The European Agency for the Evaluation of Medicinal Products
*Veterinary Medicines Evaluation Unit*

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# COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

## ATROPA BELLADONNA

## SUMMARY REPORT

1. ***Atropa belladonna L.*, synonym Deadly nightshade, is a plant species of the family *Solanaceae*. The mother tincture of *Atropa belladonna* is prepared by ethanolic extraction of the whole fresh plant at the end of the blooming period without the ligneous parts of the stalks according to the German Homeopathic Pharmacopoeia (HAB). The dilution 1:100 is containing a maximum of 1% of the original plant material. The degree of extractability of the plant constituents by homeopathic manufacturing procedures is not known. However, due to the provisions in the pharmacopoeia (HAB) the maximum alkaloid content in the mother tincture is not allowed to exceed 0.1%, calculated as hyoscyamine base. The use follows the principles of homeopathic therapy where animals are diagnosed on basis of the individual pattern of clinical signs. A usual dose for a parenteral administration is in the range from 5 ml for pig, sheep and goat to 10 ml for horse and cattle once daily. Dosing may be repeated but a fixed dosage schedule is not common in homeopathy. It was not indicated if the substance is used orally. In conventional veterinary medicine, atropine, the major alkaloid of *Atropa belladonna*, is used in species like horse, cattle, pigs or sheep at usual parenteral daily doses between 0.02 to 0.2 mg/kg bw. Respective oral doses are about threefold those used parenterally.**

   **In human phytotherapy *Atropa belladonna* preparations are mainly used against spasms and colic-like pains in gastro-intestinal and biliary tract. Only standardised Belladonna preparations, for example prepared belladonna herb (Belladonnae pulvis normatus) containing about 0.28 to 0.32% total alkaloids (i.e. 280 to 320 mg/100 g) calculated as hyoscyamine, are used therapeutically. The oral intake of a median single dose of 0.05 to 0.1 g prepared herb corresponds to 0.15 to 0.3 mg total alkaloids, the maximum single dose of 0.2 g contains 0.6 mg alkaloids and the maximum daily dose of 0.6 g up to 1.8 mg.**

2. **Constituents of *Atropa belladonna* of possible relevance for consumer safety are the pharmacologically active tropane alkaloids: The total alkaloid content of the overground parts of the plant is reported to be 0.2 to 2.0% in the dry matter with average values from 0.3% to 0.5% while the alkaloid content in the roots lies within the range from 0.2% to 1.2%. The main alkaloid of the total alkaloid complex is (S)-hyoscyamine coming up to 87.6% in the leaves (root: 68.7%). *In vitro*, i.e. in solution, (S)-hyoscyamine is undergoing rapid racemisation to atropine, which is R,S-hyoscyamine. Further alkaloids in the leaves are apoatropine (syn. atropamine; 6.7%), tropine (3%), scopolamine (1.9%), aposcopolamine (0.5%), 3-α-phenyl-acetoxytropane (0.3%) and tropinone (0.2%). Additionally flavonoids, coumarines and tannins have been determined. Compared to the leaves the root is reported to contain a somewhat wider spectrum of alkaloids.**

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3. **The principle pharmacodynamic activity of *Atropa belladonna* constituents is associated with**
**(S)-hyoscyamine, the levorotatory enatiomer of the racemate atropine. Hyoscyamine/atropine is an antimuscarinic agent competetively inhibiting the action of acetylcholine at the muscarinic receptors of postganglionic parasympathetic nerves. To some extent it also inhibits effects of acetylcholine on smooth muscle cells that respond to acetylcholine but lack cholinergic innervation. Hyoscyamine/atropine exerts peripheral and central effects, however, the action is not equally effective throughout the body because of the different susceptibility of the respective nerve endings. The influence of the remaining alkaloids on the overall effect is considered being negligible.**

4. **Specific pharmacokinetic data for herbal or total plant preparations of *Atropa belladonna* were not available. The alkaloids of belladonna preparations were reported to be quickly and completely absorbed from the gastro-intestinal tract. Absorption from the intact or injured skin appears to be moderate. Plasma protein binding of the alkaloids was found to be 30 to 50%, volume of distribution was relatively high with 2 to 4 l/kg. Like atropine, belladonna alkaloids cross the blood-brain barrier and the placenta and traces may appear in milk. In humans the plasma half-life of the alkaloids is moderate ranging from 13 to 38 hours. About 50% of the dose was reported to be excreted unchanged in urine. However, no specific data are available.**

5. **Acute toxicity of the plant *Atropa belladonna* and its preparations is mainly associated with the alkaloid hyoscyamine/atropine. There is considerable intra- and interspecies variation in the toxicity of belladonna or hyoscyamine/atropine indicating herbivore as usually being much more resistant than carnivore. Also the route of administration is important. A quite strong resistance to oral intake of tropane alkaloid containing plants is observed in rabbits, guinea pigs and birds because of effective detoxifying mechanisms. Horses, cattle and goats are reported to be relatively resistant to oral administration of belladonna compared to parenteral injection of atropine whereas swine appear to be quite susceptible to ingested belladonna. Signs of acute intoxication are similar in all mammalian species. Concerning the peripheral drug action the symptoms may also appear during therapeutical use and are described as dryness of the mouth with difficulty of swallowing, thirst, tachycardia, mydriasis and flushing and dryness of the skin. In humans effects on the central nervous system like excitement, hallucinations and disorientation may occur in doses of 3 mg atropine and more. Concerning atropine the following $LD_{50}$ values are available following oral administration: rat: 622 mg/kg bw; mouse: 400 mg/kg bw. In human adults the oral intake of 100 mg of atropine is considered the minimum lethal dose, in children a few milligrams. In case of (S)-hyoscyamine an oral dose of 10 mg and more is said to be lethal in human adults.**

6. **Information on repeated dose toxicity was not available.**

7. **No studies on genotoxicity or reproductive effects including teratogenicity of *Atropa belladonna* or its constituents have been performed. There is however no published evidence of genotoxic properties of belladonna alkaloids nor do these substances appear to possess structures alerting for genotoxicity. Belladonna alkaloids or atropine have not been associated with reproductive toxicity or teratogenic effects.**

8. **No studies on carcinogenic properties were provided. However, there is no indication of carcinogenicity of belladonna alkaloids in published literature.**

9. **No specific studies on immunotoxicity were provided. As with atropine, it was reported that occasionally hypersensitivity reactions might occur in humans at worst resulting in anaphylactic shock in doses below 1 mg belladonna alkaloids.**

10. **In humans intoxications have been observed following therapeutical overdosage due to mistake or carelessness. Also poisoning resulting from drinking of herbal "health" teas contaminated with dried parts of belladonna have been mentioned. Another source of poisoning is the intake of the cherry-like belladonna berries containing 0.65% tropane**

**alkaloids on average. Without any treatment the intake of 2 to 5 berries in children and 10 to 20 berries in adults is considered lethal.**

11. **It was not possible from available information to establish a complete pharmacological and toxicological profile including NOELs and an ADI for belladonna extracts.**

12. **Consumer safety considerations for *Atropa belladonna* may be based on a combination of worst-case assumptions:**

    - **on the basis that the alkaloid content in the mother tincture is limited to the amount of 0.1% of alkaloids, calculated as hyoscyamine, the 1:100 dilution can contain a maximum of 0.001% alkaloids (0.01 mg/ml),**
    - **using intravenous administration, the total bioavailable alkaloid content in a maximum dose can be calculated between 0.1 and 0.05 mg of alkaloids for large (500 kg bw) and smaller animals (150 kg bw), respectively,**
    - **assuming no metabolism and excretion, a standard edible portion for meat would in this hypothetical situation contain far less than 1 µg of alkaloids (0.1 to 0.17 µg),**
    - **only trace amounts of belladonna alkaloids have been found in milk; assuming elimination of a high proportion of 2% of the dose into milk residues are in the order of 0.05 to 0.1 µg/l (20 l/day/500 kg cow).**

    **Further to this worst-case calculation it has to be kept in mind that atropine the major belladonna alkaloid has already been recommended for Annex II of Council Regulation (EEC) No 2377/90 for use in conventional veterinary medicine.**

**Conclusions and recommendation**

**Having considered:**

- ***Atropa belladonna* is used as a diluted extract not exceeding one part per hundred prepared according to homeopathic pharmacopoeias with an adjusted total alkaloid content below 0.001%,**
- **atropine the main belladonna alkaloid has already been recommended for inclusion into Annex II of Council Regulation (EEC) 2377/90,**
- ***Atropa belladonna* is used in a small number of individual animals for non-regular treatments in accordance with the principles of homeopathic therapy,**
- **the animals are unlikely to be sent for slaughter during or immediately after treatment,**

**the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for the homeopathic preparation *Atropa belladonna* and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:**

| Pharmacologically active substance(s) | Animal species | Other provisions |
|---|---|---|
| *Atropa belladonna* | All food producing species | For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias, at concentrations in the products not exceeding one part per hundred only |