0.08) per 1,000 PY They also mentioned a |

| Important identified risk < Serious hypersensitivity (allergic) reactions and increased risk for certain serious skin reactions particularly in people of Han Chinese or Thai origin > | |
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| | study where the incidence of TEN (toxic epidermal necrolysis) and SJS (Stevens-Johnson syndrome) in the general population was reported to be generally low and estimated at 0.4 to 1.2 and 1 to 6 cases per million PY, respectively (Kim et al. 2013).<br>Atzori and colleagues reported an estimated incidence of 5.5 cases of SJS/TEN per million inhabitants in southern Sardinia (Atzori et al. 2012), while according to Schwartz and colleagues, SJS has an annual incidence of 1.2 to 6 per million people, whereas TEN has an estimated incidence of 0.4 to 1.9 per million people annually worldwide. The overall combined incidence of Stevens-Johnson syndrome (SJS), SJS/TEN overlap, and TEN is estimated to be 2 to 7 per million cases per year (Schwartz et al. 2013).<br>Furthermore, López-Rocha reported an incidence of 1/1000 to 10 000 exposures in the general population for DRESS (López-Rocha et al. 2014).<br>The greatest known risk factor for AHS is the presence of the HLA B*5801 allele, which is most prevalent in patients of Han Chinese ethnicity (Stamp et al. 2016). Indeed, a strong association between HLA B*5801 and allopurinol-induced sCARs has been observed in populations of Eastern Asia (Han Chinese, Thai, and Koreans) (Hung et al. 2005, Tassaneeyakul et al. 2009, Kang et al. 2011). Weaker associations have been observed in European, Japanese, and Portuguese populations (Lonjou et al. 2008, Kaniwa et al. 2008, Goncalo et al. 2013) because these patients have a low prevalence of this HLA allele.<br>Other risk factors for AHS include the time from start of treatment, starting dose of allopurinol, age, female sex and concomitant diuretic use (Ramasamy et al. 2013, Stamp et al. 2012, Stamp et al. 2016). The relationship between renal function and the risk of AHS remains unclear, as a number of studies have presented cases of AHS occurring in patients with normal renal function (Day et al. 2016). Ryu and colleagues have also proposed that colchicine and statins are risk factors for allopurinol-induced adverse events including skin rash and AHS (Ryu et al. 2013).<br>In addition, a hypothesis that a high plasma concentration of oxypurinol increases the risk of subsequent adverse reactions to allopurinol was also proposed (Stamp et al. 2016). |
| Risk minimisation measures | *Routine risk minimisation measures:*<br>Routine risk communication:<br>– Statements within Sections 4.4 and 4.8 of the SmPC<br>– Statement within Sections 2 and 4 of the PL<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>– Recommendations for healthcare professionals regarding the potential role of screening for HLA-B*5801 before starting treatment with allopurinol are included in SmPC Section 4.4 |

| Important potential risk < MACE (mainly in patients with a history of cardiovascular disorders) > | |
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| Evidence for linking the risk to the medicine | In trials with lesinurad, serious cardiac events such as heart attacks, strokes, and sudden death were reviewed. There were a small number of patients who had these events; however there were slightly more in the groups treated with lesinurad 200 mg and 400 mg. All of the patients with events who received lesinurad 200 mg had a history of CV diseases such as heart failure, stroke, or |

| Important potential risk < MACE (mainly in patients with a history of cardiovascular disorders) > | |
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| | heart attack that were in stable condition at least for 12 months. It has not been determined that lesinurad is the cause of these events. |
| Risk factors and risk groups | There is increasing evidence that high serum uric acid (sUA) levels are an independent cardiovascular risk factor. The Preventive Cardiology Information System Database Cohort Study, which assessed the prognostic value of sUA in 3,098 persons aged 18 to 87 years who were at risk for cardiovascular disease, found that sUA was an independent predictor of cardiovascular death (Ioachimescu et al. 2008). This relationship does not appear to be entirely straightforward. A study of patients in Taiwan found a U shaped relationship, where high, but also very low levels, seemed to be associated with increased risk of cardiovascular mortality (Kuo et al. 2013a). In a recent publication on the US CARDIA prospective cohort investigating cardiovascular disease (CVD) risk, baseline sUA concentration was positively associated with incident CVD over 27 years of follow-up, hazard ratio (HR) per mg/dL 1.21, 95% CI 1.05, 1.39, but the association weakened and became less non-significant after adjustment for other CV risk factors, HR 1.09, 95% CI 0.94, 1.27) (Wang et al. 2015). However, sUA at later time points again showed stronger associations, suggesting that the prediction of CVD by sUA may strengthen with age. |
| Risk minimisation measures | *Routine risk minimisation measures:*<br>Routine risk communication:<br>– Statements within Sections 4.4 and 4.8 of the SmPC<br>– Statement within Section 2 of the PL |

| Important potential risk < Concomitant administration of ampicillin/amoxicillin > | |
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| Evidence for linking the risk to the medicine | In the scientific literature, an increased frequency of skin rash has been reported among patients receiving ampicillin or amoxicillin concomitantly with allopurinol compared to patients who are not receiving both drugs. The cause of the reported association has not been established. |
| Risk factors and risk groups | In the analyses performed, several factors were excluded as possibly accounting for the higher frequency of rashes among patients receiving concomitantly allopurinol and ampicillin compared to ampicillin alone including age, sex, hospitalization, duration of hospitalization, admission blood urea nitrogen (BUN), survival and discharge diagnosis. As uric acid levels were not available, it is not clear whether the increased frequency in rashes can be attributed to allopurinol itself only or whether the presence of hyperuricemia can be attributed as a risk factor. |
| Risk minimisation measures | *Routine risk minimisation measures:*<br>Routine risk communication:<br>– Statements within Section 4.5 of the SmPC<br>– Statement within Section 2 of the PL |

| Missing information < Use in children > | |
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| Risk minimisation measures | *Routine risk minimisation measures:*<br>Routine risk communication:<br>– Statements within Section 4.2 of the SmPC |

| Missing information < Use in children > | |
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| | – Statement within Section 2 of the PL |

| Missing information < Use in pregnant or lactating women > | |
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| Risk minimisation measures | *Routine risk minimisation measures:*<br>Routine risk communication:<br>– Statements within Section 4.6 of the SmPC<br>– Statement within Section 2 of the PL |

| Missing information < Use in pre-existing hepatic impairment > | |
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| Risk minimisation measures | *Routine risk minimisation measures:*<br>Routine risk communication:<br>– Statements within Section 4.2 of the SmPC<br>– No specific statement in the PL |

| Missing information < Use in subjects > 75 years of age > | |
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| Risk minimisation measures | *Routine risk minimisation measures:*<br>Routine risk communication:<br>– Statement within Section 4.2 of the SmPC<br>– No specific statement in the PL |

| Missing information < Use in patients with moderate renal impairment with CrCl 30-45 ml/min > | |
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| Risk minimisation measures | *Routine risk minimisation measures:*<br>Routine risk communication:<br>– Statements within Sections 4.2 and 4.4 of the SmPC<br>– Statement within Section 2 of the PL |

## II.C Post-authorisation development plan

*II.C.1 Studies which are conditions of the marketing authorization*

There are no studies which are conditions of the marketing authorization or specific obligations of the allopurinol/lesinurad FDC.

*II.C.2 Other studies in post-authorisation development plan*

There are no studies required for the allopurinol/lesinurad FDC.