**Nitrosamine Risk assessment**

**Assessment Report <Preliminary> <Final>Outcome step 2**

**<Invented Name>, strength, form**

**<(Active Substance)>**

**<EU Procedure number> *for MR/DCP***

**Marketing Authorisation Holder (in RMS):**

**Date:**

The RMS has received the ‘Outcome of confirmatory testing nitrosamine Step 2’- nitrosamine detected’ for the above product(s)

The MAH has highlighted that ‘Scenario a’ applies and:

*Choose <> as appropriate*:

<Nitrosamine detected is above the acceptable intake (AI) limit>/ < More than one nitrosamine is present and the acceptable risk level of 1:100,000 as outlined in ICH M7(R1) in the final product is exceeded>

The RMS confirms that as levels detected are above the limit, this has or will be notified by the RMS via Rapid Alert Network to competent authorities for further review.

<The Excel ‘Step 2 – Nitrosamine detected response template’ has been provided by the MAH>

<The MAH has provided: testing results expressed in ng and ppm, interim investigation

report including (preliminary) root cause, risk mitigating plan and benefit/risk assessment as well

as proposed CAPAs>

<The Excel ‘Scenario A for critical medicinal products’ will be requested from the MAH>

**<Preliminary> <Final> Assessment report**

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| --- |
| **Confirmed presence of nitrosamines in product – review of responses as RMS** |
| **Product name:** | **MAH:** |
| **MA numbers:**  | **EU Procedure number:** |
| **CMS’s:**  |  |
| **Active substance:**  | **Pharmaceutical Form and Strength:** |
| **API manufacturer:** | **Finished product manufacturer / Site responsible for batch release:** |
| **Date of preliminary AR:** |  |
| **Date of final AR** |  |
|  **Step 2 requirements:** |  |
| **Initial notification:**Presence of nitrosamine* Was nitrosamine above AI detected in the Finished Product (FP)

If so which nitrosamine impurity/nitrosamine impurities? * At what level was each nitrosamine seen. *State in ng and ppm, and provide range*
* How many batches (API and/or FP) have been tested? Is the amount and selection of batches considered to be representative and in accordance with Q&A 8 \*?
* What is the maximum daily dose in the SmPC according to the MAH (in mg)?
* What is the acceptable limit for each nitrosamine impurity (in ng/day) according to Q&A 10\*?
* For single nitrosamine detection: What is the acceptable limit AI (in ppm) calculated in accordance with Q&A 10\* based on the maximum daily dose?
* Where more than one nitrosamine has been detected, does the total daily intake of all identified nitrosamines exceed the AI of the most potent n-nitrosamine detected, or does the total risk level of the sum of all detected nitrosamines exceed the 1 in 100,000 lifetime risk.
* Where a new impurity not listed in the Q &A Q10\* has been identified, the RMS confirms that the AI has been agreed by NcWP or else the default class specific TTC of 18ng/day has been applied
* Has the limit been correctly calculated by the MAH?
 | Assessor comments |
| **Initial notification**Analytical methodState type of analytical method used:* Is the analytical method used suitable and properly validated?
* State LoD
* State LoQ
* Are limit of detection (LoD)/Limit of quantification (LoQ) sufficiently low to ensure a total risk of not more than 1 in 100000?
 | Assessor comments |
| **Investigation report** Root cause <preliminary> where available:* Was a root cause identified? *State*
* Was the investigation thorough, considering all currently identified root causes for presence of nitrosamines (Q&A 4)?
* If a root cause is proposed, is the identified root cause plausible? Has a thorough investigation been performed, including for example, control experiments and robust data been provided??

<Final> Conclusion of root cause investigation:* Root cause <confirmed>*- provide detail*<cannot be confirmed>
 | Assessor comments |
| **Risk mitigating plan** * Has the applicant proposed an interim measure until CAPA implementation?
* Is there a possibility for a higher interim limit in accordance with Q&A22? *State limit and time period*
* Is there a need for NMEG consultation? (critical medicinal products for which Q&A22 is not applicable or interim limit is exceeded) *Request MAH to fill in the Excel ‘Scenario A for critical medicinal products’*
* Is release testing for the finished product being proposed as an interim measure to ensure only compliant batches are released? If so, what is the timeline for this? Is this reasonable?
* Is a recall proposed by the MAH?
 |  |
| **Benefit/Risk assessment** * Is the risk assessment comprehensive?
* Does the RMS agree with the MAH’s conclusion of the benefit/risk assessment?
* Is the overall benefit risk balance of the medicine still positive according to RMS?

RMS <Preliminary><Final> conclusion on Benefit/Risk assessment (including preliminary recommendation market actions based on RAN criticality assessment).  |  |
| **CAPAs** * Have CAPAs been proposed by applicant? *Provide a summary list of all CAPAs proposed*
* Do proposed CAPAs address all identified root causes? Do they sufficiently address the problem and are the timelines reasonable?

RMS <Preliminary><Final> recommendation on acceptability of CAPAs (*note related variations will be assessed separately*) |  |
| **MAH Conclusion of risk assessment:** |  |
| **RMS<preliminary> <final> overall conclusion on risk assessment** |  |

**\***[**https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-questions-answers-marketing-authorisation-holders/applicants-chmp-opinion-article-53-regulation-ec-no-726/2004-referral-nitrosamine-impurities-human-medicinal-products\_en.pdf**](https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-questions-answers-marketing-authorisation-holders/applicants-chmp-opinion-article-53-regulation-ec-no-726/2004-referral-nitrosamine-impurities-human-medicinal-products_en.pdf)