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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Gentiana lutea* L., radix

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HMPC decision on review of monograph *Gentiana lutea* L., radix adopted on 20 November 2018	31 January 2024
Call for scientific data (start and end date)	From 01 March 2024 to 31 May 2024
Discussion in Committee on Herbal Medicinal Products (HMPC)	January 2025 March 2025
Adoption by HMPC	19 March 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

PubMed was searched on 30-12-2024 with search terms "Gentiana lutea" and "gentian" not "gentian violet", filtered for reviews resulted in 27 hits. A separate search with search terms "Gentiana lutea" and "genotoxicity" resulted in 5 hits.

☒ Pharmacovigilance databases

☒ data from EudraVigilance

☒ from other sources (e.g. data from VigiBase, national databases)

☐ Other

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: data submitted by Interested Parties

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 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

During the review three new references not yet available during the first/previous assessment were identified dealing with safety/genotoxicity. Also a reference form 2013 is added which adresses this topic. Also a safety assessment on *Gentiana lutea* extract has been developed for its use in animal food in 2021 with an addendum in 2023 focused on genotoxicity.

During the call for data one reaction was received from an Interested Party, which pointed to a review of local and global literature for 2023, including L2A reports in Eudravigilance, stating that no adverse events or special situations were identified. Based on the information the Interested Party did not expect any impact on the safety profile.

Assessment of new data

New scientific data that could trigger a revision of the monograph

Eudravigilance was searched on 12 December 2024 with search term gentian root.

The reports were exclusively for combination products and not on individual gentian root extract.

Moreover, 36 reports of nausea were found, of which 24 were reported for one herbal combination product containing *Gentiana lutea* root extract without co-medication.

Nineteen suicide attempts were reported in relation to the use of gentian containing (combination-) products together with other medicines in concomitant use of a combination herbal product, containing gentian. The use of gentian cannot be linked to such reaction.

A Vigibase search on 12 December 2024 retrieved five case reports.

One case report of a birth defect after exposure to gentian-containing product during pregnancy without other reported co-medication. It is difficult to assess if there is a causal relationship, and it is considered not likely.

Two reports about kidney injury and another two for skin reactions reported co-medication and therefore a causal relationship cannot be established too.

Assessors comment:
It is concluded that reported side effects in Eudravigilance and Vigibase do not give reason for change of the EU herbal monograph, because the reactions were reported for combination products, or a causal relationship was unlikely or could not be established.

New regulatory practice that could trigger a revision of the monograph

There have been no new authorised/registered preparations containing gentianae radix reported since 2017.
The registration for the tincture of gentianae radix (1:5) extraction solvent: ethanol 70% (V/V) expired on 30-06-2022 because of written renouncement from the pharmaceutical company.
There are two combination products containing gentianae radix on the market, one used as a laxative in Italy, and in several EU countries a combination product containing *Gentiana lutea* extract related to rhinosinusitis.

Assessors comment:
No new herbal medicinal products with Gentiana lutea root extract as the sole active substance have been registered/authorized since the last revision in 2017. For one product, containing an extract of Gentiana lutea root (DER 1:5; 70% ethanol) that is in the monograph, the registration has been expired. However, this has no consequence for the EU herbal monograph. Combination products have been registered; however, they are out of scope and have no influence on the EU herbal monograph.

Inconsistency that could trigger a revision of the monograph

Not applicable.

Other issues that could trigger a revision of the monograph

Not applicable.

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

In the Drosophila wing spot test a water extract of *Gentiana lutea* roots (5g per 200ml) did not show genotoxic potential. However, in combination with methyl methanesulphonate (MMS) (both co- and post- treatment) the genotocicity potential of MMS was increased with 23 and 27% respectively. (Patenkovic, 2013)

Assessors comment:
Gentiana lutea root water extract did not show genotoxic potential in the drosophila wing spot test.

The genotoxic potential of *Gentiana lutea root* was tested in human peripheral blood mononuclear cells (herbal material dissolved into 50% ethanol 50 mg/ml). Chemical analysis through UPLC showed high content of gentiopicroside alongside loganic acid, swertiamarin and sweroside. The mononucleated blood cells (1x106 viable cells/ml) were incubated during 48 hours with the gentian root extract (0.5, 1 and 2 mg/ml). Both 1 and 2 mg/ml showed significant increase in fluorescence in the comet assay ($p<0.001$), indicating DNA damage. Furthermore, chromosomal breaks increased significantly in a concentration-dependent manner after 48 hours incubation with *Gentiana lutea lyophilized* root extract. After 72 hours incubation there was also a concentration dependent increase of chromosomal aberrations; however to a lesser extent than after 48 hours. (Sobot *et al*., 2020).

In order to study the effect of *Gentiana lutea* extract on UVA and UVC induced DNA damage in fetal lung fibroblasts (MRC-5) and human melanoma cells (Hs 294T) the genotoxic and cytotoxic effect of different concentrations of *Gentiana lutea* extract were established. *Gentiana lutea* roots were extracted with methanol (DER 1:10), filtrated and evaporated till dryness. The dried material was dissolved into DMSO to 200 mg/ml.

Cytotoxicity was measured by survival of the cells, which was estimated by measuring the absorbance at 570nm. In the Hs294T cells none of the concentrations of the extract (0.0625-2 mg/ml) showed significant toxicity. In the MRC-5 cells the highest dose was related to a 27% decrease in survival.

Genotoxicity was evaluated by the alkaline comet assay, measuring the tail intensity of electrophoresed lysed cells as a measure of DNA damage. The extract of the roots did not cause a significant increase in the tail intensity. (Cvetkovic, 2023)

Assessors comment:
In vitro studies have been identified studying the cytotoxic and genotoxic effect of Gentiana lutea root extract. These studies are at the moment not relevant for the revision of the EU herbal monograph, because they do not change the conclusion on safety.

References

Patenkovic D, Stamenkovic-Radak M, Nikolic D et.al. Synergistic effectof Gentiana lutea L. on methylmethanesulfonate genotoxicity in the Drosophila wing spot test. *Journal of Ethnopharmacology* 2013*;* 146: 632–636

Sobot AV, Draculic D, Joksic G et.al. Yellow gentian root extract provokes concentration- and time-dependent response in peripheral blood mononuclear cells. *Arh Hig Rada Toksikol* 2020;71:320-328

Cvetkovic S, Vuletic S, Vunduk J et.al. The role of Gentiana lutea extract in reducing UV-induced DNA damage. *Mutagenesis* 2023; 38: 71-80

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