22 January 2025
EMA/HMPC/331773/2024
Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Avena sativa* L., herba and *Avena sativa* L., fructus

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HMPC decision on review of monograph *Avena sativa* L., herba and *Avena sativa* L., fructus adopted on 4 September 2008	31 January 2024
Call for scientific data (start and end date)	From 1 March 2024 to 31 May 2024
Discussion in Committee on Herbal Medicinal Products (HMPC)	September 2024 November 2024 January 2025
Adoption by HMPC	22 January 2025

Review of new data

Periodic review (from 2017 to 2024)

Sources checked for new information:

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

- ☒ Scientific/Medical/Toxicological databases
- ☒ Pharmacovigilance databases
  - ☒ data from EudraVigilance
  - ☒ from other sources (e.g. data from VigiBase, national databases)
- ☐ Other

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Regulatory practice

☒ Old market overview in AR (i.e. check products fulfilling 30/15 years of TU or 10 years of WEU on the market)

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

☒ PSUSA

☒ Feedback from experiences with the monograph during MRP/DCP procedures

☒ 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: Standard terms for pharmaceutical form

Availability of new information that could trigger a revision of the monograph

Scientific data	Yes	No
New non-clinical safety data that could trigger a revision of the monograph	☐	☒
New clinical safety data that could trigger a revision 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 that could trigger a revision of the monograph	☐	☒
New clinical studies introducing a possibility for new WEU indication/preparation	☐	☒
Other scientific data that could trigger a revision 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	☐	☒
New recommendations from a finalised PSUSA	☐	☒
Feedback from experiences with the monograph during MRP/DCP procedures that could trigger a revision of the monograph	☐	☒
New/Updated Ph. Eur. monograph that could trigger a revision of the monograph	☐	☒
Other regulatory practices that could trigger a revision of the monograph	☐	☒
Consistency	Yes	No
New or revised public statements or other HMPC decisions that could trigger a revision of the monograph	☐	☒

Relevant inconsistencies with other monographs within the therapeutic area that could trigger a revision of the monograph	☐	☒
Other relevant inconsistencies that could trigger a revision of the monograph	☒	☐

Summary of new references

PubMed search dated 2-7-2024 with search terms "avena sativa" and "green oat", filters other animals and humans resulted in 22 hits. A separate search with search terms "avena sativa" and "dermatitis" revealed 15 hits; "avena sativa" AND "cardiovascular OR hyperlipidemic OR diabetic", with filters: Other "Animals, Humans" and "from 2017 – 2024" resulted in 75 hits.

During the review 12 new references not yet available during the first/previous assessment were identified. Out of these new references 11 references were considered to be relevant for the monograph and six references about *Avena sativa* L., herba and 4 references about *Avena sativa* L., fructus. No reference triggers a revision of the monographs.

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

Assessment of new data

New scientific data that could trigger a revision of the monograph

Pathak MP, Policegoudra RS, Goyary D et al. Safety evaluation of an oat grain alkaloid gramine by genotoxicity assays. Drug and Chemical Toxicology 2017; 41(2): 147-154

Gramine is a natural indole alkaloid that is present in *Avena sativa* L.. The mutagenic and genotoxic potential of gramine was studied using Ames bacterial reverse mutation test, and the mouse bone marrow micronucleus assay as well as chromosomal aberration test. Four concentrations of gramine (1250 mcg/plate, 2500 mcg/plate, 5000 mcg/plate, and 10 000 mcg/plate) were employed in *Salmonella typhimurium* strains to study the mutagenicity in the presence and absence of standard mutagens, 2-aminofluorene (2-AF), sodium azide (SA), and 2-nitrofluorene (2-NF). Three doses, i.e. 0.1, 0.2, and 0.3 x the LD50 of gramine (i.e. 50mg/kg, 100mg/kg, and 150mg/kg) were administered orally to either sex of Swiss albino mice for 48h to study the genotoxic activity in micronucleus assay as well as chromosomal aberration. Gramine at the given dose lacks mutagenicity as well was found to possess antimutagenic activity. There was no significant increase in the frequency of micronucleated polychromatic erythrocytes (MNPCEs), as well as no significant difference in the percentage of chromosomal aberrations was observed between the gramine groups and the negative control groups but percentage of polychromatic erythrocytes (PCEs) is found to be higher in all the gramine groups. These results indicate significant non-mutagenic as well as non-genotoxic activity of gramine *in vitro* and *in vivo* in the given doses.

Assessors comment:
The Ames test of a component of oat grain (gramine) might be relevant for the EU herbal monograph on Avena sativa L., fructus, however, it is not changing the conclusion on safety, because the study is only about a single component and therefore is not a trigger for change of the monograph.

Pharmacovigilance

Eudravigilance was searched on 4 july 2024 with search term "avena sativa" over the period 2017-2024. Several side effects have been reported; however it was not clear in all cases if the report was

for the herb or the fruit. The most reported side effect was jaundice (four reports, reporting odds ratio ROR=20). All cases had a lot of co-medication or co-administered herbal products. It is not possible to make a causality assessment.

Three cases of anaphylactic reaction were reported in relation to allergic skin test which involved *Avena sativa* L., among many others (herbal) substances (ROR=6). It is not possible to conclude on the causality of individual products.

Assessors comment:
It is concluded that the side effects reported in Eurdavigilance do not give reason for change of the EU herbal monograph.

A Vigibase search between 2017 and 2024 retrieved 10 case reports with *Avena sativa* L. without co-medication.

For topical use (=*Avena sativa* L., fructus) without co-medication there were seven unique reaction reports, varying from application site reactions (blister, skin irritation, pruritus (2x), burning sensation (2x), papules (2x), irritation, urticaria (2x), rash, erythema, cellulitis, eczema, peripheral swelling (severe swelling of the hands and pain). Also, one anaphylactic reaction was reported. For oral use one report was present for diarrhoea.

For oral use (=*Avena sativa* L., herba) without co-medication there were 2 unique reports. Reported side effects were sleep disorder, sputum increased and nightmare.

Assessors comment:
In the EU herbal monograph for Avena sativa L., fructus the following side effect is reported under 4.8 : "Skin reactions may occur in atopic patients and in patients with contact dermatitis".

In section 4.3 of the monograph on Avena sativa L., herba the following general contraindication has been taken up: "Hypersensitivity to the active substance". In section 4.8 side effects it is stated "None known".

Overall, the reported side effects do not give reason for change of the monographs.

New regulatory practice that could trigger a revision of the monograph

No new herbal substances/preparations with 30/15 years of TU or 10 years of WEU have been reported.

Inconsistency that could trigger a revision of the monograph
Not applicable

Other issues that could trigger a revision of the monograph

Pharmaceutical form
In the EU herbal monograph on *Avena sativa* L., fructus the pharmaceutical form has been described as: "Dried fruits comminuted to oat flour 'Colloidal oatmeal'"

Assessors comment:
The pharmaceutical form is not in accordance with the standard terms, e.g. bath additive, cream etc.

New information not considered to trigger a revision at present but that could be relevant for the next review

***Avena sativa L.*, herba**

Kennedy DO, Bonnländer B, Lang SC et al. Acute and Chronic Effects of Green Oat (Avena sativa) Extract on Cognitive Function and Mood during a Laboratory Stressor in Healthy Adults: A Randomised, Double-Blind, Placebo-Controlled Study in Healthy Humans. Nutrients 2020; 12: 1598-1617.

A placebo-controlled parallel groups RCT has been performed in healthy adults (n=132; 35-65 y) to study the effect of green oat extract on cognitive function, mood and psychological state. The green oat extract (*Avena sativa* L., herba) had a DER of 4-6:1 and the extraction solvent was 30% m/m ethanol. The dosing regime was 1 capsule per day, containing placebo, 300, 600 and 900 mg *Avena sativa* L., herba extract, respectively n=33, n=33, n=32 and n=28.

Cognitive function, mood and changes in psychological state during a laboratory stressor (Observed Multitasking Stressor) were tested pre-dose and at 2 h and 4h post-dose on day-1 and day-29 of treatment.

The results showed that a single dose of 900 mg resulted in significantly improved performance on a computerised version of the Corsi Blocks working memory task ($p<0.05$) and a multitasking task (verbal serial subtractions and computerised tracking; $p<0.05$) in comparison to placebo. The lower doses had no significant effect.

After four weeks, 300 and 900 mg of *Avena sativa* L., herba extract resulted in significantly improved performance on a computerised version of the Corsi Blocks working memory task ($p<0.05$) and in the multitasking task 900 mg of *Avena sativa* L., herba extract showed significant improvement of accuracy ($p<0.001$) in comparison to placebo, but not for speed.

After four weeks, 900 mg of *Avena sativa* L., herba extract also decreased significantly galvanic skin response compared to placebo ($p<0.05$), which was used as a measure for physiological response to a stressor. There were no treatment-related effects on mood. The authors conclude that chronic treatment with *Avena sativa* L., herba extract can benefit cognitive function and modulate the physiological response to a stressor.

Assessors comment:
The study of Kennedy (2020), it is noted that extract has DER 4-6 : 1 whereas the extract in the EU herbal monograph has DER 1 : 4-6. Both use extraction solvent 30% m/m ethanol. The study does not a trigger for change of the monograph, but could be relevant in the future.

***Avena sativa* L., fructus**

Atopic dermatitis

Capone K, Kirchner F, Klein AL and Tierney NK Effects of Colloidal Oatmeal Topical Atopic Dermatitis Cream on Skin Microbiome and Skin Barrier Properties. J Drugs Dermatol. 2020;19(5)

Atopic dermatitis is characterized by dry, itchy, inflamed skin with a dysbiotic microbiome.

A RCT was undertaken to study the effect of 1% colloidal oat eczema cream on the skin microbiome and skin barrier function in patients with mild to moderate eczema (n=30) compared to a standard daily moisturizer (n=31). At 14 days, the 1% colloidal oat eczema cream reduced mean Eczema Area Severity Index and Atopic Dermatitis Severity Index scores by 51% and 54%, respectively. Unlike treatment with the standard moisturizer, treatment with the 1% colloidal oat eczema cream was associated with trends towards lower prevalence of Staphylococcus species and higher microbiome diversity at lesion sites. The 1% colloidal oat eczema cream significantly improved skin pH, skin

barrier function, and skin hydration from baseline to day 14, whereas the standard moisturizer improved hydration. The authors concluded that 1% colloidal oat eczema cream improves skin microbiome composition and significantly repairs skin barrier defects.

Assessors comment:
This study might be relevant for the revision of the EU herbal monograph in the future.

Wound healing

Kussie HC, Hahn W, Sivaraj D et al. Avenanthramide and β-Glucan Therapeutics Accelerate Wound Healing Via Distinct and Nonoverlapping Mechanisms. Advances in Wound Care 2024; 13(4)

Two components of *Avena sativa* L., fructus (avenanthramide (AVN) and β-glucan) have been studied in a splinted excisional wound model that mimics human-like wound healing and performed subcutaneous AVN and β-Glucan injections in 15-week-old C57BL/6 mice. Histological and immunohistochemical analyses were performed on the explanted scar tissue to assess changes in collagen architecture and cellular responses.

AVN and β-Glucan treatment provided therapeutic benefits at a 1% dose by weight in a phosphate-buffered saline vehicle, including accelerated healing time, beneficial cellular recruitment, and improved tissue architecture of healed scars. One percent AVN treatment promoted an extracellular matrix (ECM) architecture similar to unwounded skin, with shorter, more randomly aligned collagen fibers and reduced inflammatory cell presence in the healed tissue. Treatment with 1% β-Glucan promoted a tissue architecture characterized by long, thick bundles of collagen with increased blood vessel density.

AVN and β-Glucan accelerated wound closure compared to controls through distinct mechanisms. AVN-treated scars displayed a more regenerative tissue architecture with reduced inflammatory cell recruitment, while β-Glucan demonstrated increased angiogenesis with more highly aligned tissue architecture more indicative of fibrosis. A deeper understanding of the mechanisms driving healing in these two naturally derived therapeutics will be important for translation to human use.

Assessors comment:
This study might be relevant for the revision of the monograph in the future. In the addendum to the assessment report from 2018 there are also several studies about the use of Avena sativa L., herba or its constituents, m.n. β-glucans that show support in wound healing. If a revision of the EU herbal monograph is considered these studies also have to be assessed.

Several other studies were on the effect of dietary oat meals on cardiovascular health, hyperlipidemia and diabetes. These are considered linked to the use of oats as a food and are therefore not relevant for the revision of the monograph.

Dimpfel W, Storni C and Verbruggen M Ingested Oat Herb Extract (Avena sativa) Changes EEG Spectral Frequencies in Healthy Subjects. J of Alt and Compl Medicine 2011; V17, No 5

A crossover RCT was performed on healthy subjects (n=20; 30-60 year old) to study the effect of a single dose of 1250 or 2500 mg of a dried extract of *Avena sativa* L., herba (DER 3.5 : 1, extraction solvent 30% m/m ethanol) on electric brain activity (EEG) during mental work, compared to placebo.

An electroencephalogram was recorded 1,2,3 and 4 hours after ingestion, while the subject had eyes open for 6 minutes, eyes closed for 4 minutes, performance of a concentration test (d2) for 5 minutes, and performance of mental arithmetic (KLT) for 5 minutes. Data were analyzed from 1.25 to 35 Hz using the CATEEM® software (NeuroCode AG). In this software, the resulting frequency

spectra are divided into six frequency bands: δ (delta; 1.25–4.50 Hz), θ (thèta; 4.75–6.75 Hz), α1 (alfa1; 7.00–9.50 Hz), α2 (alfa2; 9.75–12.50 Hz), β1 (beta1; 12.75–18.50 Hz) and β 2 (bèta2; 18.75–35.00 Hz). This frequency analysis is based on absolute spectral power values. Changes were averaged to give one value for each frequency range. Using this approach, it is possible to visualize spectral frequency changes taking place during the performance of mental tasks in comparison to the relaxation state.

θ waves are associated with states of focused concentration and increases of θ during performance of mental tasks have been related to better mental fitness. δ waves are related to a state of relaxation, and the mind is usually not very active. Lower δ waves make it easier to focus on cognitive task or physical performance.

The ingestion of oat herb extract did not significantly change the general electric activity. With eyes open, circadian rhythm–dependent increase of θ and α1 are transiently inhibited during the 2nd hour after ingestion of the higher dose ($p=0.115$ and $p<0.05$, respectively).

With eyes closed, where the visual perception is disabled, δ and θ were clearly reduced compared to placebo ($p<0.05$ for both) in the 3rd and 4th hour after ingestion of the higher dosage.

The main effects were observed in the left frontotemporal area, known to be involved in cognitive tasks. Statistically significant differences were observed during rest (lowering of δ) and during performance of the d2-concentration test (enhancement of θ) ($p<0.01$ and $p<0.05$, respectively). Also, during performance of mental arithmetic, greater enhancement of θ was observed but the effect was not significant ($p=0.115$). No effects could be seen during presentation of a visual stimulus.

The authors state that, taking into account the limitations of a rather small study population to reach statistical significance, the results indicate that cognitive performance–related electric changes, obtained 1-4 hours after ingestion of different doses of an oat herb extract, differ from placebo and that this study can be considered first proof that oat herb extract influences human brain activity during performance tasks, supporting the obtained positive effects with regard to behavioral changes after subchronic treatment of rats with the oat herb preparation.

The authors conclude that the changes suggest that oat herb extract might have a positive impact on cognitive performance.

Assessors comment:
In the study Dimpfel et al. (2011), the extract that has been studied is more concentrated than the ones taken up in the TU monograph. Therefore, it is concluded that the study does not directly trigger a revision of the EU herbal monograph on Avena sativa L., herba, but might be relevant in the future.

Wong RHX, Howe PRC, Bryan J et al. Chronic Effects of a Wild Green Oat Extract Supplementation on Cognitive Performance in Older Adults: A Randomised, Double-Blind, Placebo-Controlled, Crossover Trial. Nutrients 2012, 4, 331-342

A cross-over placebo-controlled randomized clinical trial was performed to investigate the effect of wild green oat extract (WGOE) on cognitive function. During 12 weeks 37 healthy adults aged 67 ±0.8 years were treated with 1500 mg WGOE/day. Cognitive assessment included the Stroop colour-word test, letter cancellation, the rule-shift task, a computerised multi-tasking test battery and the trail-making task. All assessments were conducted in week 12 and repeated in week 24. The treatment had no effect on cognition.

Wong RXH, Howe PRC, Coates AM, Buckley JD, Berry NM Chronic consumption of a wild green oat extract (Neuravena) improves brachial flow-mediated dilatation and cerebrovascular responsiveness in older adults. J. of Hypertension 2013; 31(1):p192-200

In the same study the effect of WGOE on vasodilator function in systemic and cerebral arteries was studied. Flow-mediated dilatation (FMD) of the brachial artery and hypercapnia-induced increases of blood flow in the middle cerebral artery were used to measure systemic and cerebral vasodilator responsiveness (CVR), respectively. Compared with placebo, WGOE increased CVR and FMD to a similar extent (42 and 41%, respectively, $P < 0.01$ for both). The improvements in CVR and FMD were not correlated. Resting blood pressure did not change. Dose and treatment duration were well tolerated by participants. It is concluded that WGOE can improve vasodilator function in systemic and cerebral arteries, suggesting a potential role in the maintenance of cardiovascular health.

Kennedy DO, Jackson PA, Foster J et al. Acute effects of a wild green-oat (Avena sativa) extract on cognitive function in middle-aged adults: A double-blind, placebo-controlled, within-subjects trial. Nutr Neurosci 2017; 20(2):135-151

A double-blind, placebo-controlled, cross-over study has been performed in adults (40-65 y) with self-reported decline in memory. The effect of a single dose of 800 of 1600 mg green oat extract (GOE) on memory and cognition was tested pre-dose and 1, 2.5, 4 and 6 hours post-dose and compared with placebo. Cognitive function was assessed with a range of computerized tasks measuring attention, spatial/working/episodic memory. The results showed that 800 mg GOE increased the speed of performance across post-dose assessments on a global measure including data from all of the timed tasks. It also improved performance of a delayed word recall task in terms of errors and an executive function task (Peg and Ball) in terms of decreased thinking time and overall completion time. Working memory span (Corsi blocks) was also increased, but only on the second occasion that this dose was taken. The authors concluded that these results confirm the acute cognitive effects of GOE seen in previous research, and suggested that the optimal dose lies at or below 800 mg.

Martinez-Horta S, Ivanir E, Perrinjaquet-Moccetti T et al. Effects of a Green Oat Herb Extract on Cognitive Performance and Neurophysiological Activity: A Randomized Double-Blind Placebo-Controlled Study. Front. Neurosci. 2021; 15: 748188

A RCT has been performed in healthy adults (n=20; 26±4 years) to study the effect of a single dose of 800 mg dried ethanolic extract of *Avena sativa* L., herba (DER 3.5 : 1; extraction solvent 30% m/m ethanol) on neurophysiological correlates of processing speed, attention, performance-monitoring and inhibitory control and compared to placebo.

Electroencephalographic (EEG) signals were measured while participants carried out the modified Eriksen flanker and oddball tasks. Both groups were compared on measures of behavioral task performance, and a set of event-related potentials (ERPs) components related to performance monitoring (the error-related negativity; ERN and the N2), target detection, and attention (P3a/P3b).

Following active-intervention N2, ERN, and P3a/P3b were significantly reduced and performance was faster, with no loss of accuracy. Conversely, no neurophysiological differences were found in the placebo group before and after treatment and performance worsened significantly in terms of reaction time and accuracy, which is interpreted as tiredness during task performance.

It is concluded that a single dose of 800 mg of dried ethanolic extract of *Avena sativa* L., herba appears to enhance the optimization of neural resources and positively influences cognitive performance in tasks associated with executive functions, processing speed and attention.

Assessors comment:
Several clinical studies have been identified studying the effect of Avena sativa L., herba extracts on cognitive functioning. These studies are at the moment not relevant for the revision of the EU herbal monograph, because they are not related to the current accepted TU indication, nor are there products with this indication in the EU that fulfill the requirements for TU or WEU.

References

***Avena sativa* L., herba**

Dimpfel W, Storni C and Verbruggen M Ingested Oat Herb Extract (*Avena sativa*) Changes EEG Spectral Frequencies in Healthy Subjects. J of Alt and Compl Medicine 2011; V17, No 5

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Rapporteur's proposal on revision

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

☐ Revision likely to have an impact on the corresponding list entry (if applicable)

☒ 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