Type II variation
2nd Updated Final Variation Assessment Report

GLUCOPHAGE
Film-coated tablets, 500mg, 850mg, 100mg

STAGID
Tablets, 700 mg

GLUCOVANCE
Film-coated tablets, 500/2.5mg, 500/5mg, 1000/5mg

Metformin hydrochloride
Metformin embonate
Metformin hydrochloride/Glibenclamide

FR/H/xxxx/WS/245

Marketing Authorisation Holder: Merck Sante

Date: 11/03/2022

TABLE OF CONTENTS

ADMINISTRATIVE INFORMATION

Name of the medicinal product(s) in the RMS	Glucophage, Stagid, Glucovance
Name of the active substance (INN, common name):	metformin hydrochloride metformin embonate metformin hydrochloride/glibenclamide
Pharmaco-therapeutic group (ATC code)	A10BA02
Pharmaceutical form(s) and strength(s)	Film-coated tablets, 500mg, 850mg, 100mg Tablets, 700 mg Film-coated tablets, 500/2.5mg, 500/5mg, 1000/5mg

Procedure number	FR/H/xxxx/WS/245
Member States concerned	AT, BE, BG, CY, CZ, DE, DK, EL, ES, FI, HR, HU, IE, IS, IT, LU, LV, NL, NO, PL, PT, RO SI, SK, SE and UK(NI)

RMS contact person	[redacted] Email: [redacted]
Names of the assessors	[redacted]

Nature of change/s requested	**C.I.4:** Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data. The scope of this variation is to submit a safety update of the Product Information (SmPC Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects; PIL Section 4 Possible side effects) with regards to the identified risk of vitamin B12 deficiency in association with metformin use. This worksharing procedure comprise editorial changes.

I. RECOMMENDATION

Based on the review of the data on safety the RMS considers that the group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008 for Glucophade (metformin), in the treatment of Treatment of type 2 diabetes in adults, as replacement for previous combination therapy with metformin and glibenclamide in patients whose glycaemia is stable and well-controlled for the following proposed changes:

is approvable

II. EXECUTIVE SUMMARY

II.1 Scope of the variation

This Clinical Overview Addendum aims to support the safety variation to amend the product information on the identified risk of vitamin B12 deficiency. Decrease of vitamin B12 absorption with decrease of serum levels is already covered in the Company's Reference Safety Information (RSI) and is a known consequence of long-term treatment with metformin (De Jager et al., 2010; Ting et al., 2006). On 05 Feb 2021, Merck received an inquiry from [redacted] concerning vitamin B12 decrease / deficiency in association with metformin hydrochloride with reference to frequency of vitamin B12 decrease / deficiency with metformin use and the risk of low vitamin B12 levels / vitamin B12 deficiency with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency.

III. SCIENTIFIC DISCUSSION

III.1 Clinical aspects

III.1.1 Clinical pharmacology

Several mechanisms by which metformin may induce a vitamin B12 deficit have been suggested, such as diminished absorption by changes in gut microbiota, interference with the intestinal absorption of the intrinsic factor-B12 complex via inhibition of the Ca^{2+}-influenced binding of IF– vitamin B-12 to the cubilin-amnionless receptor complex or alterations in intrinsic factor levels. Another potential explanation for metformin-induced vitamin B12 malabsorption and deficiency is that metformin may have an effect on calcium-dependent membrane function in the terminal ileum.
Metformin also progressively increases serum methyl malonic acid (MMA) as well as serum homocysteine. MMA may have a direct neurotoxic affect as an organic acid causing dysfunctional myelination or through overstimulation of the N-methyl-D-aspartate receptor causing neuronal cell death through an influx of calcium ions and oxidative stress. Therefore, vitamin B12 insufficiency, leading to elevated homocysteine and MMA levels, may possibly be a preventable cause of neurodegenerative disease.

Low serum vitamin B12 levels are associated with neurodegenerative disease and cognitive impairment. There is a small subset of dementias that are reversible with vitamin B12 therapy and this treatment is inexpensive and safe. Vitamin B12 therapy does not improve cognition in patients without pre-existing deficiency. Two studies reported that the vitamin B12 deficiency among metformin-treated patients was associated with worsened cognitive performance and increased risk of depression. This is also supported by Porter et al., (2019) who concluded that use of metformin was associated with higher risk of deficiency of vitamin B12 and vitamin B6 associated in older adults with poorer cognitive performance. Koo et al., (2019) investigated the effects on metformin on cognitive function in a prospective cohort of older adults

and metformin treatment was more frequently associated with rapid deterioration of mini-mental state examination and verbal immediate recall scores.

III.1.2 Clinical safety

Vitamin B12 decrease/deficiency is a well-known risk of metformin therapy and is covered in the adverse drug reaction (ADR) section of the Company's RSI.

To assess whether the product information may need an update regarding vitamin B12 decrease/deficiency, the Company has assessed both the clinical data and post-marketing data:

The Company has analyzed evidence from the pivotal Diabetes Prevention Program (DPP) / Diabetes Prevention Program Outcome Study (DPPOS) program, which has been published by Aroda et al. (2016) which included the use of the Company's Glucophage®. Furthermore, data from two Merck studies (Study 87-1D-6023, Study 87-2D-6023) performed with Glucophage® 500mg and 850mg have also been analyzed.

The Company also performed a broad and comprehensive literature search up to and including the DLP of 11 Feb 2021 which covered various synonyms and controlled terms in both Medline and Embase databases respectively. To optimize the results, the free-text terms covered various synonyms and were searched in abstracts and titles with respect to proximity operators. The search was focused to the subheadings regarding aspects of Safety and Toxicology. The following databases were searched: Medline, Embase (Experta Medica), Biosis, Science Scisearch (Science citation index) and TOXCENTERSM (Toxicology Center) on STN®. Duplicates were removed by an automated procedure and articles were screened at the abstract level ensuring inclusion of articles with key findings relevant for safety assessment.

Frequency of the adverse Drug Reaction (ADR) vitamin B12 deficiency/decrease

The pivotal studies (Study 87-1D-6023 and Study 87-2D-6023), confirm that metformin influences vitamin B12 levels, presumably through decrease of its absorption, resulting in subnormal serum vitamin B12 levels in approximately 7% of patients treated for six months with metformin, either alone or in combination with sulfonylurea. The mechanism of this decreased absorption may be related to interaction of metformin with ionic calcium, thereby interfering the vitamin B12/intrinsic factor complex interaction at its ileal receptor. Hematologic manifestations are very rare and neurologic manifestation of such deficiency have not been reported. During the pivotal clinical trials, neither hematologic nor neurologic consequences of vitamin B12 deficiency were seen.

Also, the analysis of Aroda et al. (2016) of the DPP (randomized)/ DPPOS (open follow-up) program (investigator sponsored study, ISS) where the Merck Glucophage® was used assessed the frequency of vitamin B12 decrease. Enrolled were patients with impaired glucose tolerance and fasting blood glucose of 95 to 125 mg/dl, at least 25 years of age and BMI of 24 kg/m2 or higher. The authors performed a secondary analysis of DPP/DPPOS to assess the risk of vitamin B12 deficiency with metformin use. The main outcomes assessed were vitamin B12 deficiency, anemia, and peripheral neuropathy at a mean 5 years and 13 years of follow-up. The study population for this analysis comprised participants randomized to placebo (n=902, mean age 56.0±9.9 years) or metformin (n=898, mean age 56.7±10.1 years, 1,700mg metformin daily) during DPP who had available serum stored from either DPPOS years 1 or 9 measured for vitamin B12 levels.

Low vitamin B12 (≤203pg/ml) occurred more often in metformin group than placebo at 5 years (4.3 vs 2.3%; p=0.02) but not at 13 years (7.4 vs 5.4%; p=0.12). Combined low and borderline low vitamin B12 (≤298pg/mL) was more common in metformin at 5 years (19.1 vs 9.5%; p<0.01) and 13 years (20.3 vs 15.6%; p=0.02). Years of metformin use were associated with increased risk of vitamin B12 deficiency (Odds Ratio, OR, B12 deficiency/year metformin use, 1.13; 95% confidence interval CI, 1.06–1.20).

The authors concluded that long-term use of metformin in DPPOS was associated with biochemical vitamin B12 deficiency and anemia. The prevalence of vitamin B12 deficiency after 5 years was 4.3%. Routine testing of vitamin B12 levels in metformin-treated patients should be considered.

The frequency reported in the studies above represents a "common" adverse reaction.

The frequency of decreased vitamin B 12 shown in the studies varied widely from 0.6% to 33%. This could be due to the different cut-off values for vitamin B12 deficiency used in the studies leading to the over- or underestimation of the incidence of vitamin B12 deficiency, and also lack of standardization for serum vitamin B 12 measurement. Moreover, the differences in the prevalence of vitamin B12 deficiency could be attributable to the differences in inclusion criteria or risk factors for vitamin B12 deficiency (such as patient age, underlying diseases, genetic predisposition (e.g. in Africa), or patients' diet).

Based on the assessment of all recently published articles on the prevalence or frequency of vitamin B12 deficiency with the use of metformin, the Company concludes that the frequency of vitamin B12 deficiency should no longer be considered very rare (although this frequency is still indicated by the view of ICSRs from the GSD), but that the frequency is considered by the Company to be common, mainly based on Aroda et al. (2016) and the two pivotal studies 87-1D6023 and 87-2D-6023. The Aroda study in particular was considered significant by the Company as this was secondary analysis from a RCT with long-term follow-up, having reasonable patient size, and inclusion of younger patients thereby limiting the confounding bias. This information is in line with other published studies (Reinstatler et al., 2012; Kancherla et al., 2017). The change of frequency should be reflected in the product information.

The frequency of decreased vitamin B 12 shown in the studies varied widely from 0.6% to 33%. This could be due to the different cut-off values for vitamin B12 deficiency used in the studies leading to the over- or underestimation of the incidence of vitamin B12 deficiency, and also lack of standardization for serum vitamin B 12 measurement (Yang et al., 2019). Moreover, the differences in the prevalence of vitamin B12 deficiency could be attributable to the differences in inclusion criteria or risk factors for vitamin B12 deficiency (such as patient age, underlying diseases, genetic predisposition (e.g. in Africa), or patients' diet).

Based on the assessment of all recently published articles on the prevalence or frequency of vitamin B12 deficiency with the use of metformin, the Company concludes that the frequency of vitamin B12 deficiency should no longer be considered **very rare** (although this frequency is still indicated by the view of ICSRs from the GSD), but that the frequency is considered by the Company to be **common,** mainly based on Aroda et al. (2016) and the two pivotal studies 87-1D6023 and 87-2D-6023. The Aroda study in particular was considered significant by the Company as this was secondary analysis from a RCT with long-term follow-up, having reasonable patient size, and inclusion of younger patients thereby limiting the confounding bias. This information is in line with other published studies (Reinstatler et al., 2012; Kancherla et al., 2017). The change of frequency should be reflected in the product information.

Time to Onset (TTO) for vitamin B12 deficiency/decrease in association with metformin use

The only clinical data to be assessed in this regard is the analysis of Aroda et al. (2016) of the DPP/DPPOS program (ISS) where the Merck Glucophage® was used. Each year of metformin use was associated with increased risk of B12 deficiency (odds ratio, B12 deficiency/year metformin use, 1.13; 95% confidence interval, 1.06–1.20).

Out of 480 AEs identified in the GSD, the metformin dose latency was reported in 137 AEs where the mean was calculated as 5.6 years and median: 6.6 years.

The Company is of the opinion that the risk of vitamin B12 deficiency increases with the metformin treatment duration as shown in the studies presented above. As per Aroda et al. (2016), each year of metformin use was associated with significantly increased risk of vitamin B12 deficiency (OR, vitamin B12 deficiency/year metformin use, 1.13; 95% CI, 1.06–1.20).

Aroda et al. (2016) had their first time point of assessing the risk at 5 years, which is in line with the time to onset in the case reports, which was found to be a median of 6 years. Other literature (e.g. Zalaket et al., 2018) however already describe an increased risk in patients having at least 3 months of duration of metformin use. The product information should reflect that the risk of vitamin B12 deficiency increases with the metformin treatment duration.

Metformin dosage and risk of vitamin B12 deficiency/decrease

The Company is of the opinion that the risk of vitamin B12 deficiency increases not only with a longer duration of metformin treatment, but also with a higher daily dose of metformin. However, a clear cut-off dose cannot be established. The product information should reflect this increased risk of vitamin B12 decrease / deficiency with increasing metformin dose.

Risks factors associated with vitamin B12 deficiency decrease

Furthermore, other risk factors concerning vitamin B12 deficiency include: advanced age, genetic predisposition, intestinal diseases, vegetarian / vegan diet and certain drugs (for example PPIs and H2-receptor antagonists), where screening may be warranted (Grober, Schmidt and Kisters, 2020 and Langan and Goodbred, 2017)

The Company proposes to annually monitor vitamin B12 serum levels in patients treated with metformin hydrochloride use with other risk factors known to reduce vitamin B12 levels in general.

Metformin use and the need for screening and periodic monitoring of vitamin B12 and hematologic parameters

The Company is of the opinion that there is a need for regular annual vitamin B12 monitoring by the treating physician. The pivotal studies of Glucophage® IR confirm that metformin influences vitamin B12 levels, presumably through decreased absorption of vitamin B12. However, during the course of the pivotal studies, neither hematologic nor neurologic consequences of vitamin B12 deficiency were seen. In support of the study data, on cumulative review of all cases from the global safety database till DLP 05 Feb 2021 for associated hematological abnormalities with vitamin B12 deficiency, the reporting rate is considerably low in patients with vitamin B12 deficiency while on metformin. The Literature review again supports the need for regular vitamin B12 monitoring while using metformin, but do not specifically recommend the need for hematological monitoring as a result of metformin use. This is further highlighted by key studies such as Aroda et al. (2016) and Yang et al. 2019 (a large meta-analysis) which concluded the need for vitamin B12 monitoring only. In fact, on review of the large meta-analysis by Yang et al. 2019, the authors concluded that although the annual assessment of vitamin B12 levels in diabetic patients taking metformin is recommended, and the appropriate preventive and therapeutic measures should be taken when necessary, the analyses revealed no significant association between metformin use and the prevalence of anemia or neuropathy. Therefore, appropriate corrective treatment should be carried out by the treating physician with the continuation of metformin treatment. Based on the overall safety assessment conducted, the Company agrees that regular vitamin B12 monitoring is required annually and reflected in the label, however, considers that the treating physician will initiate appropriate treatment of vitamin B12 deficiency with the continuation of metformin treatment and initiate respective follow-up and assessment of hematological consequences of vitamin B12 deficiency, as soon as it is detected. A routine monitoring of other hematological parameters, such as the hemoglobin or hematocrit values, should not be mandated in the label.

Assessor's comments

The scope of this variation is the assessment of the risk of vitamin B12 deficiency following an inquiry from [redacted] on February 2021. But the MAH did not specify the conclusion of this request.

Vitamin B12 deficiency can lead to hematologic and neurologic symptoms, such as anemia, neuropathy and ataxia. According to Moore *et al.*, 2012, low serum vitamin B12 levels are associated with neurodegenerative disease and cognitive impairment. But vitamin B12 therapy does not improve cognition in patients without preexisting deficiency.

Currently, vitamin B12 deficiency/decrease due to metformin is already noticed in the metformin product information in Section 4.8. Several mechanism has been suggested, but no confirmed explanation has been conclude on the mechanism of the deficiency.

Data collected by the MAH confirmed the influence of metformin on low vitamin B12 serum level. Analysis of Aroda *et al.*, 2016 shows a higher risk of low and borderline low B12 serum levels in patients with metformin. Furthermore, years of metformin use were associated with increased risk of B12 deficiency. Anemia prevalence was higher in the metformin group, but did not differ by B12 status. Neuropathy prevalence was higher in metformin group with low B12 levels.

The vitamin B12 deficiency seems associated with cognitive dysfunction in patients at risks (Porter *et al*., 2019). No confirmed data are reported in general population.

The rapporteur agrees with the MAH on the frequency of the adverse event "vitamin B12 deficiency/decrease", which should no longer be considered as very rare, but common regarding Aroda *et al.*, 2016 results which report 19.1% of low and borderline low vitamin B12 at 5 years (19.1 vs 9.5%; $p<0.01$), and 20.3% at 13 years (20.3 vs 15.6%; $p=0.02$).

In the standards of medical Care in Diabetes, 2021, published by the American Diabetes Association (ADA), the authors notice that long-term use of metformin may be associated with biochemical vitamin B12 deficiency; consider periodic measurement of vitamin B12 levels in metformin treated patients, especially in those with anemia or peripheral neuropathy. The ADA recommendations call for monitoring vitamin B12 levels, especially for patients with anemia or neuropathy.

The RMS considers that the frequency should be update to "common". However, monitoring of vitamin B12 levels should be realise only for patients with risk factors, patients with anemia or neuropathy.

III.2 Product information

Additions in **bold**, deletions in ~~strikethrough~~

III.4.1 Summary of Product Characteristics

4.4 Special warnings and precautions for use

Other precautions

It is recommended that vitamin B12 serum levels are monitored annually. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency (see section 4.8).

Assessor's comments

The assessor agrees with the MAH to update Section 4.4 regarding precautions on vitamin B12 decrease serum level. Nevertheless, there are insufficient data to update product information with a recommendation on annual monitoring. Vitamin B12 serum levels should be monitored only in case of suspicion vitamin B12 deficiency such as anemia or neuropathy.

The assessor suggests the following wording, highlighted in **bold**:

~~It is recommended that vitamin B12 serum levels are monitored annually~~. **Metformin may reduce vitamin B12 serum levels.** The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency (see section 4.8). **In case of suspicion vitamin B12 deficiency such as anemia or neuropathy, vitamin B12 serum levels should be monitored.**

4.8 Undesirable effects

Metabolism and nutrition disorders:

Hypoglycaemia (see section 4.4).
Uncommon: Crises of hepatic porphyria and porphyria cutanea.
Common: **Vitamin B12 deficiency**
Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia (see section 4.4).
Very rare: Lactic acidosis (see section 4.4).
~~Decrease of vitamin B_{12} absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.~~
Disulfiram-like reaction with alcohol intake.

Assessor's comments

The assessor agrees with the MAH to update the frequency of the adverse event "vitamin B12 deficiency/decrease", regarding data from publication. However, the adverse event should still be "Vitamin B12 decrease/deficiency" and not "Vitamin B12 decrease/deficiency". Data reported by the MAH show a decrease of the vitamin B12 serum levels. This information is to be entered in the product information.

III.4.2 Package leaflet and user test

4. Possible side effects

Common side effects (may affect up to 1 in 10 people)
- taste disturbance
- **low vitamin B12 levels in the blood**

Very rare side effects (may affect up to 1 in 10.000 people)

(…)
- ~~Decreased vitamin B12 levels in the blood~~

Assessor's comments

The assessor agrees with the MAH to update the frequency of the adverse event "vitamin B12 deficiency/decrease". Nevertheless, wording should be "decreased or low vitamin B12 levels un the blood".

IV. OVERALL CONCLUSION

Based on the review of the data on safety the RMS considers that the variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008 for Glucophage, Stagid (metformin hydrochloride, metformin embonate) for the following proposed changes in the SmPC Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects; PIL Section 4 Possible side effects with regards to the identified risk of vitamin B12 deficiency in association with metformin use applies to all products in this worksharing is not approvable unless the MAH can provide satisfactory responses to the request for supplementary information. The details of these request are provided in section V.

The benefit-risk balance of metformin in the treatment of type 2 diabetes mellitus remains positive.

V. REQUEST FOR SUPPLEMENTARY INFORMATION AS PROPOSED BY THE RMS

V.1 Major objections

V.1.1 Product information

The RMS considers that no mention of annual monitoring for all patients should be listed in Section 4.4. However, monitoring of vitamin B12 levels should be realise only for patients with risk factors of deficiency of vitamin B12 serum levels, or with aetiology of deficiency of vitamin B12 levels serum such as anaemia or neuropathy.

V.2 Other concerns

V.2.1 Product information

Adverse effect listed in section 4.8 should be “Vitamin B12 decrease/deficiency”.

VI. CONCERNED MEMBER STATES COMMENTS

[redacted]

We do not agree with the RMS that annual monitoring of vitamin B12 levels is only required for the subset of metformin-treated patients with risk factors or symptoms of B12 deficiency like anemia or neuropathy. First, due to the “common” occurrence of decreased vitamin B12 in metformin-treated patients, long-term metformin use may by itself be considered a risk factor, which would warrant annual vitamin B12 monitoring. Moreover, vitamin B12 deficiency may often be underdiagnosed due to subtle and rather non-specific symptoms. Specifically, many long-term metformin users are expected to be elderly people, where symptoms of vitamin B12 deficiency like lethargy, asthenia, muscle cramps etc. may easily be considered age-related rather than caused by vitamin B12 deficiency. Thus, without regular vitamin B12 monitoring, such patients would possibly receive only inadequate treatment, leading to a reduced quality of life. We therefore support the applicant’s proposal to recommend annual vitamin B12 monitoring, specifically in long-term metformin users.

[redacted]

[redacted] at Day 55 agrees with the RMS assessment and has an additional comment regarding the section 4.4 of the SmPC.

I should be considered that it is nearly impossible to clinically distinguish neuropathy caused by vitamin B12 deficiency from diabetic neuropathy. Moreover, according to the scientific literature vitamin B 12 deficiency should be established based on a wider scale of laboratory parameters such us haematological abnormalities, folate levels, elevated serum total homocysteine and methylmalonic acid levels. As has been reported, vitamin B12 deficiency due to metformin use maybe not be related to neuropathy if it is a

simple plasma deficiency (de Jager J, Kooy A, Lehert P, Wulffelé MG, van der Kolk J, Bets D, Verburg J, Donker AJ, Stehouwer CD. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. BMJ. 2010 May 20;340:c2181. doi: 10.1136/bmj.c2181. PMID: 20488910; PMCID: PMC2874129.) Therefore, we do not consider the recommendation to monitor only vitamin B12 serum level sufficient and propose the wording as follows:
- Proposal to delete: In case of suspicion vitamin B12 deficiency such as anemia or neuropathy, vitamin B12 serum levels should be monitored.
- Proposal to replace with: In case of anemia or neuropathy, vitamin B12 deficiency should be ruled out.

VII. ASSESSMENT OF THE RESPONSES TO THE REQUEST FOR SUPPLEMENTARY INFORMATION

In order to increase the awareness on the vitamin B12 deficiency, the Company propose to keep the recommendation for annual monitoring in the product information based on our overall safety assessment provided in the Clinical Overview Addendum. We agree to also include the possible consequences of vitamin B 12 deficiency, anaemia and neuropathy. Anaemia is including megaloblastic anaemia currently listed in section 4.8, which is why this addition to section 4.4. is considered to make the statement in section 4.8 redundant.
Please refer to the new proposal below: Summary of Product Characteristics (SmPC) section 4.4 (see also revised EU product information for Glucophage® film-coated tablets and Glucovance film-coated tablets in Module 1.3.1); new text underlined and bold, text to be removed crossed-out:

Present SmPC	Proposed text by the company	RMS Response in the uPVAR	New proposal by the company
4.4 Special warnings and precautions for use Other precautions […] - […]	4.4 Special warnings and precautions for use Other precautions […] **It is recommended that vitamin B12 serum levels are monitored annually. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency (see section 4.8).** […]	4.4 Special warnings and precautions for use Other precautions […] ~~It is recommended that vitamin B12 serum levels are monitored annually.~~[1] **Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency (see section 4.8). In case of suspicion vitamin B12 deficiency such as anemia or neuropathy, vitamin B12 serum levels should be monitored.** [2] […]	4.4 Special warnings and precautions for use Other precautions […] ~~It is recommended that vitamin B12 serum levels are monitored annually, especially in patients presenting with anemia or neuropathy.~~ **Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. ~~(see section 4.8).~~ It is recommended that vitamin B12 serum levels are monitored annually, especially in patients presenting with anaemia or neuropathy. (see section 4.8).** […]

[1] Comment from [redacted]: Annual monitoring of Vitamin B12 serum levels should be kept
[2] Comment from [redacted]: Proposal to replace sentence by 'In case of anemia or neuropathy, vitamin B12 deficiency should be ruled out'

Assessor's comments

Regarding Section 4.4, [redacted] considered that the vitamin B12 annual monitoring should be listed in this Section, as the applicant's proposal.
We are of opinion that data provided are not enough to add this strong recommendation. The literature reported by the MAH did not provide any new information on this side effect. Moreover, vitamin B12 monitoring is already listed in the metformin containing products. No other active substance with vitaminB12 deficiency known specifies such a strong recommendation in the Product Information. [redacted] agrees with the RMS on this point. Moreover, they precise that neuropathy caused by vitamin B12 deficiency and diabetic neuropathy could not be distinguished. Furthermore, metformin is known to possibly decrease plasmatic vitamin B12 level, but the link between the deficiency of vitamin B12 and neuropathy (regarding time to onset after the deficiency, risk factors of the patients...) is not clearly established in literature. It is complicated to distinguish risk factors of the diabetic patients, and causality of the vitamin B12 deficiency.

The RMS proposed a new wording highlighted in **bold**:

Section 4.4 Special warnings and precautions for use
Other precautions

[…] ~~*It is recommended that vitamin B12 serum levels are monitored annually*~~. ***Metformin may reduce vitamin B12 serum levels.*** *The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency* ~~*(see section 4.8)*~~. ***Vitamin B12 monitoring should be realised in case of suspicion of vitamin B12 (such as anaemia, neuropathy…). Vitamin B12 monitoring could be necessary in patients with risk factors of vitamin B12 deficiency.***

Moreover, the MAH is requested to provide the response to [redacted] inquiry.

Issue not solved

The Company accepts proposed changes by the RMS to the Summary of Product Characteristics (SmPC) section 4.8 and package leaflet section 4 by adding 'Vitamin B12 decrease/deficiency'. The information on patients presenting with megaloblastic anaemia is considered covered by the addition of the consequence "anaemia" to section 4.4, and additional consequence is presented there. Therefore, the company proposes to simplify section 4.8 for Vitamin B12 decrease/deficiency by referring from 4.8 to 4.4, and to delete the consequence "megaloblastic anaemia".

Present SmPC	Proposed text by the company	RMS Response in the uPVAR	New proposal by the company
4.8 Undesirable effects Metabolism and nutrition disorders Very rare • Lactic acidosis (see section 4.4). • Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.	4.8 Undesirable effects Metabolism and nutrition disorders Common: • **Vitamin B12 deficiency** *Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia (see section 4.4).* Very rare • Lactic acidosis (see section 4.4). • ~~Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.~~	4.8 Undesirable effects Metabolism and nutrition disorders Common: • **Vitamin B12 decrease/deficiency** *Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia (see section 4.4).* Very rare • Lactic acidosis (see section 4.4). • ~~Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.~~	4.8 Undesirable effects Metabolism and nutrition disorders Common: • **Vitamin B12 decrease/deficiency** ~~*Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia (see section 4.4).*~~ Very rare • Lactic acidosis (see section 4.4). • ~~Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.~~

Present package leaflet	Proposed text by the company	RMS Response in the uPVAR	New proposal by the company
4. Possible side effects […] Common side effects (in less than 1 in 10 people) • changes in taste. • - Very rare side effects (in less than 1 in 10.000 people) • […] • ~~low vitamin B12 levels in the blood.~~	4. Possible side effects […] Common side effects (in less than 1 in 10 people) • changes in taste. • *low vitamin B12 levels in the blood* Very rare side effects (in less than 1 in 10.000 people) • […] • ~~low vitamin B12 levels in the blood.~~	4. Possible side effects […] Common side effects (in less than 1 in 10 people) • changes in taste. • **decrease or** *low vitamin B12 levels in the blood* Very rare side effects (in less than 1 in 10.000 people) • […] • ~~low vitamin B12 levels in the blood.~~	4. Possible side effects […] Common side effects (in less than 1 in 10 people) • changes in taste. • **decrease or** *low vitamin B12 levels in the blood* Very rare side effects (in less than 1 in 10.000 people) • […] • ~~low vitamin B12 levels in the blood.~~

Assessor's comments

Regarding Section 4.8, the RMS agrees the changes proposed by the MAH regarding the simplification of the wording of "vitamin B12 decrease/deficiency". However, anaemia is considered covered by this term. Moreover, the cross reference is sufficient to explain the adverse event. Patient Leaflet could be updated as proposed by the MAH.

Issue solved

VIII. 2ND OVERALL CONCLUSION

Regarding Section 4.8, the RMS agrees with the applicant regarding the proposed wording.

Regarding Section 4.4, the wording proposed is not agreed. Data reported is not sufficient to support an annual monitoring of vitamin B12. A new wording is proposed by the RMS taking into account risk factors of patients with diabetes.

IX. 2ND REQUEST FOR SUPPLEMENTARY INFORMATION AS PROPOSED BY THE RMS

IX.1 Major objections

Product information

Data provided by the applicant is not sufficient to add a wording regarding annual monitoring of the vitamin B12. The RMS considers that a monitoring should be done in case of risk factors or deficiency of vitamin B12.

The RMS proposed a new wording highlighted in bold:

Section 4.4 Special warnings and precautions for use
Other precautions

[…] ~~*It is recommended that vitamin B12 serum levels are monitored annually*~~*.* ***Metformin may reduce vitamin B12 serum levels.*** *The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency* ~~*(see section 4.8)*~~*.* ***Vitamin B12 monitoring should be realised in case of suspicion of vitamin B12 (such as anaemia, neuropathy…). Vitamin B12 monitoring could be necessary in patients with risk factors of vitamin B12 deficiency.***

Moreover, the MAH is requested to provide the response to [redacted] inquiry.

X. CONCERNED MEMBER STATES COMMENTS

[redacted]
We generally agree with the RMS assessment, however we are of the opinion that the proposal regarding monitoring vitamin B12 should be amended.

RMS current proposal:
Section 4.4 Special warnings and precautions for use
Other precautions
[.] ~~*It is recommended that vitamin B12 serum levels are monitored annually*~~*.* ***Metformin may reduce vitamin B12 serum levels.*** *The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency* ~~*(see section 4.8)*~~*.* ***Vitamin B12 monitoring should be realised in case of suspicion of vitamin B12 (such as anaemia, neuropathy.). Vitamin B12 monitoring could be necessary in patients with risk factors of vitamin B12 deficiency.***

As we already pointed out in the previous round of this procedure: according to the scientific literature vitamin B 12 deficiency **should be established based on a wider scale of laboratory parameters** such us haematological abnormalities, folate levels, elevated serum total homocysteine and methylmalonic acid levels. As has been reported, vitamin B12 deficiency due to metformin use maybe not be related to neuropathy if it is a simple plasma deficiency. Therefore, we do not consider the recommendation to monitor only vitamin B 12 level sufficient and propose slightly amend the wording as follows:

Section 4.4 Special warnings and precautions for use
Other precautions
[.] ~~*It is recommended that vitamin B12 serum levels are monitored annually*~~. ***Metformin may reduce vitamin B12 serum levels.*** *The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency* ~~*(see section 4.8)*~~. ***Vitamin B12 deficiency*** ~~***monitoring***~~ ***should be*** ~~***realized***~~ ***ruled out in case of suspicion*** ~~***of vitamin B12***~~ ***(such as anaemia, neuropathy.). Vitamin B12 monitoring could be necessary in patients with risk factors of vitamin B12 deficiency.***

[redacted] does not agree with the overall conclusions of the RMS for the following reasons:

[redacted] does not support the proposed MO on the re-wording of SmPC section 4.4 as suggested by the RMS. In view of the data submitted, monitoring of vitamin B12 levels should be done regularly, as the risk of developing vitamin B12 deficiency increases along treatment time, especially at higher doses.

As most patients with type2 diabetes and metformin-induced vitamin B12 deficiency are asymptomatic or have vague symptoms, [redacted] is of the opinion that all patients taking metformin should be tested for vitamin B12 levels at least once a year. Limiting the recommendation of vitamin B12 monitoring only to patients with anaemia and/or neuropathy may diminish the efficacy of vitamin B12 screening, as only patients who already developed symptoms would be tested.

Thus, update of the wording in section 4.4 as suggested by the MAH is preferred.
SmPC section 4.4
Please see discussion above. The update of the wording in section 4.4, as suggested by the MAH, is preferred:
Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. It is recommended that vitamin B12 serum levels are monitored annually, especially in patients presenting with anaemia or neuropathy (see section 4.8).

[redacted]
According to the national treatment guideline on Type 2 diabetes in [redacted], B12 should be checked every 3 to 5 years during metformin treatment, and whenever B12 deficiency is suspected. We propose that the recommendation in the Product Information should be updated according to this recommendation.

[redacted]
The wording in section 4.4 of proposed SmPC as suggested by the MAH is preferred.

[redacted] agrees to the conclusions of the RMS and consents to the implementation of the wording as proposed by the RMS in section 4.4. It is agreed that Vit B12 levels do not have to be determined on a regular annual basis and that a risk based approach can be followed. The risk of vitamin B12 deficiency is considered sufficiently addressed. Changes to 4.8 are likewise agreed.

[redacted]
SmPC:
Section 4.4:
[redacted] notes the RMS's conclusions in the FVAR and the section 4.4 SmPC updates proposed, however, we would like to propose additional updates for the following reasons:

- In order to help further clarify the proposed warning(s) and to expand the list of relevant symptoms of vitamin B12 deficiency

- With regards to the recommendation to monitor vitamin B12 levels in patients, "regular" monitoring of vitamin B12 levels in patients with risk factors for vitamin B12 deficiency is proposed. [redacted] considers that recommending "regular" monitoring for vitamin B12 deficiency allows the treating HCP to use their discretion based on the individual health status of their patient, in the context of the patient's associated exposure to metformin.

- It is also noted that while the proposed section 4.4 of the SmPC includes reference to "*patients with risk factors known to cause vitamin B12 deficiency*", these risk factors have not been stated, the [redacted] therefore proposes revising this section in order to include examples of some potential risk factors that are may contribute to the development of vitamin B12 deficiency.

- To include an additional statement to highlight that monitoring of vitamin B12 levels should take into consideration whether the patient has developed any relevant symptoms as well as the results of other relevant investigations when suspecting vitamin B12 deficiency.

- To provide guidance for prescribers on whether metformin should be discontinued if a patient develops vitamin B12 deficiency during therapy.

[redacted] proposes the following additional updates to the RMS proposal in section 4.4 of the SmPC - ([redacted] = **green** text):

SmPC

Section 4.4: Special warnings and precautions for use

[…]

~~It is recommended that vitamin B12 serum levels are monitored annually.~~ **Metformin may reduce vitamin B12 serum levels.** The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency ~~(see section 4.8)~~. **Vitamin B12 monitoring should be ~~realised~~ considered in patients in whom ~~case of suspicion of~~ vitamin B12 decrease/deficiency is suspected (such as those with anaemia, ~~or~~ neuropathy, visual disturbance, memory loss or psychiatric abnormalities). Regular vitamin B12 monitoring is recommended ~~could be necessary~~ in patients with risk factors ~~of~~ for vitamin B12 deficiency, including those receiving metformin over a prolonged period of time or at higher doses, with baseline vitamin B12 levels at the lower end of the normal range, who are taking concomitant medication known to impair vitamin B12 absorption (e.g. proton pump inhibitors, nitrous oxide, colchicine or H2-receptor antagonists), and individuals with other risk factors for reduced vitamin B12 absorption (such as the elderly). A diagnosis of vitamin B12 deficiency should take into consideration whether the patient has developed any relevant symptoms as well as the results of other investigations. Metformin therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.**

Package Leaflet (PL):

(i) **Section 2 - Warnings and precautions**:

[redacted] proposes that the MAH should also consider updating section 2 of the PL '**Warnings and precautions'** to include related patient-friendly information, to align the PL with the SmPC changes proposed in section 4.4.

(ii) **Section 4 - Possible side effects:**

[redacted] also proposes the addition of examples of possible symptoms that may occur in association with low levels of vitamin B12/vitamin B12 deficiency – this is in order for patients to be made aware of these. It is considered that the inclusion of the list of some of the key possible symptoms will provide useful information for patients to help them identify the potential signs of low

vitamin B12 levels/deficiency they need to look out for (see text proposed in **green)**:

4. Possible side effects
[…]
Common side effects (may affect up to 1 in 10 people)
- changes in taste.

decreased or low vitamin B12 levels in the blood **(symptoms may include extreme tiredness (fatigue), lack of energy (lethargy), breathlessness, numbness or pins and needles in hands or feet (paraesthesia), a sore and red tongue (glossitis), mouth ulcers, pale or yellow skin, muscle weakness, loss of balance or co-ordination, sensitivity to pain/impaired sensation, palpitations, disturbances in vision and/or changes in mood, memory loss and thinking/reasoning problems).**
Your doctor may arrange some tests to find out the cause of your symptoms because some of these may also be caused by diabetes or due to other unrelated health problems.

XI. ASSESSMENT OF THE RESPONSES TO THE 2ND REQUEST FOR SUPPLEMENTARY INFORMATION

Question 1:

Data provided by the applicant is not sufficient to add a wording regarding annual monitoring of the vitamin B12. The RMS considers that a monitoring should be done in case of risk factors or deficiency of vitamin B12.

The RMS proposed a new wording highlighted in bold:

Section 4.4 Special warnings and precautions for use
Other precautions

[…] ~~*It is recommended that vitamin B12 serum levels are monitored annually*~~. ***Metformin may reduce vitamin B12 serum levels.*** *The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency* ~~*(see section 4.8)*~~. ***Vitamin B12 monitoring should be realised in case of suspicion of vitamin B12 (such as anaemia, neuropathy…). Vitamin B12 monitoring could be necessary in patients with risk factors of vitamin B12 deficiency.***

Response MAH:

The company has received diverse and contrasting comments regarding the frequency of monitoring of vitamin B12. EASD 2018 and ADA 2022 use the term "periodic monitoring", which we consider appropriate, and we propose to not further specify the frequency of vitamin B12 monitoring.

Furthermore, editorial changes are proposed for clarification and simplification in the case of suspicion of vitamin B12 deficiency.

Company's proposal to accommodate the RMS and CMSs' comments, therefore is:

Section 4.4 Special warnings and precautions for use
Other precautions
[…] Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. Vitamin B12 monitoring should be realised in case of suspicion of vitamin B12 (such as anaemia, neuropathy …). **In case of suspicion of vitamin B12 deficiency (such as anemia or neuropathy), vitamin B12 serum levels should be monitored**. **Periodic**

vitamin B12 monitoring could be necessary in patients with risk factors of vitamin B12 deficiency. ~~It is recommended that vitamin B12 serum levels are monitored annually, especially in patients presenting with anaemia or neuropathy~~ (see section 4.8). […]

Question #2:
Moreover, the MAH is requested to provide the response to [redacted] inquiry.

Response MAH:
Labelling approved in [redacted] in metformin containing products is

SmPC 4.4: Addition of new entry
"Daily treatment with metformin over a prolonged period of time (several years) can impair absorption of vitamin B12 (cobalamin) leading to vitamin B12 deficiency. Patients at higher risk of experiencing vitamin B12 deficiency include those receiving higher doses of metformin, with baseline vitamin B12 levels at the lower end of the normal range, and patients on concomitant medication known to impair vitamin B12 absorption i.e. proton pump inhibitors and colchicine. Vitamin B12 deficiency should be considered in patients requiring long-term treatment with metformin, individuals with reduced body stores or risk factors for reduced vitamin B12 absorption (such as the elderly), or if relevant clinical symptoms are observed. Consideration of vitamin B12 deficiency is recommended if a patient taking metformin presents with megaloblastic anaemia."

SmPC section 4.8: Amend existing entry Replace current entry with the following ADR entry "*Vitamin B12 deficiency*" The current entry can be retained as a footnote = *"Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia."*

Response to [redacted] comments
In our opinion, we as the company have added the most important symptoms of symptomatic vitamin B12 deficiency (anemia and neuropathy) to the proposed wording in section 4.4. of the SmPC, and we therefore propose to not further expand this list to potential signs and symptoms that are less clearly attributable to vitamin B12 use, but often occur in underlying diabetes and the metabolic syndrome, specifically visual disturbances (e.g. diabetic retinopathy, Kovacova, 2022) and psychiatric abnormalities (Kalra, 2018, Khassawneh 2020). Regarding memory loss, the company would like to highlight that we are following up the close monitoring event of 'cognitive impairment due to vitamin B12 deficiency', and as informed in the last Periodic Benefit-Risk Evaluation Report (PBRER) (PBRER, 2021) no relevant safety information with impact on the overall benefit-risk profile of metformin has been identified from the review of the ICSRs received in the review period. This event will again be analyzed and presented with the next PBRER with data lock point 01 Apr 2024, covering period of 3 years. Furthermore, there is evidence that metformin may even counter memory loss (Tseng, 2019, Markovicz, 2017).
In general, the company agrees that a reminder to the physician to consider unrelated risk factors for vitamin B12 deficiency should be made and this is part of the latest proposed wording submitted in the response to the comments from RMS and CMS on 03 Mar 2022. However, as presented to [redacted] on 31 Mar 2021, a cumulative review of the cases in the safety database did not conclude that a combination of metformin with either PPI, H2-receptor antagonists or colchicine was associated with a significant increase in vitamin B12 deficiency / decrease. Review of the literature also did not support an additive risk in concomitant use of PPIs and metformin: Long et al. (2012) presented a patient retrospective chart review (individual patient case details were not available), and Hansen (2016) indicated that vitamin B12 level was actually less in patients treated with PPI's only (235.5 pmol/l) compared to patients treated with both metformin and PPI's (262.0 pmol/l). Therefore, the company conclusion remains to not specifically list specific drugs as risk factors for vitamin B12 deficiency in the SmPC.
Age is also a known risk factor for vitamin B12 deficiency. Again, the company proposes to not complicate the warning with some risk factors for vitamin B12 deficiency whilst omitting others, e.g. vegetarian/vegan diet or genetic predisposition.

The same applies to the emphasize on "those receiving metformin over a prolonged period of time or at higher doses, with baseline vitamin B12 levels at the lower end of the normal range." The exposure dose- and time-dependent effect of metformin has already been covered in a preceding sentence of the warning ("The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency"), and duplication should be avoided.
Furthermore, the company does not consider the basic medical guidance in "A diagnosis of vitamin B12 deficiency should take into consideration whether the patient has developed any relevant symptoms as well as the results of other investigations." as needed in warnings and precaution, and therefore proposes to omit this part.

Last but not least, highlighting that vitamin B12 deficiency does not prompt the treating physician to discontinue metformin, but that treatment should generally include metformin if not contraindicated (ADA, 2022; NICE, 2022), is considered beneficial. The company is therefore proposing to include the wording by CMS [redacted] that once metformin therapy is initiated it should be continued for as long as it is tolerated and not contraindicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines. The benefit-risk decision regarding metformin use in (symptomatic) vitamin B12 deficiency should then be carried by the treating HCP accordingly.
The company would therefore like to propose the following amendment to the SmPC section 4.4 compared to the CMS [redacted] proposal (see also revised EU product information for Glucophage® and Glucovance® film-coated tablets in Module 1.3.1); new text: underlined and bold, text to be removed crossed out, text to be shifted italic:

Latest proposed by the company text (03Mar2022)	**RMS and CMS [redacted] proposal**	**New company proposal**
Metformin may reduce vitamin B12 serum levels.	~~It is recommended that vitamin B12 serum levels are monitored annually.~~ **Metformin may reduce vitamin B12 serum levels.**	Metformin may reduce vitamin B12 serum levels.
The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency.	The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency ~~(see section 4.8)~~.	The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency.

In case of suspicion of vitamin B12 deficiency (such as anemia or neuropathy), vitamin B12 serum levels should be monitored.	**Vitamin B12 monitoring should be ~~realised~~ considered in patients in whom ~~case of suspicion of~~ vitamin B12 decrease/deficiency is suspected (such as those with anaemia, ~~or~~ neuropathy, visual disturbance, memory loss or psychiatric abnormalities).**	In case of suspicion of vitamin B12 deficiency (such as anemia or neuropathy), vitamin B12 serum levels should be monitored.
Periodic vitamin B12 monitoring could be necessary in patients with risk factors of vitamin B12 deficiency.	**Regular vitamin B12 monitoring is recommended ~~could be necessary~~ in patients with risk factors ~~of~~ for vitamin B12 deficiency, including those receiving metformin over a prolonged period of time or at higher doses, with baseline vitamin B12 levels at the lower end of the normal range, who are taking concomitant medication known to impair vitamin B12 absorption (e.g. proton pump inhibitors, nitrous oxide, colchicine or H2-receptor antagonists), and individuals with other risk factors for reduced vitamin B12 absorption (such as the elderly).**	**Periodic** vitamin B12 monitoring could be necessary in patients with risk factors **for** vitamin B12 deficiency.
	A diagnosis of vitamin B12 deficiency should take into consideration whether the patient has developed any relevant symptoms as well as the results of other investigations.	
	Metformin therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.	**Metformin therapy should be continued for as long as it is tolerated and not contraindicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.**

With regard to the proposed amendments by [redacted] to the package leaflet, the company is of the opinion to not include an exhaustive description of the potential symptoms of a vitamin B12 deficiency, as it is asymptomatic in the majority of cases (Wakeman, 2020). Moreover, as already stated by CMS [redacted] these symptoms can be caused by diabetes or due to other unrelated health problems.

We appreciate the correction of the typing error.

RMS Comments:

Regarding Section 4.4, the CMS, the RMS and the MAH agree on the addition of a warning regarding monitoring of vitamin B12 in patients with vitamin B12 deficiency. However, we noticed a discrepancy between all the CMS opinions regarding the possible addition of a frequency (annual frequency has been first suggest by the MAH), and on the monitoring in all patients taking metformin containing products.

No sufficient scientific data has been reported on the benefit of an annual monitoring. Moreover, the MAH proposes to not further specify the frequency of vitamin B12 monitoring. This variation was started following a request form [redacted] on this point. But no frequency has been added in [redacted] Product Information. Regarding the frequency of the monitoring, a CMS noticed that its

national treatment guideline on Type 2 diabetes recommends a 3 to 5 year checking of vitamin B12 deficiency.

Regarding comments from [redacted] we endorse the comment: vitamin B12 deficiency could be caused by many risks factors, and have many symptoms. However we agree with the MAH. We consider that the description of all risk factors should be included in national guideline, and not in Product Information. First of all, these data are unclear in the SmPC. Some of the deficiency in vitamin B12 symptoms could also be attributable to underlying diabetes, and vitamin B12 deficiency could also be asymptomatic. Then, some symptoms or risks could be missing and be misleading to health care professionals. Only the most important symptoms and risk factors should be included in the Product Information.

Moreover, the labelling regarding the continuation of metformin treatment seems to be informative according to us. We propose to keep this labelling at the end of the paragraph, as agreed also by the MAH. Practitioners could be helped by this recommendation not to stop treatment in case of vitamin B12 deficiency.

We are of the opinion that frequency of the vitamin B12 monitoring, symptoms and risks associated to vitamin B12 deficiency should be recommended in each member state in its own guideline of type 2 diabetes treatment according to each point of view. Moreover, the warning of the risk of deficiency should be clearly noticed in metformin containing products, in Section 4.4.

The RMS agree with the new wording proposed by the MAH (highlighted in **bold)**:
- Section 4.4 Special warnings and precautions for use
Other precautions

[…] Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anemia or neuropathy), vitamin B12 serum levels should be monitored.~~Vitamin B12 monitoring should be realised in case of suspicion of vitamin B12 deficiency (such as anaemia, neuropathy…).~~ **Periodic** vitamin B12 monitoring could be necessary in patients with risk factors for ~~of~~ vitamin B12 deficiency ~~(See Section 4.8)~~. **Metformin therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.**

No update of the PL is necessary.

Issue solved

XII. 3RD OVERALL CONCLUSION

Regarding Section 4.4, we agree with the MAH not to specify the frequency of vitamin B12 monitoring. A new wording has been proposed with no mention of the frequency, but the necessity of a periodic monitoring in patients with risk factors. Moreover, labelling regarding the continuation of treatment in case of vitamin B12 deficiency is added.

XIII. CONCERNED MEMBER STATES COMMENTS

[redacted]
Regarding the above-mentioned procedure, we endorse the RMS assessment and have no further comments.

[redacted]

Please be informed that [redacted] finds the product information, as now proposed by the applicant, acceptable. We therefore support the conclusion of the RMS and have no further comments.

[redacted] Comments

Following the MA holder's responses and the RMS's Updated FVAR, the [redacted] accepts the updated changes to section 4.4 of the SmPC. However, the [redacted] would like to make additional comments regarding the package leaflet as follows:

Package Leaflet (PL):

4. Possible side effects:

[redacted] notes the MAH's response and RMS's conclusions. We do not accept the rationale provided by the MAH to not include the expanded wording describing relevant symptoms of Vitamin B12 deficiency after the listed ADR ***'decreased or low vitamin B12 levels in the*** blood' as Wakeman et al (2020) also recognises that while early vitamin B12 deficiency is asymptomatic, when it does become manifest, it presents as a peripheral neuropathy (and neurological effects of this deficiency are permanent). Ankar and Kumar (2021)[1] also suggest that "*B12 deficiency manifests as macrocytic anemia, and thus, the presenting symptoms often include signs of anemia, such as fatigue and pallor. Due to the increased hemolysis caused by impaired red blood cell formation, jaundice may also be a presenting symptom."*.

It is therefore proposed that in line with the QRD template guidance (which suggests inclusion of overt clinical signs and symptoms to enable the patient to recognise all side effects), the information in section 4 of the leaflet should be expanded to include patient-friendly descriptions of the relevant '*overt clinical signs and symptoms'* that may be associated with vitamin B12 deficiency, with a focus on key symptoms of peripheral neuropathy and anaemia as agreed in the SmPC section 4.4 wording, and the following is suggested:

"decreased or low vitamin B12 levels in the blood **(symptoms may include extreme tiredness (fatigue), breathlessness, a sore and red tongue (glossitis), numbness or pins and needles in hands or feet (paraesthesia), loss of balance/co-ordination or pale or yellow skin).**"

XIV. ASSESSMENT OF THE RESPONSES TO THE MS REQUEST FOR SUPPLEMENTARY INFORMATION

Response:

The company is of the opinion that the inclusion of the overt clinical signs and symptoms as suggested by [redacted] in the Package Leaflet is still too broad and may prevent the patients from taking this medicine, because it may be perceived by the patient of having a negative impact on the benefit-risk balance of metformin.

Therefore, the company proposes to align the presented signs and symptoms to those presented by NHS*, namely extreme tiredness (fatigue), pins and needles (paraesthesia), a sore and red tongue (glossitis), pale or yellow skin and add the sentence (previously proposed by [redacted] with the day-80 comments) "*Your doctor may arrange some tests to find out the cause of your symptoms because some of these may also be caused by diabetes or due to other unrelated health problems",* to balance the unspecific nature of symptoms and encourage vitamin B12 testing for a root cause analysis and diagnosis verification.

Proposed text by the company for the Package Leaflet (~~strikethrough~~ text to be deleted; **bold** new text):

[1] Ankar A, Kumar A. Vitamin B12 Deficiency. [Updated 2021 Jun 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441923/

Package Leaflet (PL):
4. Possible side effects:

"decreased or low vitamin B12 levels in the blood (symptoms may include **extreme tiredness (fatigue)** ~~breathlessness~~**, a sore and red tongue (glossitis),** ~~numbness or~~ **pins and needles** ~~in hands or feet~~ **(paraesthesia),** ~~loss of balance/co-ordination~~ **or pale or yellow skin).**" **Your doctor may arrange some tests to find out the cause of your symptoms because some of these may also be caused by diabetes or due to other unrelated health problems.**

*NHS: https://www.nhs.uk/conditions/vitamin-b12-or-folate-deficiency-anaemia/

RMS Comments:

The [redacted] suggests to add a labelling in the PL to describe symptoms of vitamin B12 deficiency.
We agree with the MAH, labelling should be updated but according the NHS wording and not too brad as initially proposed by [redacted] Moreover, wording regarding the line to take for patients is also approved

XV. 4TH OVERALL CONCLUSION

Regarding Section 4.4, we agree with the MAH on the wording of PIL. Addition of symptoms of vitamin B12 deficiency is in line with the ones presented by NHS recommendation. Moreover, a wording on the line to take for the patients is approved.