



To whom it may concern

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Revision 2

Nitrosamines – EMA/369136/2020

MEGGLE Product: RetaLac®

The product is a co-processed, directly compressible spray agglomerate comprising 50 % Lactose Monohydrate (Ph. Eur. / USP-NF / JP) and 50 % Hypromellose (Ph. Eur. / USP-NF / JP).

Regarding EMA's Human Medicines committee (CHMP) request that marketing authorisation holders for human medicines containing chemically synthesised active substances review their medicines for the possible presence of nitrosamines it is informed as follows:

A Risk Evaluation was conducted based on the IPEC Questionnaire.

Nitrosamines are produced from nitrites and secondary amines as relevant precursors. Their formation is enhanced under strongly acidic conditions and high temperatures.

Starting materials

- Lactose monohydrate is not chemically synthesized. Nitrites and secondary amines, e.g. as organic solvents are not used. Lactose monohydrate is isolated and purified from whey which is a by-product of cheese manufacturing. Raw material whey is bought according to specification and tested and approved by MEGGLE. Whey does not contain relevant amounts of nitrates (as precursor of nitrites), nitrites and secondary amines. Testing on nitrates and nitrites is conducted as part of incoming goods inspection. The acceptance limits are as follows: Nitrate < 50 ppm, Nitrite < 5 ppm. Strongly acidic conditions as necessary prerequisite for the formation of nitrosamines are not achieved during manufacturing process.
- Hypromellose is synthesized without the use of nitrites and secondary amines.

Manufacturing of RetaLac®

Strongly acidic conditions as necessary prerequisite for the formation of nitrosamines are not achieved at the manufacturing process of the product.

Conclusion: Neither the chemical composition of the starting materials nor the processing conditions indicate any possibility for nitrosamine contamination and formation in the process or storage of the MEGGLE product.

Best regards

MEGGLE GmbH & Co. KG

Dr. Stefan Dreiheller



Nitrosamine Risk Evaluation

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1) Is sodium nitrite (NaNO ₂) or any other nitrite or nitrosating agent: <ul style="list-style-type: none"> - used in any steps in the manufacturing process as reagents/catalyst? - known to be used in the preparation of raw materials or intermediates used in the manufacturing process? - known to be used in the preparation of reagents/catalysts/processing aids used in the manufacturing process? - known to be generated as impurities during the manufacturing process? 	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> YES	<input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> NO	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <i>Test result, if available</i>
2) Have you analysed, and are the results available for the excipient for: <ul style="list-style-type: none"> - Nitrites? - Nitrates? - Nitrosamines? Method: FIA, for Nitrites with Cd reduction; in contracted laboratory; LOD 0.2 ppm; LOQ: 0.5 ppm	<input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/>	2.7 ppm 17 ppm
3) If water is used in the manufacturing process ² , is it prepared by distillation, by ion exchange or by reverse osmosis? If "No", please inform about the maximum level of <ul style="list-style-type: none"> - Nitrites - Nitrates 	<input checked="" type="checkbox"/> ___ ppm ___ ppm	NO <input type="checkbox"/> <i>Not specific</i> <i>d</i> <input type="checkbox"/> <input type="checkbox"/>	<i>Not applicable</i> <input type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/>
4) Is there any secondary and/or tertiary amine present in the manufacturing process ² as: <ul style="list-style-type: none"> - Raw material? - Intermediate? - Reagent? - Processing aids? - Catalyst / Base? - Solvent? If yes, are those amines present in the <ul style="list-style-type: none"> - Same - Previous - Subsequent step as any nitrosating agent mentioned in section 1?	YES <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	NO <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>Not applicable</i> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/>
5) Is there any amide, primary amine or ammonium salt used or present in the substance manufacturing process ² as: <ul style="list-style-type: none"> - Raw material? - Intermediate? - Reagent? - Processing aids? - Catalyst / Base? - Solvent? - Washing Fluid? 	YES <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	NO <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/>	
6) Recycled/recovered Solvents: <ul style="list-style-type: none"> - Are recycled / recovered nitrogen containing solvents used in the manufacturing process²? 	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	
7) Multipurpose Equipment: <ul style="list-style-type: none"> - Is the substance produced in multipurpose equipment? In case of multipurpose equipment, is the equipment used for manufacturing of any material involving nitrites, nitrosating agents or material with identified risk of formation of nitrosamines?	YES <input checked="" type="checkbox"/> <input type="checkbox"/>	NO <input type="checkbox"/> <input checked="" type="checkbox"/>	<i>Not applicable</i> <input type="checkbox"/>



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Annex¹:

Guidance 1 (Sources of nitrosating agents)

Nitrosating agents to be considered include; nitrites (e.g. sodium nitrite, NaNO₂) and nitrous acid (HNO₂), nitric oxide (NO), nitrosyl halides (e.g. ClNO, BrNO), dinitrogen trioxide (N₂O₃), dinitrogen tetroxide (N₂O₄) and organic nitrites (e.g. t-BuONO).

Other potential nitrosation risks:

- Side reaction in nitration reactions. Nitric acid typically contains nitric oxide as an impurity, additional nitrous acid may also be produced, leading to nitrosation, if any reducing agents are present.
- Hydroxylamine under oxidative conditions.
- Chloramines are known to generate N-nitrosamines under certain conditions and so should also be considered.²
- Ozone may lead to the formation of N-nitrosamines by initial oxidation of amines to nitrite.
- Use of azide salts and azide compounds is commonly followed by quenching with nitrous acid or nitrites and may lead to nitrite residues.
- Nitric acid and nitrates under reducing conditions may result in by-products with nitrosating activity.

This evaluation must include the use of all chemicals within a process, including those used during the quench and work-up as well as during reactive chemistry.

Guidance 2 (Sources of secondary and tertiary amines)³

Secondary amines are of greatest concern, however tertiary amines can also undergo nitrosation via more complex pathways. All secondary and tertiary aliphatic and aromatic amines should therefore be considered including those present as part of the starting material, intermediate or final structure as well as those introduced as reagents, catalysts, solvents or as impurities.

Tertiary amine bases (i.e. triethylamine, diisopropylethylamine and N-methylmorpholine) are known to degrade to secondary amines and have been implicated in N-nitrosamine formation.

Amines may also be introduced as impurities or degradants:

- Of common amide containing solvents such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAC) and N-methylpyrrolidinone (NMP)
- Of quaternary ammonium salts such as tetrabutylammonium bromide (TBAB)
- Of primary amines such as monoethylamine
- Of starting materials, intermediates or the product itself

This evaluation must include the use of all chemicals within a process, including those used during the quench and work-up as well as during reactive chemistry.

Guidance 3 (Potential contamination risks)

Consider all potential sources of contamination in input materials.

Use of recovered materials (solvents, reagents, catalysts) is of particular concern if appropriate controls are not put in place. The materials DMF, ortho-xylene and tributyltin chloride were highlighted by the EMA as materials at risk of cross contamination by N-nitrosamines. Sodium azide was highlighted by Health Canada for risk of cross contamination with nitrite.

Cross contamination from other processes using shared equipment should be considered. Steps performed under GMP (using solvents/reagents with appropriate controls, and controls on their recovery and reuse) are considered to be a lower cross contamination risk.

Guidance 4 (Determining an acceptable level)

Interim acceptable daily intakes for chronic exposure to several common N-nitrosamines have been defined. See literature reference⁴ for EMA interim acceptable daily intake for chronic exposure to common N-nitrosamines.

Processes to determine acceptable intakes for all other N-nitrosamines should be in alignment with the EFPIA paper.⁵

These levels should be adjusted for less than lifetime exposures as described in ICH M7.⁶

Calculate acceptable limits in ppm relative to the substance using the maximum daily dose. Higher limits may be justified for ICH S9 indications.⁷

Guidance 5 (Conducting purge assessments)⁸

Where a nitrosating agent and amine have the potential to be concurrently present an assessment of the process conditions should be conducted to determine if a N-nitrosamine could potentially be formed and what the maximum realistic level could be. Nitrosation occurs more rapidly under acidic conditions (apart from organic nitrites) and may also be catalysed by certain anions and aldehydes (notably thiocyanate and formaldehyde).⁹

During purge calculations consider the likely physicochemical characteristics of the N-nitrosamine which may be formed. For instance, NDMA has a BP of 153 °C and will partition in both aqueous and organic layers. It is highly soluble in water and organic solvents. Other, higher molecular weight, N-nitrosamines will behave differently.

N-nitrosamines are relatively stable compounds though the following conditions are known to result in de-nitrosation:

- Strongly acidic condition with a nucleophile trap (e.g. HCl with MeOH)
- Metal reducing conditions (e.g. Zn AcOH; Ni/Al KOH)
- Pd/C Hydrogenation
- Grignards
- Strong oxidants (H₂O₂; KMNO₄)

¹ This information is transferred from the EFPIA decision tree for drug substances, published 1 Nov 2019

² Nawrocki, J et al. Nitrosamines and Water, J. Hazard. Mater. 2011, 189, 1-18.

³ SCCS (Scientific Committee on Consumer Safety), Opinion on Nitrosamines and Secondary Amines in Cosmetic Products, 27 March 2012.

⁴ EMA, Temporary interim limits for NMBA, DIPNA and EIPNA impurities in sartan blood pressure medicines, 20 August 20, 2019.

⁵ EFPIA position with respect to safety related aspects of EMA and Health Canada requests for N-nitrosamine evaluations, 2019.

⁶ ICH M7, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, 31 March 2017.

⁷ ICH S9, Nonclinical Evaluation for Anticancer Pharmaceuticals, 29 October 2009.

⁸ Barber, C et al. A consortium-driven framework to guide the implementation of ICH M7 Option 4 control strategies. Regul. Toxicol. Pharmacol. 2017, 90, 22-28.

⁹ Williams, D. L. H. Nitrosation reactions and the chemistry of nitric oxide. 2004, Amsterdam, Elsevier.

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