AIFA – Agenzia Italiana del Farmaco

Revisione nitrosammine: disponibili per i titolari AIC i modelli da utilizzare nelle diverse fasi della procedura

L'Agenzia Europea per i Medicinali (EMA) e il Gruppo di Coordinamento per le Procedure di Mutuo Riconoscimento e Decentrate (CMDh) hanno reso disponibili sui propri siti (CMDh, EMA) le informazioni e i modelli (*template*) per i titolari di AIC che sono tenuti a revisionare tutti i loro farmaci di sintesi chimica per la possibile presenza di nitrosammine (Revisione secondo l'art. 5(3) del Regolamento 726/2004).

Per ciascuna fase di valutazione sono stati pubblicati i modelli (e le relative tabelle in formato Excel) che i titolari di AIC devono utilizzare per l'invio dei riscontri alle autorità competenti.

Per i medicinali autorizzati con procedura nazionale (NAP), di mutuo riconoscimento (MRP) o decentrata (DCP), i titolati di AIC devono fare riferimento alle informazioni sulle nitrosammine per i titolari AIC pubblicate sul sito del CMDh e alla linea guida "CMDh practical guidance for Marketing Authorisation Holders of nationally authorised products (incl. MRP/DCP) in relation to the Art. 5(3) Referral on Nitrosamines" che deve essere seguita per ogni singolo step di valutazione.

I modelli (e i file Excel) da inviare all'AIFA devono essere trasmessi all'indirizzo di posta elettronica nitrosamine@aifa.gov.it, identificando nel titolo delle email ogni singolo step della valutazione, come riportato nella suddetta linea guida del CMDh.

Per i medicinali autorizzati con procedura centralizzata i template compilati dovranno essere inviati all'indirizzo di posta elettronica nitrosamines.review.cap@ema.europa.eu, secondo le modalità e i tempi indicati per le diverse fasi di valutazione sul sito dell'EMA.

Pubblicato il: 29 ottobre 2019

CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

October 2019
CMDh/412/2019

CMDh practical guidance for Marketing Authorisation Holders of nationally authorised products (incl. MRP/DCP) in relation to the Art. 5(3) Referral on Nitrosamines

With regard to the Art. 5(3) referral, MAHs are requested to evaluate the risk of the presence of nitrosamine impurities in their human medicinal products containing chemically synthesized active pharmaceutical ingredients ("Information on nitrosamines for marketing authorisation holders"). This evaluation should be performed in 3 sequential steps:

Step 1 – Risk evaluation

Step 2 – Confirmatory testing

Step 3 – Changes to the marketing authorization

This practical guidance is prepared in order to explain the necessary steps for fulfilling the requested risk assessment. Q/As are enclosed for each of the three steps. Further details on how to proceed with the confirmatory testing and necessary changes of the marketing authorization will later be added to this living document. Furthermore, questions from MAHs/API manufacturers might also be included in this document at a later stage if regarded necessary.

Step 1 – Risk evaluation

MAH should perform risk evaluation of their medicinal products containing chemically synthesized API. The risk assessments should be prioritized according to the published "Questions and answers on "Information on nitrosamines for marketing authorisation holders" and the outcome templates should be submitted per product as soon as available. MAHs are obliged to submit the conclusions of the risk assessments for all of their products until 26.03.2020 as outlined below.

1. *How should I submit the outcome of the risk assessment to the competent authorities?*

Two templates have been prepared (https://www.hma.eu/226.html) for the outcomes "no risk identified" and "risk identified". The relevant template for each medicinal product has to be sent to all national competent authorities where the respective product is authorized as soon as the individual risk assessment is finalized:

- By attaching it to an email (see Annex below);

- The heading should include "Outcome of risk assessment nitrosamines - Step 1" and in case of MRP/DCP the EU procedure number;
- Guidance given by authorities on national websites also has to be regarded (see Annex below).

The risk assessment documents do not have to be submitted to the authorities at this moment, but should be available upon request.

The Excel sheet (https://www.hma.eu/226.html) does not have to be submitted with each notification email but might be submitted at the end of the risk assessment for all products of a MAH or on request of the member states.

Step 2 – confirmatory testing

2. *When should I perform confirmatory testing for nitrosamines?*

Confirmatory timely testing should be performed as soon as the risk assessment indicates a potential risk for the formation of, or contamination with nitrosamines. In case a high risk is identified the confirmatory testing should be initiated immediately. Member states should be informed as soon as possible. All confirmatory testing should be finalized until 26.09.2022 at the latest (see Q/A 7 in "Questions and answers on "Information on nitrosamines for marketing authorisation holders").

3. *To whom should the outcome of the testing be sent when nitrosamines are actually detected?*

The outcome of the confirmatory testing should include the results and an investigation report detailing the risk assessment and proposed CAPAs.

Please send these documents immediately after detection to the email addresses (as given below to) to the concerned national competent authorities in case of purely national MAs, to the RMS in case of MRP/DCP products (copying the CMS's)or to the EMA in case of CAPs including "Outcome of confirmatory testing nitrosamines - Step 2" in the heading. For MRP/DCP products the EU procedure number should be added as well. Please also regard guidance given by national competent authorities in this respect. The RMS will evaluate the results and then inform the CMSs that the results have been submitted, so that the CMSs are aware that the MAH has performed and finalised Step 2. Necessary measures will then be decided on by the authorities.

Furthermore, please also take into account guidance from national competent authorities regarding the notification of product defects and recalls

Step 3 Changes to the marketing authorization

The necessary variations for amendment of the quality dossier should also be submitted within 3 years (26.09.2022) to the RMS according to the usual channels (see Q/A 8 in "Questions and answers on "Information on nitrosamines for marketing authorisation holders"). Worksharing is highly recommended in all cases where the same variation applies to several national or MRP/DCP products.

Annex: Member States' email addresses and links to published guidance

MS	Email address	Published guidance to be considered
AT	N/A	https://www.basg.gv.at/en/for-companies/medicinal-products/quality-of-medicines#c20671
BE	N/A	Nitrosamine risk evaluation outcome: • No risk identified: https://www.famhp.be/en/nitrosamines_risk_evaluation_outcome_confirmation_of_no_risk_identified • Risk of nitrosamine presence identified: https://www.famhp.be/en/nitrosamines_risk_evaluation_outcome_risk_of_nitrosamine_presence_identified
BG		
CY	nitrosamines@phs.moh.gov.cy	
CZ	nitrosaminy@sukl.cz	
DE	nitrosamines@bfarm.de	https://www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/EN/RV_STP/m-r/nitrosamin_2019-09-26.html
DK	nitrosamines@dkma.dk	
EE	nitrosamines@ravimiamet.ee	
EL	nitrosamines@eof.gr	
FI	nitrosamines@fimea.fi	
FR	nitrosamines@ansm.sante.fr	
HR	nitrosamines@halmed.hr	
HU	nitrozamin@ogyei.gov.hu	https://ogyei.gov.hu
IS	nitrosamines@ima.is	
IT	nitrosamine@aifa.gov.it	
LT		
LU		
LV	nitrosamines@zva.gov.lv	
MT		
NL	nitrosamines@cbg-meb.nl	
NO	nitrosamines@noma.no	
PL	nitrozoaminy@urpl.gov.pl	
PT		
RO	nitrozamine@anm.ro	
SE	RIC@mpa.se	
SI	nitrosamines@jazmp.si	
SK	nitrosamines@sukl.sk	
UK		