

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

DRAFT OPINION ON AN APPLICATION UNDER THE NOVEL FOODS REGULATION FOR 1-METHYLNICOTINAMIDE CHLORIDE

Applicant: Pharmena SA
Responsible Person: Marzena Wieczorkowska
EC Classification: 1.1

Introduction

1. An application from Pharmena SA for methylnicotinamide chloride (1-MNA), as a novel ingredient was accepted by the Food Standards Agency on 18 September 2013. A copy of the application was placed on the Agency's website for public consultation.
2. 1-Methylnicotinamide is formed endogenously during the metabolism of niacin (vitamin B3, nicotinic acid, vitamin PP). Its chloride salt is currently used in the cosmetic industry. The applicant intends that 1-MNA will be used in food supplements. 1-MNA has the chemical formula $C_7H_9N_2OCl$ and the following structure:



3. 1- MNA has been classified as a complex novel food from non-GM source. The source of the novel food, Niacin, has a history of food use in the EU (class 1.1) according to the scheme in Commission Recommendation 97/618 (EC).

I. Specification of the novel food

4. The applicant has provided detailed specifications for 1-MNA including descriptions of the methods employed to measure each of the parameters. This is summarised below:

Parameter	Description or Limit
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Appearance, solubility test/USP	White or off white, crystalline solid, very soluble in water, soluble in methanol, practically insoluble in 2-propanol and dichloromethane
Purity	Not less than 98.5 % and not more than 101.5 % (as anhydrous substance)
Loss on drying	Not more than 1.0 %
Residue on ignition/	Not more than 0.1 %
Heavy metals	Not more than 20 ppm
Trigonelline	Not more than 0.05 %
Nicotinic Acid	Not more than 0.10 %
Nicotinamide	Not more than 0.10 %
Largest unknown impurity	Not more than 0.05 %
Sum of unknown impurities	Not more than 0.20 %
Sum of all impurities	Not more than 0.50 %
Residual solvent	Not more than 3000 ppm
Methanol	
Microbiological Specification	
Total Aerobic Microbial Count	Not more than 100 cfu/g
Mold and Yeasts Count	Not more than 10 cfu/g
<i>Pseudomonas aeruginosa</i>	Not present in 1 g
<i>Staphylococcus aureus</i>	Not present in 1 g
<i>Enterobacteriaceae</i>	Not present in 1 g

5. The applicant advises that the product has a high purity with information provided in the dossier for three batches which show 1-MNA to be present in the range 99.8 – 100.9%. The applicant noted that one HPLC method to quantify the 1-MNA relative to a known standard this has acceptance criteria of 98.5%-101.5%. A different HPLC method is used to determine the level of impurities (limit 0.5%). The applicant also notes that the acceptance criteria for both methods are in line with the requirements for an active pharmaceutical ingredient.

Discussion: The Committee did not raise any concerns relating to this section of the dossier.

II. Effect of the production process applied to the novel food

6. The applicant has provided details of the production process in the confidential version of the dossier. 1-MNA is a crystalline product produced by the methylation of nicotinamide using water, methanol and other key reagents. The applicant states that all batches of 1-MNA will be tested to ensure compliance with the specification.

7. The applicant provided reassurance that the product shows good stability of 1-MNA with the composition of the product remaining within the specification over a 36 month period. The dossier also provided stability information on 1-MNA in a final product which the applicant considered showed good stability over a 24 month period.

Discussion: The Committee did not raise any concerns relating to this section of the dossier.

III. History of the organism used as a source of the novel food

8. The applicant states that the starting material for 1-MNA production, nicotinamide, has similar activity to nicotinic acid and provides a commentary about the importance of B vitamins, dietary sources (meat, poultry, fish, dairy and grain). Pellagra, the condition associated with niacin deficiency, typically occurs in individuals who are malnourished but can also occur in chronic alcoholics and in areas of the world where the diet is maize rich (maize is the only grain low in digestible niacin). The applicant reports nicotinic acid and nicotinamide as having similar activity but states that nicotinamide does not induce the antihyperlipemic effect seen for nicotinic acid and notes that studies which highlight a number of perceived health effects, e.g. positive effects on insulin-dependent diabetes, are not generally accepted.

Discussion: The Committee did not raise any concerns relating to this section of the dossier.

IX. Anticipated intake/extent of use of the novel food

9. The applicant intends to use 1-MNA only in food supplements (58 mg/day).
10. The applicant reports that only low levels of 1-MNA can be obtained from dietary sources, which are foods that are rarely consumed by the general population in the UK. Foods such as brown seaweed (*Undaria pinnaatifida*), leaves of green tea and natto contain low levels of 1-MNA. The main source of exposure to 1-MNA in the population is likely to be from metabolism of Niacin.

Discussion: The Committee noted a potential issue might arise in relation to cumulative intake of the novel food in combination with Niacin.

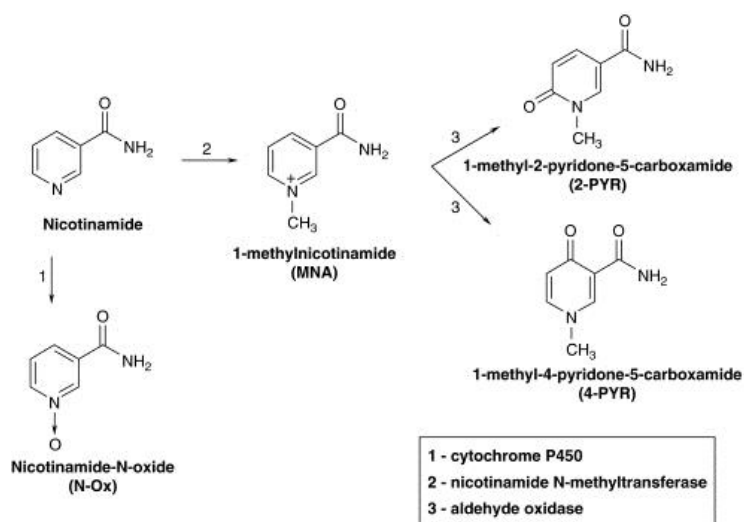
X Information from previous human exposure to the NF or its source

11. The applicant notes the main source of exposure is the endogenous metabolism of niacin. Use of 1-MNA at up to 0.4% in a relatively wide range of cosmetics (typically skin creams) has also been reported.

Discussion: The Committee did not raise any concerns relating to this section of the dossier.

XI. Nutritional information on the novel food

12. The applicant notes that 1-MNA will be consumed in dietary supplement form and has no nutritional value in terms of protein, fat, carbohydrate etc. The applicant has advised that 1-MNA would be used to reduce risk factors related to the progression of atherosclerosis, a use which would require the provision of necessary efficacy data for review by the European Food Safety Authority. The applicant is of the view that 1-MNA exerts a physical effect in the endothelium, where it is able to counterbalance the effect of endothelin by acting as an endogenous activator of prostacyclin (which is produced in endothelial cells). It is outside the scope of this evaluation to evaluate scientific evidence for potential health benefits from consuming the product.
13. The applicant also refers to other effects which may have benefits in relation to the progression of atherosclerosis, in particular in relation to hypertriglyceridemia. These effects, which may be regarded to be “medicinal by function”, require the consumption of significantly higher levels of 1-MNA than is proposed.
14. Information regarding the metabolic fate of 1-MNA, in the context of niacin metabolism, was provided by the applicant. Niacin is metabolised in the liver via two pathways: the first is via glycine conjugation to form nicotinuric acid and the second contributes to the formation of nicotinamide adenine dinucleotide (NAD), a co-enzyme found in all cells which is important in the catabolism e.g. of fats, carbohydrates etc. In this pathway, which has not yet been completely elucidated, niacin is converted to nicotinamide then methylated to 1-MNA or conjugated to form NAD in the presence of the enzyme nicotinamide N-methyltransferase. 1-MNA is then metabolised to 1-methyl-2-pyridone-5-carboxamide (2-PYR, referred to as 2PY in the dossier) and 1-methyl-4-pyridone-5-carboxamide (4-PYR, referred to as 4PY in the dossier). The applicant indicates that, based on published studies, 1-MNA and its metabolites are excreted via the kidneys.



Discussion: The Committee requested further information from the applicant on the metabolic pathway for 1-MNA. Information was also requested to understand the impact of 1-MNA supplementation on niacin metabolism in particular in those taking high doses of niacin used for the treatment of cholesterolaemia.

In responding to this request the applicant provided further information on the metabolic pathway. While the pathway is not fully characterised, this suggested that 1-MNA is one of the downstream metabolites of niacin, and the likely impact of taking both niacin and 1-MNA supplementation would be an increase in 1-MNA's metabolites, 2PY and 4PY. A toxicokinetic assessment of 1-MNA metabolism in rats was also undertaken to support the applicant's analysis.

A 10 week study was commissioned by the applicant to investigate the safety and effect on lipid profile parameters following combined administration of statins and 1-MNA. The findings of this study indicated that 1-MNA and 90mg/day statins was safe and well tolerated. Additional data submitted by the applicant on co-consumption of high doses of niacin and 1-MNA provided reassurance that the 1-MNA would not negatively impact the effectiveness of niacin treatment, with 1-MNA supplementation providing a small contribution to the pathway compared to the high dose of niacin.

XII. Microbiological information on the novel food

15. The applicant states that every batch of 1-MNA is tested for the presence of a range of microorganisms. Appropriate limits for total aerobic and pathogenic are detailed in the specification. The applicant has presented microbiological analyses illustrating that the levels of microbial contamination in the product are low.

Discussion: The Committee did not raise any concerns relating to this section of the dossier.

XIII. Toxicological information on the novel food

16. The applicant has presented a number of studies in support of the safety of 1-MNA.

Pharmacokinetic and metabolic studies

17. The applicant presents four studies to demonstrate the metabolic pathway of 1 MNA. In the first 1-MNA was administered to rats at a range of doses from 125-500 mg/kg body weight/day resulting in substantial, dose dependent levels of 1-MNA in plasma, which were approximately 20 fold higher than endogenous levels. Levels of the metabolite 2PY were dose dependent and up to 40 times higher than endogenous levels, while levels of 4PY were not dose dependent.

18. Three rat studies showed dose dependent findings for 1-MNA and 2PY where animals were given 1-MNA or nicotinic acid. Based on the results of these studies the authors concluded that the half-life of 1-MNA in rats is in excess of 24 hours. The one human study presented, showed a gender based difference, with higher concentrations of 1-MNA in plasma seen in females.

Acute Toxicity Studies

19. An acute oral toxicity study in rats, indicated an LD50 in excess of 2000mg/kg body weight. The applicant regards this low toxicity to have been confirmed following administration of intraperitoneal injections which, according to the 'Hodge-Sterner' toxicity classification is indicative of 1-MNA being practically non-toxic.

Sub-acute toxicity

20. The sub-acute toxicity of 1-MNA was assessed in three studies. A 28 day oral toxicity study was carried out in rats using three doses (250, 500 and 1000 mg/kg body weight/day). There was no treatment related mortality. The applicant considered the few statistically significant changes in biochemical markers seen were not adverse. The changes seen included the calcium concentration in male rats given the highest dose (1000mg/kg body weight/day), an increase in leukocytes and a decrease in urine pH.

21. Two animals (1 male and 1 female) from the highest dose group had a necrotic focus in the liver. In the absence of other treatment related findings the applicant suggested that the lesions are unlikely to be related to 1-MNA. The applicant concluded that the 1000 mg/kg/body weight/day level to be the no-observed adverse effect level (NOAEL).

22. Two other sub-acute studies of 28 days in rats are also presented by the applicant. The doses of 1-MNA tested were 1000 mg /day and 1402 mg/day respectively. No macroscopic aberrations were observed in the first study and the body weights and food intake of both treatment groups were similar to the control group. In the second study, no biologically significant differences in organ weight parameters were observed, and differences in organ weights across groups were attributed to biological variability or slight differences in the amount of tissue that was harvested.

Genotoxicity

23. Results from an Ames test for 1-MNA showed no mutagenic activity. A mammalian cell micronucleus test with a highest dose of 1.72 mg/ml 1-MNA did not induce any increase in micronuclei frequency in the exposed cell cultures.

Human Studies

24. The applicant has not carried out any human toxicity studies but refers to two clinical studies, summarised below.

Human clinical trials

Study description	Patient population and sample size	Safety outcomes
Randomized, double-blind, placebo-controlled, single dose crossover study	Healthy adult volunteers (N=20); N=16 exposed to 1-MNA at 90 or 270 mg.	12 mild-moderate. Adverse Effects in 8 subjects. More than one Adverse Effect: 1 (headache). No Serious Adverse Effects.
Randomised placebo-controlled double-blind trial	405 subjects screened. 339 subjects entered placebo lead in. 211 dyslipidemic patients enrolled; 71 received 1-MNA 30 mg, 67 received 1-MNA 90 mg, 73 received placebo.	4 patients reported Serious Adverse Effects; (1 patient on Placebo, 1 patient on 90 mg 1-MNA 2 patients on 270 mg 1-MNA) all Serious Adverse Effect's not related to study drug. No deaths.

Discussion: *The Committee considered in further detail some of the findings in the 28 day acute toxicity study. In their view some of the findings could not be ruled out as adverse.*

To address this, the applicant commissioned a 91 day rat feeding study. The results of this study suggested some of the previous findings were not of concern. It also showed statistically significant increases in calcium levels in urine and decreases in urine pH, in both sexes at the highest 2 doses (500 mg/kg/day and 1000 mg/day respectively). The applicant suggested that these were not adverse events as the effect on urine did not correlate to effects on serum calcium and phosphorus; or to histopathologic changes in the kidney, parathyroid; or alterations

in bone or bone density. The applicant also highlighted problems with collecting urine in some groups with the analysis therefore being based on a few animals in some cases. The Committee's view was that as it could not be ruled out that the findings were adverse, and for the purpose of the assessment the NOAEL should be lowered to 250 mg/kg.

The applicant also provided information suggesting that niacin, of which 1-MNA is a downstream metabolite, was tolerated. The Committee considered that these human studies contributed to the assessment suggesting there was some tolerance of 1-MNA. However, they also commented that a quantitative link, between the dose of niacin received and level of 1-MNA to which participants were exposed, could not be made. It was considered that there remained uncertainties associated with both intra-individual and within individual variability and therefore a larger margin of exposure should be used to manage these uncertainties.

CONCLUSION

The ACNFP has completed its assessment of 1-MNA as a novel ingredient for use in food supplements.

The Committee requested further information from the applicant on the following:

- The metabolic pathway of 1-MNA.
- The impact of 1-MNA supplementation on those taking high doses of niacin to treat hypocholesterolaemia..
- A further 90 day animal study to support the selection of the NOAEL and therefore the dose that can be safely included in products for consumers.

After reviewing the applicant's response to these issues, and the amendment of the dose of 1-MNA to be used in products, the Committee did not have any outstanding safety concerns

The Committee has suggested, and the applicant agreed that children and pregnant women should not take the product as insufficient data on its safety in these groups is available.

The Committee strongly supports the applicant's commitment to post-market monitoring scheme (such as adverse effects monitoring). This would provide additional reassurance that any potential effects from taking the product are monitored.

Based on the evidence provided the ACNFP therefore concluded that 1-MNA at the dose of 58 mg per day proposed by the applicant is unlikely to present a health risk to consumers.

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