SUMMARY OF THE PRODUCT CHARACTERISTICS

1. **DRUG DENOMINATION**
   LORMETAZEPAM ABC
   2,5 mg/ml oral drops, solution

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**
   1 ml of solution contains:
   Active principle: Lormetazepam 2,5 mg

   For the excipients refer to 6.1

3. **PHARMACEUTICAL FORM**
   Oral drops, solution.

4. **CLINICAL INFORMATION**
   4.1. **Therapeutic indications**
   Troubles of getting asleep and sleep continuity, especially on anxious basis.

   4.2. **Posology and administration modality**
   The treatment must be of the shortest possible duration. The patient must be followed with regularity attentively evaluating the necessity of continuing the treatment, with a particular modality when the patient becomes asymptomatic. The treatment total duration varies from a few days to 2 weeks, up to a maximum of 4 weeks, including the period of the gradual suspension.
   Unless medical different prescription the individual dose in adults is 1-2 mg (1 mg is equal to 10 drops).
   In the old patients the individual dose is 0.5 - 1 mg. The treatment should be started with the lowest dose, to be incremented having care not to exceed the maximum dose, and for the possible shortest time. In case of prolonged treatment (exceeding two weeks) the LORMETAZEPAM ABC administration shall not be suspended suddenly, since the sleep troubles could temporary resume with stronger intensity. For such reason it is recommended to conclude the treatment through a gradual reduction of the doses, facilitated also by the pharmaceutical forms. In determinate cases it may be necessary the extension beyond the period of maximum treatment; in such case, this should not happen without a previous review, by the physician, of the patient conditions. In subjects with altered kidney functionality the lormetazepam biological half-life is not prolonged, whilst the glycuronic metabolite biological half-life is increased and the relevant elimination through the biliary tract; the medicinal drug clinical effects are not therefore modified, inasmuch as the glycurol-conjugation makes it inactive. Hepatic disorder does not substantially influence the drug inactivation. The availability of the drop formulation makes the posology modality easy. The drops must be taken diluted in a small amount of liquid half an hour before going to sleep.

   4.3. **Contraindications**
   Hypersensitivity to the active principle or to any one of the excipients. Myasthenia gravis. Narrow angle glaucoma. Severe respiratory insufficiency. Severe liver failure. Night apnea syndrome.
Generally contraindicated in pregnancy and breast-feeding (see paragraph 4.6).

4.4. **Special cautions and suitable use precautions**
The benzodiazepine and the benzodiazepine-similar agents are only indicated when the trouble is severe, disabling or submit the subject to a serious discomfort.

**Tolerance.**
After a repeated use for some weeks it may develop a certain loss of efficacy towards the hypnotic effects of the benzodiazepine.

**Dependence.**
The benzodiazepine use may result in the development of tolerance, physical and psychic dependence on these medicines. The dependence risk increases with the dose and treatment duration; this is higher in patients having a story of drug or alcohol addiction.

Once the physical dependence has been developed, the treatment abrupt interruption will be followed by abstinence syndrome. It may be found headache, muscular ache, extreme anxiety, tension, restlessness, confusion and irritability. In the serious cases the following symptoms may be evidenced: de-realization, de-personalization, hyperacusia, extremities numbness and formication, hypersensitivity to the light, to the noise and to the physical contact, hallucinations or epileptic crises. Insomnia and rebound anxiety: at the treatment interruption may arise a transient syndrome in which recur, in aggravated form, the same symptoms which have led to the benzodiazepine treatment and sometimes other reactions, including mood changes, anxiety, restlessness or sleep troubles.

Since the risk of abstinence syndrome or rebound is greater after the abrupt treatment suspension, it is recommended to perform a gradual dosage reduction.

**Treatment duration.**
The treatment duration should be as brief as possible (see 4.2 “Posology and administration modality”) in relation to the indication, and it should not exceed the four weeks for the insomnia, including a period of gradual suspension. The therapy extension, beyond these periods, should not occur without the re-evaluation of the clinical situation.

It is important that the patient be informed of the rebound phenomena in order to minimize the anxious reaction that the contingent appearance of such symptoms could cause at the drug treatment suspension.

There are elements to be foreseen which, in the case of the benzodiazepine use with a short action duration, the abstinence syndrome could become manifest inside the interval of administration between a dose and the other, particularly in the case of high dosage. When long action benzodiazepine duration are used, it is important to warn the patient that the sudden change with a benzodiazepine brief action duration is not advisable, as abstinence syndrome may arise.

**Amnesia.**
The benzodiazepine may lead to anterograde amnesia. This happens more often several hours after the drug assumption and then, to reduce the risk it must be ascertained that the patient could have an unbroken sleep of 7-8 hours (see 4.8 “Undesired effects”).

**Psychiatric and paradoxical reactions.**
It is common knowledge that with the benzodiazepine use may arise reactions like relentlessness, agitation, irritability, aggressiveness, delirium, anger, nightmare, hallucinations, psychosis, behavior alterations. Should this happen, the use of the
medicine should be suspended. Such reactions are more frequent in children and old patients.

**Specific groups of patients.**
The benzodiazepine should not be administered to children without an attentive evaluation of the real necessity of the treatment; the treatment duration must be the shortest possible. The ancients should take a reduced dose (see 4.2 “Posology and administration mode”). Similarly a reduced dose is recommended for patients suffering with chronic respiratory insufficiency because of the risk of a respiratory depression. The benzodiazepines are not indicated in patients with serious hepatic insufficiency since these kind of medicines may cause the hepatic insufficiency evolution. The benzodiazepines are not suggested for the primary treatment of the psychotic disease. The benzodiazepines should not be used as the sole remedy for treating the depressive disorder or anxiety connected with depression (suicide may be precipitated in such patients). The benzodiazepines should be used with extreme attention in patients with a story of drug addiction or alcohol abuse. This medicinal product contains only small quantity of ethanol (ethyl alcohol): less than 100 mg per dose.

4.5. **Interactions with other medicines and other forms of interactions**
The concurrent assumption of the medicinal and alcohol must be avoided since the sedative effect might be increased. This negatively influences the driving capacity or the use of machineries.

**Association with medicinal drugs which depress the SNC (Central Nervous System).**

The central depressive effect may be increased in the cases of concurrent use of anti-psychotic (neuroleptics), hypnotics, tranquillizers/sedatives, anti-depressives, analgesics narcotics, anti-epiletics, anesthetics and antihistamine sedatives. In the case of the analgesics narcotics it may be found an increase of the euphoria which may lead to an increase of the psychic dependence.

Aggregates inhibiting specific hepatic enzymes (particularly cytochrome P450) may increase the benzodiazepine activity. In a lower grade, this is applied also to the benzodiazepine which are metabolized only through conjugation.

4.6. **Pregnancy and breast feeding**

If the product is prescribed to a woman in fertile age, she will have to contact her own physician, either if she intend to initiate a pregnancy or if she suspects to be pregnant, as to what concerns the medicine suspension.

If, for medical serious motivations, the product is administered during the last period of the pregnancy, or during the childbirth labor at the high doses, there may have effects on the newborn such as hypothermia, hypotonia and moderate respiratory depression due to the medicine pharmacologic action.

In addition to, newborn children, born from mothers who have taken chronically benzodiazepine during the pregnancy advanced phases may develop physical dependence and may present a certain risk of developing the abstinence symptoms in the post-born period. Since the benzodiazepine are excreted into the maternal milk, they should not be administered to the mother during breast-feeding.

4.7. **Effects on the capacity of driving vehicles and of using machineries**
The sedation, the amnesia, the alteration of the concentration and of the muscular function as well, may negatively influence the driving capacity of driving or of using machineries. If the sleep duration has been insufficient, the probability that the vigilance be altered may be increased (see 4.5 “Interactions with other medicines and other forms of interactions”).

4.8. **Undesired effects**
LORMETAZEPAM ABC is, generally, well tolerated.
If the posology is not adapted to the individual exigencies, may, anyway, appear the following undesired effects: sleepiness during daytime, dullness of the emotions, reduction of the vigilance, confusion, fatigue, headache, dizziness, muscular weakness, ataxia, double vision. These phenomena appear mainly at the start of the therapy and usually disappear with the subsequent administrations. Occasionally, other adverse reactions have been signaled, which comprise: gastrointestinal disorder, libido alterations and reactions on the dermis.

Amnesia.

Anterograde amnesia may show up also at therapeutic dosages; the risk increases at the higher dosages. The amnesia effects may be associated with behavior alterations (see 4.4 “Specific cautions and use precautions”).

Depression.

During the use of benzodiazepine may be unmasked a pre-existent depression state. The benzodiazepine and benzodiazepine-similar aggregates may cause reactions like: restlessness, aggressiveness, delirium, anger, nightmares, hallucinations, psychosis, behaviour alterations. Such reactions may be quite serious. They are more probable with children and old people.

Dependence.

The use of the benzodiazepine (also at the therapeutic doses) may lead to the development of physical dependence: the therapy suspension may cause rebound abstinence phenomena (see 4.4 “Specific cautions and precautions for use”). It may arise psychic dependence. It has been signaled the benzodiazepine abuse.

4.9. Overdosage

AS for the other benzodiazepine, an excessive dose of LORMETAZEPAM ABC should not present a life risk, unless there is a concurrent assumption of other antidepressants of the SNC (Central Nervous System) (including alcohol). In the over-dosage treatment of any medicine, it should be considered the possibility that other substances have also been concurrently taken.

The benzodiazepine over-dosage usually occurs with various degree of central nervous system depression which varies from darkening of mind to coma. In the light cases, the symptoms include mind obnubilation, mind confusion and lethargy. In the serious cases, the symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and, very rarely, death.

As a consequence of an excessive dose of benzodiazepine for oral use it should be induced the emesis (within one hour) if the patient is conscious, or it should be carried out the gastric washing with protection of the respiratory tract if the patient is in a state lacking conscious awareness.

If an improvement is not observed with the emptying of the stomach, it should be administered activated carbon in order to reduce the absorption. Special attention should be dedicated to the respiratory and cardiovascular functions in the urgency therapy. The “Flumazenil” may be useful as an antidote.

5. PHARMACOLOGIC PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutical category: hypnotic and sedative, benzodiazepinic derivatives, code ATC: N05CD06

In the course of the studies on the animals for the substance neuro-pharmacologic characterization it has been found out that the lormetazepam possesses the typical sedative action spectrum of the benzodiazepines.
As for the hypnotic-sedative action, the lormetazepam has shown to possess an effect (reduction of the motor activity) five times greater than that of the lorazepam and ten times greater than that of the flurazepam and of the diazepam. Out of the effect on the central nervous system the lormetazepam does not perform pharmacodynamic actions on the respiratory, cardiocirculatory and renal excretory functions. Lormetazepam, in addition, has no interference either on the hepatic function or on the glycicidal metabolism.

5.2. Pharmacokinetic properties
From the animal and man pharmacokinetic studies derives the lormetazepam classification among the brief-action duration hypno-inducting benzodiazepine: After oral administration the drug is rapidly and completely absorbed with the maximum plasmatic peak achievement within 2 hours ca.. Already at 30 minutes from administration, lormetazepam is found non-modified in plasma, conjugated with glycuronic acid. The benzodiazepine, which does not suffer metabolic demolitions, binds itself for more than 85% together with the plasmatic proteins. The plasmatic concentration decreases into two subsequent phases with halving times of about 2 hours (distribution phase) and about 10 hours (elimination phase). The lormetazepam is excreted almost completely through the urinary system under the form of unmodified substance conjugated with glycuronic acid. Only 5% of the administered dose is found in the urines as N-de-methylate metabolite not conjugated.

5.3. Pre-clinic safety data
Lormetazepam presents a very low acute toxicity.

<table>
<thead>
<tr>
<th>Animal Species</th>
<th>DL₅₀ per os</th>
<th>DL₅₀ i.p.</th>
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<tbody>
<tr>
<td>Mouse</td>
<td>1400-2000</td>
<td>1500-2000</td>
</tr>
<tr>
<td>Rat</td>
<td>&gt;5000</td>
<td>&gt;5000</td>
</tr>
<tr>
<td>Dog</td>
<td>&gt;2000</td>
<td>- -</td>
</tr>
<tr>
<td>Monkey</td>
<td>&gt;2000</td>
<td>- -</td>
</tr>
</tbody>
</table>

DL₅₀ (mg/Kg) after lormetazepam individual administration
After long term toxicologic studies, conducted on rodents, dogs and monkeys, it follows that the lormetazepam is chronic toxicity-free and can then be safely used also for long periods.
Finally, there were not shown indicative data, both for possible mutational, embryo-toxical or teratogen action, and neither at very long term, for possible cytotoxic or carcinogenic action.

6. PHARMACEUTICAL INFORMATION
6.1. Excipients list
Oral drops
Sodium saccharin, glycerol 85 per cent, ethanol 96 per cento, orange aroma, lemon essence, caramel aroma and propylene glycol.

6.2. Incompatibility
Not pertinent

6.3. Validity period
Oral drops: 5 years
The validity period after bottle first opening is 30 days.

6.4. Special precautions for the conservation
Do not keep above 25°C.

6.5. Nature and content of container
Oral drops:
20 ml type III glass bottle, with polyethylene drop-counter and secured with a white polypropylene capsule of the “Child proof” type with internal polythene covering.

6.6. **Instructions for use and manipulation**
No particular instruction.

7. **MARKETING AUTHORIZATION HOLDER**
ABC FARMACEUTICI S.P.A. – Corso Vittorio Emanuele II, 72 – 10121 Torino

8. **NUMBER OF THE MARKETING AUTHORIZATION**
2,5 mg/ml drops: A.I.C. n. 039304011

9. **DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION**
August 2011

10. **TEXT REVISION DATE**
August 2011