COMMITTEE PAPER FOR DISCUSSION **ACNFP/118/2**

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

1-METHYLNICOTINAMIDE CHLORIDE

Issue

At its meeting in November 2013 the Committee considered an application for food supplements containing 1-methylnicotinamide chloride (1-MNA). The Committee is now invited to consider whether the response from the applicant and the results of a 91 day feeding study addresses the concerns raised by members in relation to this product.

Background

1. This application, submitted to the UK on behalf of Pharmena SE of Poland, is for food supplements containing methylnicotinamide chloride (1-MNA), which is a novel food in the EU.
2. When the Committee considered this application at its meeting in November 2013 (paper ACNFP/113/2) Members highlighted the following issues:
    a) The Committee did not agree with the interpretation provided by the applicant in relation to the 28 day feeding study and indicated that the presence of liver lesions and other findings were a cause for concern. A follow up 90 day animal study was suggested to investigate these observations in more detail. The Committee advised that this study should also consider potential bone mineral changes.

    b) The Committee was not satisfied with the information provided in regard to the effect of 1-MNA supplementation on the metabolism of niacin. The Committee therefore requested that appropriate investigations are carried out to determine whether the proposed level of consumption of 1-MNA is likely to have a significant effect on niacin metabolism. It was suggested that the study should also take into account the effect of 1-MNA supplementation on high doses of niacin which are used for the treatment of cholesterolaemia.

3. The applicant's response is provided as Annex A and the report of the 91 day feeding trial and toxicokinetic study are provided in Annex B. The key findings are summarised below

a) The 90 day feeding trial – toxicological findings

4. The applicant suggests that the 91 day feeding study in rats noted no treatment related effects on clinical observations, functional observational battery parameters, locomotor activity, body weights, food consumption, ophthalmoscopic findings, clinical pathology parameters, anatomic pathology parameters, or dual energy x-ray absorptiometry parameters during the dosing or recovery period. All animals survived to the scheduled end of the study. The study reports a NOAEL of 1000mg/kg/day in male and female rats.

5. Below is summarised the events that members felt warranted further investigation from the original 28 feeding study and the insights the applicant feels the new study brings in these areas:

Observed Effect associated with 1-MNA in 28 day study	**Members' view**	**Applicants comments on 91 day study evidence**
An increase in calcium and an increase in leukocytes in the male rat urine. Decrease in urine pH.	Could be an adverse effect.	An increase in calcium in the urine and a decrease in urine pH was seen. Leukocytes rarely observed in urine.
The presence of necrotic foci is an undisputable finding and the report authors suggest that they could be treatment related as there are not present in the control group. The conclusion in the expert opinion is that the reason for their presence is unknown and it is unlikely that they are related to 1-MNA.	Do not accept the expert view that the necrotic foci can be discounted	No test article related macroscopic or microscopic hepatic findings. 1 female rat at highest dose had two small hepatodiaphragmatic nodules, one classed as mild the other as severe. Applicant suggests the findings in the 28 day study are therefore incidental.
Higher and more variable levels of aminotransferase (AST) and alanine aminotransferase (ALT). The conclusion in the expert opinion is that this is seen in all study animals and is due to an underlying problem in the animals.	Possibly, but this view requires additional invest-igation (as noted by the study authors).	No test article related effects seen on AST or ALT in any treatment group. Individual values were viewed as being in the acceptable range.
Report indicates that rats may not have been able to tolerate 1000mg/kg/day in a single dose but C_{max} values would be different if the daily dose administered to the animals was 2x500mg rather	Requires additional investigation.	The applicant notes that in this study rats tolerated well once daily doses up to 1000mg/kg/day for the 13 weeks of the study with no mortality.

than 1x 1000mg/kg/day and this could impact on the NOAEL.		
Statistically significant changes in organ weights (absolute and relative to body weight) were regarded to be accidental as they were not treatment related or confirmed histopathologically.	As anomalies only occurred in treatment groups, the observed findings should require confirmation by tissue histology. This could be an adverse effect.	The applicant considers that no definitive test article related effects on organ weights were seen in the study. Any effects seen were thought to be spontaneous as they were not dose dependant, or lack of finding in the opposite sex or microscopic correlates. Also see comments on organ weights in paragraph 10.
Effect of withdrawal from high dose treatment on latency of pain response in male rats different to that observed in female rats.	Could be an adverse effect. Differences cannot be discounted because it didn't occur in main study and hypersensitivity cannot be ruled out.	No statistically significant test article related differences or gender related differences in thermal response relative to control subjects.
Gender specific effects on haemoglobin and mean Corpuscular Haemoglobin Concentration (MCHC) in treatment groups.	Could be an adverse effect. Validity needs to be assessed, possibly by further investigation.	There were no test article related effects among hematology parameters in any treatment group. No gender related differences relative to controls were observed.
General observation: Some study findings were not subjected to an appropriate statistical analysis and, at times, it was unclear whether the observed effect was dose related.	-	The statistical analysis performed on the study endpoints are detailed in the report of the study.

Urine analysis

6. The report of the 91 day feeding trial notes a treatment related effect on urine chemistry with decreased urine pH and increased calcium excretion in both sexes at the highest 2 doses. In those in the 1000mg/kg/day dosing group the urine pH effect remained after the 28 day dose free interval. In females the increased calcium excretion was also seen after the dose free period. The study report suggests that 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. It was not considered adverse due to the small magnitude of the effect. It was noted that there was limited data for females administered the 500mg/kg/day dose due to small urine volume however, females administered 1000mg/kg/day dose did not show small urine volume.

Bone mineral density

7. The study report suggests that there were no differences in dual energy x-ray absorptiometry parameters between treated and control animals.

Macroscopic and microscopic effects

8. The applicant considers that all macroscopic findings were considered to be incidental due to a lack of correlation with microscopic findings, relationship to dose, or similar findings in the opposite sex. As described in the applicant's response, hepatodiaphragmatic nodules were seen in one test subject but are thought not to be adverse.

9. In terms of microscopic findings the feeding trial report notes a potential test article related effect of epithelial degeneration in non-glandular stomach of males at doses greater than 250mg/kg/day and females at the 1000mg/kg/day dose. The increase in incidence was not dose dependant in females and the severity of symptoms did not increase with dose in both sexes. As there were no findings of epithelial degeneration at necropsy the researcher considered the findings as incidental.

Organ weights

10. The study report suggests that there were no definitive test article related organ weight findings. It reports an increase in adrenal gland weights in males at doses above 500mg/kg/day. However, this is not considered adverse as there are no microscopic correlations to the finding, nor similar changes in adrenal weights in females.

b) Toxicokinetic assessment

11. A separate study within the feeding trial examined the toxicokinetics of 1-MNA. This considered the levels of 1-MNA and its breakdown products 2PY and 4PY in rats. The report outlines the change in Area Under Curve (AUC) and C_{max}

values following daily exposure to the novel ingredient. Values for AUC and C_{max} for 1-MNA and 2PY increase with an increase in dose up to 500mg/kg/day. At doses greater than 500mg/kg/day an increase in dose lead to a decrease in these values. 4PY AUC and C_{max} levels did not respond to increasing dose on day 1 or day 91.

12. The study report suggests that there was not accumulation of 1-MNA or its breakdown products 2PY and 4PY between day 1 and 91 of the study.

Committee Action Sought

13. The Committee is asked whether the response from the applicant is sufficient to address its concerns in regard to the issues raised in 2013.

14. If not, the Committee is asked to indicate what feedback should be given to the applicant.

Secretariat
February 2015

Annexes attached

Annex A Response from applicant.

Annex B The report of the 90 day feeding trial.