

## COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

### URGINEA MARITIMA

#### SUMMARY REPORT

1. *Urginea maritima (L) BAK.*, synonyms Squill, Sea onion; is a species group consisting of various sub-species e.g. *Urginea maritima (L) Baker s. str.*, *Urginea hesperia*, *Urginea pancratia*, *Urginea aphylla* and *Urginea numidica*. *Urginea maritima* belongs to the family *Liliaceae/Hyacinthaceae* and is widely distributed in the Mediterranean area. The plant exists as a red and a white variety. The homeopathic mother tincture is prepared according to the German Homeopathic Pharmacopoeia (HAB, method 3a) by ethanolic extraction of the fresh fleshy parts of the bulb obtained from the red variety of *Urginea maritima (L) Baker* and *Urginea maritima aggregate*. In veterinary homeopathy a dilution of 1:100 for oral administration is used for treatment of food producing animals. The use follows the principles of homeopathic therapy where animals are diagnosed on basis of the individual pattern of clinical signs. Recommended maximum doses for oral treatment are about 20 drops for large animals (assumed body weight of 500 kg), up to 4 times per day.

In human homeopathic therapy *Urginea maritima* may be used orally (dilution of 1:100 or higher dilutions) and parenterally (dilution of 1:10 000 or higher dilutions). The dried bulb of *Urginea maritima* (Squill) is also used in human phytotherapy.

2. Major *Urginea* constituents of concern are the glycosides of the bufadienolide type. From bulbs of *Urginea maritima aggregate* a large number of bufadienolides were isolated. Constituents were e.g. scilliroside, the predominant active glycoside, scillarenin-3-O-beta-D-glucoside, proscillarin A, scilliphaeosidin-3-O-beta-D-glucoside, scilliglaucoside, scilliphaeoside, 12-epi-scilliphaeoside; glucoscilliphaeoside, 12-epi-glucoscilliphaeoside, 12-beta-hydroxyscilliglaucosidin-3-O-beta-D-glucoside, 12-epi-scilliphaeosidin-3-O-beta-D-glucoside, 12-episcilliphaeosidin-3-O-alpha-L-rhamnosido-alpha-L-rhamnoside, scillaren A, gamabufotalin 3-O-alpha-L-rhamnoside, scilliglaucoside, scillirubrosidin-3-O-alpha-L-rhamnoside, scillirubroside, 12-beta-hydroxyscilliroside, 5-alpha-4,5-dihydroscillirosidein 3-O-alpha-L-thevetosido-beta-D-glucoside, deacetylscilliroside, 10-carboxy-5-beta,14-beta-dihydroxybufa-3,20,22-trienolide-5-O-beta-D-glucoside, scilliglaucogenin. Major constituents of *Urginea numidica* are the bufadienolide glycosides proscillarin A, scilliphaeosidin, 12-epi-scilliphaeosidin and scilliglaucoside. The mean bufadienolide contents in the bulbs (dry matter) of the various sub species were reported with 0.55 to 1.8%. The scilliroside content of dried bulbs ranged from 0.01 to 0.53%. Further constituents of both *Urginea numidica* and *Urginea maritima aggregate* are anthocyanes, flavonoids, fatty acids and polysaccharides. The bufadienolide glycoside content in the mother tincture is in the range of 0.04 to 0.07%. This corresponds to a maximum content of 0.0021% (21 µg/ml) in the 1:100 dilution.

3. The pharmacologically active principles of *Urginea maritima* are the cardiotrophic steroidol glycosides (bufadienolide glycosides). Number and species of the bound sugar moieties and the number of oxygen atoms in the aglycone determine the pharmacological activity of bufadienolide glycosides, which exert their action mainly by inhibition of membranous adenosine triphosphatase of cardiomuscular tissue. Cardiac glycosides act positive inotropic and negative chronotropic. Furthermore, a dose-dependant constrictor effect on veins has been reported for cats, when treated with an extract (20% ethanol) obtained from *Urginea maritima*. A diuretic action of the ethanolic extract has been reported for rats and humans.
4. Specific pharmacokinetic information on the aqueous-ethanolic extract of *Urginea maritima* has not been provided. In general, differences in polarity of cardiac glycosides can affect enteric absorption, degree of distribution in the organism and route of excretion. Increase of oxygen in the glycoside enhances the hydrophilicity and decreases the absorption from the gastro-intestinal tract. Polar species are reported to be excreted faster and predominantly in urine. The pharmacokinetic information of *Urginea maritima* relates mainly to the more hydrophobic constituent proscillarin A. After oral administration of 0.5 mg proscillarin A, 3 times per day over a period of 14 days, a constant plasma concentration of approximately 0.6 µg/l was observed with a maximum concentration of 0.74 µg/l reached 90 minutes after dosing. For proscillarin A the main route of metabolism has been reported to be conjugation to glucuronic acid and sulphuric acid and subsequent biliary excretion. Only 4 µg proscillarin A per day were excreted with the urine. The terminal elimination half-life was about 23 hours. In general, an overall oral absorption rate of 25 to 50% has been reported for glycosides obtained from *Urginea maritima*. The absorption can vary individually, depending on age and state of health of the patients. The overall excretion rate was about 50% of the dose per day.
5. Data on acute toxicity is available for the dried drug powder (standardised Squill powder) and some constituents of *Urginea maritima*. Intravenous LD values were reported as 0.55 mg/kg bw in guinea pigs and 0.28 mg/kg bw in cats for proscillarin A, 0.41 mg/kg bw in guinea pigs and 0.20 mg/kg bw in cats for scillaren A, while for scilliroside 0.15 mg/kg bw were observed in rats and 0.12 mg/kg bw in cats.

Oral LD<sub>50</sub>-values for scilliroside were 0.5 to 0.7 mg/kg bw in rats and less than 20 mg/kg bw in dogs and pigs, and oral LD value in rats was 2 to 4 mg /kg bw. Higher lethality to female rats compared to male rats was reported by several authors with a toxicity ratio of 3:1. Large differences in toxicity of red squill powder have been noted for chickens, rabbits and guinea pigs with rabbits being most susceptible to lethal effects. These differences can be partly explained by species differences in the pattern of micro-organisms in the gastrointestinal tract. These can produce hydrolysing enzymes that split the sugar moieties from the aglycones, which then are more readily absorbed.

For standardised Squill powder, which has a glycoside content equivalent to an activity of 0.2% proscillarin A, the oral LD<sub>50</sub> values were given as 320 mg/kg bw for guinea pigs, 490 mg/kg bw for rats, 100 to 500 mg/kg bw for cattle and horses, 145 mg/kg bw for dogs and cats and 250 to 500 mg/kg bw for sheep.

6. Information on repeated dose toxicity of *Urginea maritima* was not available.
7. No information on mutagenicity and carcinogenicity of *Urginea maritima* was provided. There is however no published evidence of genotoxic properties of bufadienolide glycosides nor does this class of substances appear to possess chemical structures alerting for genotoxicity.
8. No studies on reproductive effects including teratogenicity of *Urginea maritima* or its constituents have been performed. Based on published scientific literature cardiac glycosides are considered to have no teratogenic properties.
9. No specific studies on immunotoxicity were provided.

10. In human phytotherapy the dried bulb of the white variety of *Urginea maritima* (Squill) is used orally as diuretic, emetic, expectorant, and cardiotonic. Daily oral doses for adults range from 30 to 500 mg (the standardised drug is adjusted to an activity equivalent to approximately 0.2% of proscillarin A). Intoxication was observed following overdoses of phytotherapeutic *Urginea maritima* preparations. The main symptoms of oral overdoses are disorders of the gastrointestinal tract like nausea, vomiting, diarrhoea as well as irregular pulse. As a general rule toxic effects of the cardiac glycosides occur in a dose range exceeding the therapeutic dose by factor 1.5 to 3. Intoxication with fatal outcome has been described when two children (3 and 5 years old) ingested inadvertently a syrup with a content of 0.1 g of the drug (details not available). About 1.5 g of the drug is reported to be lethal for adults. Severe symptoms of intoxication were reported when bufadienolide glycosides containing rat poison was ingested with suicidal intent. A 43-year-old man deliberately ingested 4 tablets of a rodenticide containing 12 mg of scilliroside. Vomiting appeared a few minutes later and persisted for 48 hours. An electrocardiogram revealed a complete atrio-ventricular block, which disappeared on day 4. In human phytotherapy, standardised Squill powder is contraindicated when simultaneously digitalis glycosides are used.

In Greece the fresh bulbs obtained from *Urginea maritima aggregate* are distilled to prepare a certain type of spirit.

11. It was not possible from available information to establish a complete pharmacological and toxicological profile including NOELs and an ADI for homeopathic *Urginea maritima* extracts and its preparations. Considerations concerning consumer safety may be based on the following assumptions: i) on the basis that the total bufadienolide glycoside content in the mother tincture is maximally 0.07%, which corresponds to 0.021% in the 1:10 extract, the 1:100 dilution can contain a maximum amount of 21 µg of total glycosides per ml ii) using maximum recommended oral doses of about 80 drops (about 2 ml), the total glycoside content administered to large animals (assumed body weight of 500 kg) is 42 µg (0.08 µg/kg bw); iii) assuming complete oral absorption and no metabolism or excretion, a standard edible meat portion would contain 0.04 µg of total glycosides. Similar calculations can be done for milk. Assuming a very high proportion of 2% of the dose excreted into milk, worst case bufadienolide residues could amount to 0.04 µg/l (based on a milk production of 20 l/day by a 500 kg cow).

Having also in mind that *Urginea maritima* is intended for oral use only and that gastro-intestinal absorption of the cardiac glycosides is only low to moderate, the calculated maximum residues were considered negligible compared to possible levels of consumer health concern.

## Conclusions and recommendation

Having considered the criteria laid down by the Committee for Veterinary Medicinal Products for the inclusion of substances in Annex II of Council Regulation (EEC) No 2377/90 and in particular that:

- the homeopathic preparation *Urginea maritima* is a diluted extract of *Urginea maritima* at a concentration not exceeding one part per hundred,
- *Urginea maritima* is for oral use only,
- the absorption of *Urginea maritima* glycosides from the gastro-intestinal tract is considered limited,
- *Urginea maritima* is used in a small number of individual animals for non-regular treatments,
- 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 homeopathic preparations of *Urginea maritima* at concentrations not exceeding one part per hundred for oral use 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
<i>Urginea maritima</i>	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. For oral use only