SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ANSEREN 15 mg capsules, hard
ANSEREN 30 mg capsules, hard
ANSEREN 45 mg capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Ketazolam

Each hard capsule contains 15 mg, 30 mg, and 45 mg of ketazolam.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules, hard.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Anxiety, tension and other somatic or psychiatric conditions in association with anxiety disorder.

Insomnia.

Benzodiazepines are indicated only when the disorder is severe, disabling or subjecting the individual to serious distress.

4.2 Posology and method of administration

Unless prescribed otherwise, the mean daily dose is 30 mg, to be taken with some liquid, preferably in the evening, before going to bed.
Based on the individual response, this dosage may vary from 15 to 75 mg/day, with an attempt to administer the lowest effective dose, in particular in elderly, weakened patients or suffering from organic brain diseases.
Treatment should start at the lowest recommended dose.
The maximum dose should not be exceeded.

When treating elderly and hepatic and/or renal compromised patients, doctors should carefully establish posology and evaluate a possible decrease of the dosages indicated above.
Patients should be controlled regularly at the beginning of the treatment, in order to reduce the dose or the frequency of the administration, if required, to prevent overdose due to accumulation.
Treatment should be as short as possible.
In some cases, extension of use beyond the maximum recommended period may be required; this should not take place without further evaluation of the patient.
<u>Anxiety</u>
The patients should be carefully evaluated on regular basis and the need for the treatment to be continued should be carefully consider, in particular when the patient is asymptomatic. Generally, the duration of treatment should not exceed 8-12 weeks, including the period of gradual discontinuation.
<u>Insomnia</u>

Generally, the duration of treatment ranges from few days to 2 weeks, up to a maximum of 4 weeks, including the period of gradual discontinuation.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
As with other benzidazepines, the product should not be used in case of: myasthenia gravis, severe respiratory insufficiency, severe hepatic insufficiency, sleep apnoea syndrome, documented individual hypersensitivity to other benzodiazepines.
Ketazolam is also contraindicated in case of acute angle glaucoma in the acute forms and in case of acute poisoning from alcohol, analgesics, hypnotics, neuroleptics, antidepressants, lythium.

4.4 Special warnings and precautions for use

Tolerance
Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks.

Dependence
The use of benzodiazepines may lead to development of physical and psychic dependence on these drugs. The risk of dependence increases with the dose and duration of the treatment and it is further increased in patients with a history of drug or alcohol abuse.
Once physical dependence is developed, abrupt discontinuation of the treatment will be associated to withdrawal symptoms. These may consist of headache, muscle pain, severe anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalization, hyperacusis, dumbness and tingling of extremity, hypersensitivity to light, noise and physical contact, hallucinations, or seizures.
Insomnia or rebound anxiety: with the discontinuation of the treatment a transient syndrome may occur where the symptoms requiring benzodiazepine treatment recur in an aggravated form; this can be associated to other reactions, including mood changes, anxiety, restlessness or sleep disorders. As the risk of withdrawal symptoms or rebound is higher after abrupt discontinuation, it is recommended that the dosage is gradually decreased.

Duration of treatment
The duration of treatment should be as short as possible (see section 4.2 “Posology and method of administration”), but it should not exceed 8-12 weeks for anxiety and related symptoms, including the period of gradual discontinuation. The extension of use beyond this period should not take place without further evaluation of the clinical status, including a monitoring of complete blood count and hepatic function. It may be useful to inform the patient at the commencement of the treatment that this will be of limited duration, explaining how the dosage should be progressively decreased.
It is also important that the patient is aware of the possibility of rebound phenomena, in order to minimize the anxiety reaction that could be triggered by the occurrence of such symptoms when the drug is discontinued.
As ketazolam is a long-action benzodiazepine, it is important that the patient is informed that the abrupt change to a short-action benzodiazepine is not advisable as withdrawal symptoms may develop.

Amnesia
Benzodiazepines may cause anterograde amnesia. This occurs more often several hours after ingestion of the drug, so in order to reduce the risk, patients should ensure that they will be able to have an uninterrupted period of 7-8 hours of sleep (see “Undesirable effects”.).

Psychiatric and paradoxical reactions

Benzodiazepine use is known to cause reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rage, nightmares, hallucinations, psychosis, behaviour disorder. Should this occur, the use of the medicine should be discontinued. These reactions are more frequent in children and the elderly.

Special groups of patients
ANSEREN should not be used in patients aged below 18 years.
Elderly should receive a reduced dose (see section 4.2 "Posology and method of administration"). Equally, lower dosages are indicated in patients with chronic respiratory insufficiency due to the risk of respiratory depression. Benzodiazepines are not indicated in patients with severe hepatic insufficiency, as they may precipitate encephalopathy. Benzodiazepines are not intended for the primary treatment of psychotic illness. Benzodiazepines should not be used alone to treat depression or anxiety associated to depression (suicide may be precipitated in these patients). Benzodiazepines should be used with extreme caution in patients with a history of drug or alcohol abuse.
Similarly to other psychiatric medications that are active on the central nervous system, ANSEREN should be used with caution in weakened patients, those with organic brain alterations (in particular arteriosclerotic alterations), with renal function alteration or cardiac insufficiency.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant intake with alcohol should be avoided. The sedative effect may be enhanced when the product is taken with alcohol. This has a negative influence on the ability to drive and use machines.
Combination with CNS depressants: the central depressive effect may be enhanced when combined with antipsychotics (neuroleptics), hypnotics, tranquillisers/ sedatives, antidepressants, analgesic narcotics, antiepileptics, anaesthetics, and sedative antihistamines. In case of analgesic narcotics, the euphoria due to narcotics may be enhanced, leading to psychic dependence. In the case of antiepileptics, concomitant administration of ANSEREN may also lead to increased frequency and seriousness of grand mal seizures, such as to justify an increased posology of the anticonvulsant treatment; similarly, the abrupt discontinuation of the treatment with ANSEREN may be accompanied by an increased frequency and/or seriousness of convulsive seizures.
Compounds that inhibit specific hepatic enzymes (particularly cyctochrome P450) may potentiate the action of benzodiazepines. To a lesser extent, this applies also to those benzodiazepines which are metabolized only by conjugation.
ANSEREN may potentiate the action of muscle relaxants.
Finally, ANSEREN should be administered with caution in patients receiving beta-blockers, glycosides, anticoagulants, antidiabetics, and oral contraceptives as in single cases the type of interaction with ketazolam cannot be anticipated.

4.6 Fertility, pregnancy and lactation

Pregnancy
This product should not be used during the first trimester; afterwards, the product should be used only in case of actual need and under direct medical supervision. If, due to serious medical reasons, the product is administered during the late stage of pregnancy, or during labour at high doses, effects such as hypothermia, hypotonia, and moderate respiratory depression, may occur due to the action of the drug.
Moreover, there is a possibility that infants born to mothers who take benzodiazepines chronically during the later stages of pregnancy may develop physical dependence and are at risk to develop withdrawal symptoms during the postnatal period.

Breastfeeding
As benzodiazepines are excreted in breast milk, mothers who are breast-feeding should not receive benzodiazepines.

Fertility

If the product is prescribed to a woman of childbearing potential, she should contact her physician about stopping the drug if she intends to become, or suspects that she is, pregnant.

4.7 Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration, and impaired muscular function may have a negative influence on the ability to drive and use machines. After administration in the evening, reduced reflex response may persist until the following morning, especially at the beginning of the treatment and when increasing the dose.
If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see section 4.5 "Interaction with other medicinal products and other forms of interaction").

4.8 Undesirable effects

Drowsiness, decreased emotional and alertness response, confusion, fatigue, headache, vertigo, muscle weakness, ataxia, double vision. These phenomena occur mainly at the beginning of therapy and generally disappear with following administration.
Other adverse reactions were reported occasionally such as: gastrointestinal disorders, change in libido, and skin reactions, accommodative disorders, dysarthria, tremors, hypotension, jaundice, increased weight, increased appetite, dry mouth or hypersalivation, urinary incontinence or retention, alteration of blood count cells (neutropoenia), menstrual disorders, myalgias.
Amnesia
Anterograde amnesia may occur also at therapeutic doses; the risk is increased at higher doses. Amnesic effects can be associated with behaviour disorders (see section 4.4 "Special warnings and precautions for use").
Depression
A pre-existing depressive state may become manifest during the prolonged use of benzodiazepines. Benzodiazepines or benzodiazepine-like compounds may cause reactions such as: restlessness, agitation, irritability, aggressiveness, delusion, rage, nightmares, hallucinations, psychosis, behaviour alterations. Such reactions may be rather severe. These are more likely in the elderly.
Dependence
The use of benzodiazepines (also at therapeutic doses) may lead to development of physical dependence: the discontinuation of the treatment may cause rebound or withdrawal phenomena (see section 4.4 "Special warnings and precautions for use"). Psychic dependence may occur. Benzodiazepine abuse has been reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system at www.agenziafarmaco.gov.it/it/responsabili.

4.9 Overdose

As for other benzodiazepines, an excessive dose should not be a risk for life, unless there is concomitant intake of other CNS depressants (including alcohol).
In the management of overdose with any drug, it should be borne in mind that multiple agents may have been taken.
Following an overdose of oral benzodiazepines, vomit should be induced (within 1 hour) if the patient is conscious or gastric lavage should be administered protecting the airways if the patient is unconscious.
If there is no improvement in emptying the stomach, activated charcoal should be administered to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care.
Overdose of benzodiazepines is usually manifested by various degrees of CNS depression ranging from

drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion, and lethargy. In more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma, and very rarely death. Flumazenil may be a useful antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anxiolytics, Benzodiazepine derivatives, ATC code: N05BA10

ANSEREN contains the active substance ketazolam, a 1,4-benzodiazepin with prolonged anxiolytic and muscle-relaxant action. Doses up to 300 mg did not induce any significant changes in the cardiovascular and respiratory system in humans.
Laboratory studies on sleep showed that ANSEREN reduces the sleep latency, prolonging its duration and reducing night awakenings; ANSEREN determined mild decreases in sleep stage 3-4 and REM.

5.2 Pharmacokinetic properties

Absorption
After oral administration, ketazolam is rapidly absorbed; peak plasma concentrations is reached approx. 3 hours after dosing and plasm levels are dose-proportional for a range of 15 to 45 mg/day.
After repeated dosing steady state is reached at days 7-14. In vitro, ketazolam plasma protein binding is 93% (up to concentrations of 3000 ng/ml).
Biotransformation
Ketazolam mean half-life is approx. 2 hours, that of its metabolites ranges bewteen 34 and 52 hours. Its main active matobolites are diazepam, N-demethylketazolam and N-demethyldiazepam.
Elimination
Ketazolam is extensively matobolized and eliminated mainly with urine, where only traces of the unchanged compound may be found; the most important metabolite in urine is conjugated oxazepam.
17% of the total dose is eliminated via faeces.

5.3 Preclinical safety data

Acute toxicity data, in laboratory animals, are the following:

Animal species	*Administration route*	LD_{50} *(mg/kg)*
Mice	Intraperitoneal	2618
Mice	Oral	> 5000
Rats	Intraperitoneal	3911
Rats	Oral	> 5000

Single doses up to 1000 mg were relatively well tolerated in dogs and monkeys.
In chronic toxicity studies in rats, with doses of 10, 30 and 100 mg/kg/day for 15 months, signs of toxicity (ataxia) were observed only at the highest dosage; dogs treated for 2 years with doses of 1.3 and 10 mg/kg/day showed no sign of toxicity.
Studies on mice, rats and rabbits indicated that ketazolam is not teratogenic; also mutagenicity and carcinogenic potential testing were negative.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ANSEREN 15 mg capsules, hard
Carmellose calcium; vegetable oil hydrogenated.
Capsule components: gelatine, Titanium dioxide (E171).

ANSEREN 30 mg capsules, hard
Carmellose calcium; vegetable oil hydrogenated.
Capsule components: gelatine, Titanium dioxide (E171), indigo carmine (E132).

ANSEREN 45 mg capsules, hard
Carmellose calcium; vegetable oil hydrogenated.
Capsule components: gelatine, Tìtitanium dioxide (E171), indigo carmine (E132).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

ANSEREN 15 mg & 30 mg: 2 years
ANSEREN 45 mg: 3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister material: opaque PVC
ANSEREN 15 mg capsules, hard: carton with 30 hard capsules, 15 mg
ANSEREN 30 mg capsules, hard: carton with 15 hard capsules, 30 mg
ANSEREN 45 mg capsules, hard: carton with 10 hard capsules, 45 mg

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

PHOENIX LABS
Suite 12, Bunkilla Plaza, Bracetown Business Park,
Clonee Co Meath,
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

ANSEREN 15 mg capsules, hard: MA no. 026380030
ANSEREN 30 mg capsules, hard: MA no. 026380028
ANSEREN 45 mg capsules, hard: MA no. 026380016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th February, 1987
Date of latest renewal: 1st June, 2010

10. DATE OF REVISION OF THE TEXT

28-09-2019