SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

(DE) Luminaletten vet, 15 mg tablets for dogs
(AT, BE, DK, ES, FR, NL, PT, SE) Epirepress 15 mg, tablets for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substance:

Phenobarbital 15 mg

Excipients:

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White, round, slightly domed tablets, diameter 5.7 mm, with TC imprinted on one side and a breakline on the other side. The tablets cannot be divided into equal parts.

4. CLINICAL PARTICULARS

4.1 Target species

Dog

4.2 Indications for use, specifying the target species

Prevention of seizures due to generalised epilepsy in dogs.

4.3 Contraindications

Do not use in the case of hypersensitivity to the active substance or to any other barbiturates or to any of the excipients.
Do not use in animals with severe impaired hepatic function.
Do not use in animals with serious renal and/or cardiovascular/respiratory disorders.

4.4 Special warnings for each target species

The decision to start antiepileptic drug therapy with phenobarbital should be evaluated for each individual case and depends on number, frequency, duration and severity of seizures in dogs.
To achieve successful therapy, administration of tablets must be at the same time each day.
Withdrawal or transition from other types of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures.
Some of the dogs are free of epileptic seizures during the treatment, but some of the dogs show only a seizure reduction, and some of the dogs are considered to be non-responders.

4.5 Special precautions for use

Special precautions for use in animals

Caution is recommended in animals with:

- impaired hepatic and renal function
- hypovolemia, anemia and
- cardiac or respiratory dysfunction

The chance of hepatotoxic side effects can be diminished or delayed using an effective dose that is as low as possible. Monitoring of hepatic parameters is recommended in case of a prolonged therapy.
It is recommended to assess the clinical pathology of the patient 2-3 weeks after start of treatment and afterwards every 4-6 months, e. g. measurement of hepatic enzymes and serum bile acids. It is important to know that the effects of hypoxia etc. do cause increased levels of hepatic enzymes after a seizure.
Phenobarbital may increase the activity of serum alkaline phosphatase and transaminases. These may demonstrate non-pathological changes, but could also represent hepatotoxicity. Therefore, in the case of suspected hepatotoxicity, liver function tests are recommended.
In stabilised epileptic patients, it is not recommended to switch from other phenobarbital formulations to Luminaletten 15 mg or Luminal 100 mg tablets. However, if this cannot be avoided then additional caution should be taken. This includes more frequent plasma concentration sampling to ensure that therapeutic levels are maintained. Monitoring for increased side effects and for hepatic dysfunction should be conducted more regularly until stabilisation is confirmed.
Withdrawal of therapy with phenobarbital formulations should be made gradually to avoid precipitating an increase in the frequency of seizures.

Due to the formulation, the product should not be used in dogs weighting less than 6 kg.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

Barbiturates can cause hypersensitivity. People with known hypersensitivity to barbiturates should avoid contact with this veterinary medicinal product.

Accidental ingestion may cause intoxication and could be fatal, particularly for children. Take utmost care that children do not come in contact with the product.
Phenobarbital is teratogenic and may be toxic to unborn and breastfed children; it may affect the developing brain and lead to cognitive disorders. Phenobarbital is excreted in breast milk. Pregnant women, women of childbearing age and lactating women should avoid accidental ingestion and prolonged skin contact with the product.

To prevent accidental ingestion of tablets, the container should be closed immediately after withdrawing the required number of tablets for one administration.
It is advisable to wear disposable gloves during administration of the product to reduce skin contact.

In case of accidental ingestion, seek medical attention immediately, advising medical services of barbiturate poisoning; show the package leaflet or the label to the physician. If possible, the physician should be informed about the time and amount of ingestion, as this information may help to ensure that appropriate treatment is given.

Wash hands thoroughly after use.

4.6 Adverse reactions (frequency and seriousness)

Uncommonly at the start of treatment, ataxia, somnolence, listlessness and dizziness may occur. In some cases these effects may persist for the entire duration of treatment.
Sedation and ataxia commonly become significant concerns as serum levels reach the higher end of the therapeutic range.
In very rare cases, polyuria, polydipsia and polyphagia may occur at average or higher therapeutically active serum concentrations, but these effects are usually transient and disappear with continued medication.
A paradoxal hyperexcitability may occur, particularly after first starting therapy. As this hyperexcitability is not linked to overdosage, no reduction of dosage is needed.
High plasma concentrations (> 35-40 µg/ml) may be associated with hepatotoxicity.
Treating dogs with phenobarbital may lower their total thyroxin levels (TT4) or free thyroxin levels (FT4); however this may not be an indication of hypothyroidism. Treatment with thyroid hormone replacement should only be started if there are clinical signs of the disease.
Phenobarbital can have deleterious effects on stem cells from bone marrow. Consequences are immunotoxic pancytopenia and/or neutropenia. These reactions disappear after cessation of treatment.
Superficial necrolytic dermatitis may occur after administration of phenobarbital.
If adverse reactions are severe, the administered dose should be decreased.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals displaying adverse reaction(s) during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports)

4.7 Use during pregnancy, lactation or lay

Pregnancy:

Use only accordingly to the benefit-risk assessment by the responsible veterinarian.

Studies in laboratory animals have indicated that phenobarbital has an effect during prenatal growth, in particular causing permanent changes in neurological and sexual development. Neonatal bleeding tendencies have been associated with phenobarbital treatment during pregnancy.
Maternal epilepsy may be an additional risk factor for impaired foetal development. Therefore pregnancy should be avoided in epileptic dogs whenever possible. In case of pregnancy, the risk that the medication may cause an increase in the number of congenital defects must be weighed up against the risk of suspending treatment during pregnancy. Discontinuation of treatment is not advised, but the dosage should be kept as low as possible.
Phenobarbital crosses the placenta and, at high doses, (reversible) withdrawal symptoms cannot be ruled out in newborns.
The safety of the veterinary medicinal product has not been proven during pregnancy in dogs.

Lactation:

Use only accordingly to the benefit-risk assessment by the responsible veterinarian.

Phenobarbital is excreted in small amounts in breast milk and during nursing pups should be monitored carefully for undesired sedative effects. Weaning early may be an option. If somnolence/sedative effects (that could interfere with suckling) appear in nursing newborns, an artificial suckling method should be chosen.
The safety of the veterinary medicinal product has not been proven during lactation in dogs.

4.8 Interaction with other medicinal products and other forms of interaction

A therapeutic dose of phenobarbital for antiepileptic therapy can significantly induce plasma proteins (such as α1acid glycoprotein, AGP), which bind drugs. Phenobarbital may reduce the activity of some drugs by increasing the rate of metabolism through induction of drug-metabolising enzymes in liver microsomes. Therefore special attention must be paid to the pharmacokinetics and doses of drugs simultaneously administered. The plasmatic concentration of a range of drugs (for example cyclosporine, thyroid hormones, theophylline, antiepileptics, chloramphenicol, corticosteroids, doxycycline, beta blockers and metronidazole) is decreased in the case of concurrent administration of phenobarbital. The reliability of hormonal contraceptives is lower.
Concurrent use with other drugs having a central depressive action (like narcotic analgesics, morphinic derivates, phenothiazines, antihistamines, clomipramine and chloramphenicol) can increase the effect of phenobarbital.
Cimetidine and ketoconazole are inhibitors of hepatic enzymes: concurrent use with phenobarbital can induce an increase of serum concentration of phenobarbital. Phenobarbital may decrease the absorption of griseofulvin. Concurrent use with potassium bromide increases the risk of pancreatitis.
Use of phenobarbital tablets in conjunction with primidone is not recommended as primidone is predominantly metabolized to phenobarbital.
The following drugs can decrease the convulsive threshold: quinolones, high doses of β-lactam antibiotic, theophylline, aminophylline, cyclosporine and propofol for example. Medications which may alter the seizure threshold should only be used if really necessary and when no safer alternative exists.

4.9 Amounts to be administered and administration route

The required dosage will differ to some extent between individuals and with the nature and severity of the disorder.

Administration route

Only intended for oral administration in dogs.

Amount to be administered

The recommended starting dose is 5 mg phenobarbital per kg body weight per day. Please refer to the following dosing table in order to determine the correct starting dose.

	Tablets			
Body weight [kg])	Morning	Midday	Evening	Total daily dose [mg]
≥ 6 - < 9	1	-	1	30
≥ 9 - < 12	1	1	1	45
≥ 12 - < 15	2	-	2	60
≥ 15 - < 18	2	1	2	75
≥ 18 - < 20	2	2	2	90

Any adjustments to this dose are best made on the basis of clinical efficacy, blood concentrations and the occurrence of undesired effects.
The phenobarbital serum concentration considered to be therapeutically active is between 20-40 µg/ml.
Steady state serum concentrations are not reached until 1-2 weeks after treatment is initiated. The full effect of the medication occurs approximately after 2 weeks, and doses should not be increased during this time.
The phenobarbital serum concentration may be checked after steady state has been achieved, If it is less than 20 µg/ml and/or seizures are not being controlled, the dosage may be increased by 20 % at a time, with associated monitoring of serum phenobarbital levels. If seizures recur, the dose may be

increased to a maximum serum concentration of 40 µg/ml. High plasma concentrations may be associated with hepatotoxicity.
The tablets cannot be divided into equal parts. Division into halves may be done only in order to facilitate the administration to the dog.
For accuracy of dosing, dogs with less than 20 kg should commence therapy with Luminaletten vet tablets. For higher dosages Luminal vet tablets (100 mg phenobarbital) may be used.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

Symptoms

Overdosage may result in coma, severe respiratory and cardiovascular depression, hypotension and shock leading to renal failure and death.

Procedures

The primary management measures are intensive symptomatic and supportive therapy with particular attention being paid to the maintenance of cardiovascular, respiratory, and renal functions and of the electrolyte balance. Treatment of overdosage can, if necessary, consist of gastric lavage with activated charcoal administration.

There is no specific antidote, but CNS stimulants (like Doxapram) may stimulate the respiratory centre. Give oxygen support.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antiepileptics/barbiturates and derivatives
ATCvet code: QN03AA02

5.1 Pharmacodynamic properties

The antiepileptic effects of phenobarbital are probably the result of at least two mechanisms, being decreased monosynaptic transmission, which presumably results in reduced neuronal excitability and an increase in the motor cortex's threshold for electrical stimulation.

5.2 Pharmacokinetic particulars

Absorption

As a weak acid, phenobarbital is absorbed well from the gastrointestinal tract following oral administration to dogs, although peak plasma concentrations are not achieved until 4-6 hours after administration.

Distribution

Plasma protein binding of phenobarbital is 45 % and the distribution volume is 0.7 ± 0.15 l/kg. A steady-state serum concentration is achieved 8-15.5 days after treatment is initiated.
Phenobarbital is reasonably fat-soluble and crosses the blood-brain barrier slowly. The barbiturate effect therefore develops slowly, but persists for a long period of time. Due to the moderate fat solubility of phenobarbital, redistribution to adipose tissue occurs slowly. Phenobarbital crosses the placental barrier and enters breast milk.

Metabolism

Phenobarbital is converted in the liver into p-hydroxy-phenobarbital, which, due to a lower antiepileptic effect, no longer makes any significant contribution to the activity of phenobarbital. Barbiturates cause enzyme induction and thereby accelerate their own breakdown.

Elimination

About 25 % of the administered dose is excreted in the urine in unchanged form (elimination half-life: 37-75 hours) and about 75 % is excreted as p-hydroxy-phenobarbital glucuronide and sulphate derivatives and as p-hydroxy-phenobarbital itself. Following daily administration of 5.5 mg phenobarbital per kg bodyweight for 90 days, a lower elimination half-life is observed (from 88.7 ± 19.6 to 47.5± 10.7 hours).
Under alkaline conditions urinary excretion of phenobarbital is accelerated.
There is wide individual variation in the degree of phenobarbital metabolism which is caused by the effect of phenobarbital on microsomal liver enzymes. Variations in elimination half-life are not only seen between animals but also within a single animal.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline
maize starch
gelatin
lactose monohydrate
stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 5 years
Shelf life after first opening the immediate packaging: 3 months

6.4 Special precautions for storage

Store in the original container.

This veterinary medicinal product does not require any special storage conditions.

6.5 Nature and composition of immediate packaging

Carton containing a brown glass container or a white plastic container.
The glass containers (glass type III) are closed by a child-resistant plastic stopper and bellows made of polyethylene.
The white plastic (polyethylene) containers are closed with a white child-proof polypropylene screw cap

Pack sizes: 1 x 50, 1 x 100 or 2 x 100 (= 200 tablets)

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]
{Name and address}
<{tel}>
<{fax}>

8. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: DD/MM/YYYY

10. DATE OF REVISION OF THE TEXT

DD month YYYY

DISTRIBUTION

Only under veterinary prescription.

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.