15 January 2020
EMA/HMPC/611976/2019
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monograph on *Aesculus hippocastanum* L., semen (EMA/HMPC/628242/2018)

Final – Revision 1

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monograph on *Aesculus hippocastanum* L., semen as released for public consultation on 2019-06-15 until 2019-09-15.

	Organisations and/or individuals
1	AESGP - Association of the European Self-Medication Industry
2	Herbapol - Wroclawskie Zaklady Zielarskie S.A.

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
AESGP	We highly appreciate the revision of the European Union monograph on *Aesculus hippocastanum* which reflect the new Ph. Eur. monograph with regard to the definition of the well-established use dry extracts. We also highly appreciate the inclusion of a number of additional preparations under traditional use as well as the oral use for some preparations. In the following, our specific comments do not relate to the monograph, but to the assessment report where we suggest to correct the description of two marketed extracts and to include two further references. The respective SPCs and references are attached.	Endorsed, the assessment report has been updated.

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
4.2. Posology and method of administration	Herbapol	In our opinion rounding of the total content of triterpene glycosides expressed as protoescigenin to 20 mg, as proposed in the draft assessment report, is not appropriate. Taking under consideration the correlation factor provided by EDQM of 2.4, converting the content of 50 mg expressed as aescin (spectrophotometric method) to the content expressed as protoaescigenin (50 mg/2.4=20.8 mg), the correctly counted amount should be set at 21 mg level.	Partially endorsed. HMPC acknowledge the provided information. For products on the market, it is indeed important that the composition of the product is not changed due to the new assay in the Ph.Eur. The patients should expect the same outcome as before. Therefore, HMPC anticipates that for products on the market, MAH

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		In this case, the 50 mg limit content of triterpene glycosides currently expressed as aescin will correspond to 21 mg±10% (18.9 mg–23.1 mg) expressed as protoaescigenin. Assuming that 50 mg of triterpene glycosides expressed as aescin equals 20 mg expressed as protoaescigenin, limit content in the dosage unit will be 20±10% (18.0 mg–22.0 mg). The obtained values have a direct impact on the determination of the appropriate content of the total contents of triterpene glycosides in the standardised *Aesculus hippocastanum* extract. Assuming a fixed content of standardized dry extract from chestnut seeds in the dosage unit on 277.8 mg per tablet: • in the case of the average content of 20 mg per tablet, the dry chestnut seed extract should contain 7.2% triterpene glycosides expressed as protoaescigenin (6.8%-7.6% assuming a 5% deviation from average value) • in the case of average content of 21 mg per tablet, the dry chestnut seed extract should contain 7.6% triterpene glycosides expressed as protoaescigenin (7.2%-8.0% assuming a 5% deviation from average value) The difference between 7.2% and 7.6% is of significant importance while setting new limits of the content of protoaescigenin in standardised dry extract from Aesculus hippocastani semen. In addition, based on the results of our comparative internal	discuss this issue in the variation application. However, a range of correlation factors is not endorsed by the HMPC. For new market applications, it is the HMPC opinion that the best available approximation is a posology corresponding to a content of 21 mg two times daily of triterpene glycosides calculated as protoaescigenin when using the new LC-assay described in the Ph.Eur. monograph 1829.

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		test, of the total content of triterpene glycosides in the standardized dry extract from chestnut seeds (spectrophotometric method versus HPLC method), it can be concluded that the value of the correlation factor equals to an average level of 2.2. That significantly differs from the value specified in the draft assessment report (2.4). The obtained difference will have a direct impact on the determination of limit content of triterpene glycosides expressed as protoaescigenin in medicinal products. In case of using the correlation factor of 2.4, 50 mg of triterpene glycosides expressed as aescin will correspond to 20.8 mg of triterpene glycosides expressed as protoaescigenin. In the case of using the correlation factor of 2.2, 50 mg of triterpene glycosides expressed as aescin will correspond to 22.7 mg of triterpene glycosides expressed as protoaescigenin. Due to the discrepancies in the calculation of the total content of triterpene glycosides indicated above, we suggest to set the acceptable range of the average content of triterpene glycosides expressed as protoaescigenin at the level of 20-24 mg per dosage unit. In this case, the manufacturer of the medicinal product will be able to declare in the registration dossier, the content of triterpene glycosides determined with the allowable deviation from the average value (e.g.±10% from the declared value). The proposed range between 20 and 24 mg per dosage unit, is based the correlation factor values, as following: for 20 mg the	

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		correlation factor equals 2.5 and for 24 mg-2.1. By introducing the suggested modification into the monograph, it will help to avoid the problem, which manufacturers may face after implementation of the proposal. It cannot be excluded that manufacturers who had manufactured a dry extract and standardised it hitherto to the content of triterpene glycosides expressed as 50 mg of aescin in the dosage unit, due to the higher percentage of protoaescigenin in their extract will not be able to reach values of 20 mg in the medicinal product. Such situation can bring to an unreasonable rejection on quality control and disposal of previously manufactured extracts with proper aescin content. In our opinion, due to revision of monograph, MAHs who have already obtained and/or prepared marketing authorisation application for a medicinal product might face enormous problems while implementing changes suggested in the draft document. During the drug development process MAHs manufactured a series of dry extracts from horse chestnut seeds and standardised them for aescin content. Currently to meet the requirements of European Pharmacopeia manufacturers have planned to introduce additional parameter-the determination of triterpene glycoside content expressed as protoaescigenin. However, due to the proposed limit on the content of triterpene glycosides (expressed as protoaescigenin) of 20 mg per dosage unit, the introduction of these extracts to the composition of the medicinal product will result in exceeding the upper acceptance limit, i.e. 22 mg (assuming a	

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		limit level of 20 mg±10% which equals 18-22 mg per dosage unit). Conclusion: Taking under consideration the data presented above, we suggest to verify the proposed limit of total content of triterpene glycosides expressed as protoescigenin and implying the range of the average content of triterpene glycosides expressed as protoescigenin at the level between 20 mg and 24 mg per dosage unit.	