26 January 2022
EMA/HMPC/489006/2020
Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Urtica dioica* L., *Urtica urens* L., folium

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HMPC decision on review of monograph *Urtica dioica* L., *Urtica urens* L., folium adopted on 14 January 2010	15 January 2020
Call for scientific data (start and end date)	From 01 April 2020 to 30 June 2020
Adoption by Committee on Herbal Medicinal Products (HMPC)	26 January 2022

Review of new data on *Urtica dioica* L., *Urtica urens* L., folium

Periodic review (from 2010 to 2020)

Scientific data (e.g. non-clinical and clinical safety data, clinical efficacy data)

☒ Pharmacovigilance data (e.g. data from EudraVigilance, VigiBase, national databases)

EudraVigilance was searched by the Pharmacovigilance Department of OGYÉI for adverse reactions on 11 September 2020, but no new safety information was found for the reference period.

☒ Scientific/Medical/Toxicological databases

PubMed (using the search terms: "nettle OR *urtica* OR *urtica dioica* OR *urtica urens* OR urticae folium" from 2008 to present, search date: 17 August 2020, 1102 results), Embase (using the search terms "nettle OR *urtica* OR *urtica dioica* OR *urtica urens* OR urticae folium" from 2008 to present, search date: 18 August 2020, 1691 results), Cochrane Database of Systematic

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Reviews (using the search terms "nettle OR *urtica* OR *urtica dioica* OR *urtica urens* OR urticae folium" from 2008 to present, search date: 17 August 2020, 86 results)

☐ Other

Regulatory practice

☒ Old market overview in AR (i.e. products fulfilling 30/15 years on the market)

☒ New market overview (including pharmacovigilance actions taken in member states)

☐ Referral

☒ Ph. Eur. monograph

☐ Other

Consistency (e.g. scientific decisions taken by HMPC)

☒ Public statements or other decisions taken by HMPC

☒ Consistency with other monographs within the therapeutic area

☒ Other

Availability of new information (i.e. likely to lead to a relevant change of the monograph)

Scientific data	Yes	No
New non-clinical safety data likely to lead to a relevant change of the monograph	☐	☒
New clinical safety data likely to lead to a relevant change of the monograph	☐	☒
New data introducing a possibility of a new list entry	☐	☒
New clinical data regarding the paediatric population or the use during pregnancy and lactation likely to lead to a relevant change of the monograph	☐	☒
New clinical studies introducing a possibility for new WEU indication/preparation	☐	☒
Other scientific data likely to lead to a relevant change of the monograph	☐	☒
Regulatory practice	Yes	No
New herbal substances/preparations with 30/15 years of TU	☐	☒
New herbal substances/preparations with 10 years of WEU	☐	☒
Other regulatory practices likely to lead to a relevant change of the monograph	☐	☒
Referrals likely to lead to a relevant change of the monograph	☐	☒
New / Updated Ph. Eur. monograph likely to lead to a relevant change of the monograph	☐	☒
Consistency	Yes	No
New or revised public statements or other HMPC decisions likely to lead to a relevant change of the monograph	☐	☒
Relevant inconsistencies with other monographs within the therapeutic area that require a change of the monograph	☐	☒
Other relevant inconsistencies that require a change of the monograph	☐	☒

Summary and conclusions on the review

During the review, 2018 new references not yet available during the first/previous assessment were identified.

No references were provided by Interested Parties during the Call for data.

Four references were considered relevant for the assessment. Publications where only the abstract was available and thus important information was missing were not taken into account.

No references justify a revision of the monograph.

There is no new product on the market that would indicate a revision. The cited clinical trials are not suitable to support a possible well-established use (WEU) monograph and due to several limitations, they are not adequate to draw conclusion on the safety of Nettle leaves. See the details bellow.

New clinical safety data:

A study conducted by Dabagh & Nikbakht aimed to compare the effects of 8 weeks of aerobic training and *Urtica dioica* (UD) supplementation alone, and in combination, on glycaemic control in men with type 2 diabetes mellitus (T2DM). A total of 40 males with T2DM were selected and randomly divided into four groups: 1) aerobic training (Ae), 2) UD supplements (UD), 3) combination of aerobic training and UD supplements (Ae + UD), and 4) control group. In the experimental groups, 10 grams of dried Urticae folium was dissolved in yogurt 15 minutes before breakfast over a period of 8 weeks. In order to avoid a possible effect of using yogurt, allotment of yogurt was considered for every group were added. Blood samples were taken 24 hours before and 48 hours after the intervention period, following 10–12 hours of fasting. A significant decrease in fasting blood sugar (FBS) was observed in the Ae group, the UD group, and the Ae + UD group after 8 weeks. There was a significant difference in FBS between the three intervention groups and the control group. In addition, a significant difference in FBS was shown between the UD and Ae + UD groups (Dabagh & Nikbakht, 2016).

In a randomised, double-blind, placebo-controlled clinical trial performed in the Kamkar hospital (Qom, Iran) in patients suffering in type 2 diabetes mellitus (T2DM) the effects of nettle leaf extract [extraction solvent ethanol 70% (V/V), DER 5:1] combined with conventional oral anti-hyperglycaemic drugs was investigated on the blood levels of fasting glucose, postprandial glucose, glycosylated haemoglobin (HbA1c), creatinine and liver enzymes SGOT and SGPT, and systolic and diastolic blood pressures in 46 patients and compared with the placebo group (n=46). Patients received one capsule containing 500 mg extract every 8 hours for 3 months. At the end of the study, the extract lowered the blood levels of fasting glucose, 2 hours postprandial glucose, and HbA1c significantly without any significant effects on the other parameters ($p>0.05$) compared to placebo (Kianbakht *et al.,* 2013).

The study reported by Ghalavand *et al.* aimed to evaluate the effect of interval exercise and nettle supplements on blood glucose, and its role on blood pressure control in men with type 2 diabetes. 40 men with type 2 diabetes were randomly divided into 4 groups (interval training [IT], nettle supplement [NS], nettle supplement combined with interval training [IT+NS], and control). In the experimental groups (NS and NS + IT), nettle supplements were consumed 15 minutes before breakfast, lunch and dinner for 8 weeks. The applied daily dose was (10 g/d) divided into three parts. Blood pressure (BP) and fasting blood glucose (FBS) were measured at pre-test and post-test conditions. Significant differences were detected regarding FBS levels in the three experimental groups in comparison with the control group. Diastolic BP of both IT and IT+NS groups was significantly different from the control group. A significant difference in the diastolic BP between the IT+NS and the control group was found as well (Ghalavand *et al.,* 2017).

A randomised single-blind clinical trial performed in the endocrinology clinic of Rohani hospital (Babol, Iran), sixty diabetic patients were randomly divided into *verum* and control groups. The *verum* group received 20 mg/kg/d of hydro-alcoholic extract of *Urtica dioica* (UD) three times for 8 weeks and control group received placebo. Fasting blood glucose (FBG), HbA1c, insulin and AMP-activated protein kinase (AMPK) were measured and compared at the beginning and end of the study. FBG levels of the drug group were significantly decreased compared with the placebo group. Quantitative insulin

sensitivity check index increased significantly in drug group compared with the placebo group. Insulin and AMPK levels increased after taking UD; however, these changes were not significant when compared with the placebo. In this study, only one patient (n=1) suffered from itching in the end of study in the drug group. The difference between the drug and placebo groups regarding the side effects was not significant (p=0.323) (Korani *et al.,* 2017).

Assessor's comment:

The above-mentioned studies investigate Nettle leaves in type 2 diabetic patients.
No revision of the monograph (including assessment of the studies) is considered required because medicinal products corresponding to the indications described in the above-mentioned clinical studies are not reported from the EU market. Therefore, the well-established use criteria are not fulfilled.
The authors themselves mention that the studies have several limitations: "short duration", "low sample volume", "the diet of the participants could not be controlled", "individual differences of the participants resulting from heredity and lifestyle, and their culture of dietary habit".
In addition, in two of them, the studied extract is not characterised in terms of the plant parts used for its preparation; moreover, the applied extraction solvent and the DER are also missing (Ghalavand et al., 2017, Korani et al.). In the third study (Kianbakht et al., 2013), the applied extract does not comply with the ones in the Nettle leaf monograph, since it was prepared with extraction solvent ethanol 70% (V/V), not with water or 50% ethanol (V/V) and DER is different also. Interim analysis was not performed. Only one article (Korani et al., 2017) speaks about the safety findings of the study. In the add-on therapy study (Kianbakht et al., 2013), the conventional oral anti-hyperglycaemic drugs were not specified.

In view of the above, no conclusions can be drawn from the articles that could affect the safety profile of Nettle leaf and do not lead to a change in the monograph.

References

a) References relevant for the assessment:

Dabagh S, Nikbakht M. Glycemic control by exercise and *Urtica dioica* supplements in men with type 2 diabetes. *Jundishapur J Chronic Dis Care.* 2016, 5(1):e31745. Available at: https://doi.org/10.17795/jjcdc-31745

Ghalavand A, Motamedi P, Deleramnasab M, Khodadoust M. The effect of interval training and nettle supplement on glycemic control and blood pressure in men with type 2 diabetes. *Int J Basic Sci Med.* 2017, 1:33–40

Kianbakht S, Khalighi-Sigaroodi F, Dabaghian FH. Improved glycemic control in patients with advanced type 2 diabetes mellitus taking *Urtica dioica* leaf extract: A randomized double-blind placebo-controlled clinical trial. *Clin Lab* 2013; 59:1071–1076, in press, doi:10.7754/Clin.Lab.2012.121019

Korani B, Mirzapour A, Moghadamnia AA, Khafri S, Neamati N, Parsian H. The effect of *Urtica dioica* hydro-alcoholic extract on glycemic index and AMP-activated protein kinase levels in diabetic patients: A randomized single-blind clinical trial. *Iran Red Crescent Med J.* 2017, 19:e40572, in press, doi:10.5812/ircmj.40572

b) References that may justify the need for the revision of the monograph:

None

Rapporteur's proposal on revision

☐ Revision needed, i.e. new data/findings of relevance for the content of the monograph

☒ No revision needed, i.e. no new data/findings of relevance for the content of the monograph

HMPC decision on revision

☐ Revision needed, i.e. new data/findings of relevance for the content of the monograph

☒ No revision needed, i.e. no new data/findings of relevance for the content of the monograph

The HMPC agreed not to revise the monograph, assessment report and list of references on *Urtica dioica* L., *Urtica urens* L., folium, by consensus.