SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Levomethadone Molteni 5 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One millilitre of oral solution contains 5 mg of levomethadone hydrochloride.

Excipient(s) with known effect: one millilitre of oral solution contains 1.5 mg of methyl parahydroxybenzoate (E218).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

Clear and colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Substitution therapy for maintenance of opioid dependence in adults in conjunction with appropriate medical, social and psychosocial care.

4.2 Posology and method of administration

Levomethadone should preferably be prescribed in special treatment institutions as part of an integrated treatment for substitution therapy in the management of opioid addiction in adults, which includes medical, social and psychological care.

This product is for oral use only, and must not be injected.

Posology

Adults
The dose is established based on the onset of withdrawal symptoms and must be adjusted for each patient according to the individual situation and to the subjective perception. Generally once the dosage is established, the minimum maintenance dose should be aimed at.

In order to prevent overdosing, 15 to 20 mg of the initial dose of levomethadone hydrochloride (equal to 3 to 4 ml of solution) are taken on the first day, in the morning. Depending on the subjective and objective effect, the dose of 10 to 25 mg of levomethadone hydrochloride (equal to 2 to 5 ml of solution) needed in addition is administered in the evening of the first day. In patients with a low or unknown tolerance threshold (for example following a release from imprisonment) the initial dose should not exceed 15 mg of levomethadone hydrochloride (3 ml of solution).

After 1 to 6 days the daily dose is administered once a day, in the morning. The switch to once daily dosing in the morning is usually carried out stepwise with 5 mg of levomethadone hydrochloride (1 ml of solution).

In case of insufficient efficacy (onset of withdrawal symptoms) the physician may increase the dose by 5 to 10 mg of levomethadone hydrochloride (1-2 ml of solution), daily.

The maintenance dose is usually reached after 1 to 6 days and it can be up to 60 mg of levomethadone hydrochloride (12 ml of solution) and in exceptional cases it can be considerably higher. A dose higher than 50-60 mg of levomethadone hydrochloride may be administered in exceptional cases of proven necessity only, after having excluded reliably the concomitant use of other narcotic substances.

Note:
As a consequence of interactions and/or enzymatic induction caused by other medicinal products (see section 4.5) the daily dose of levomethadone needed can be increased. For this reason, even patients with adjusted stable treatment should be monitored for possible withdrawal symptoms and the dose further adjusted, if needed.

Levomethadone is approximately twice as active as the methadone racemate. There is evidence that the metabolism of levomethadone is increased secondary to the administration of methadone racemate so that the ratio ratio may be altered especially in cases of switching between racemic mixture to levometadone product. As consequence, in these cases, the dosing regimen has to be individualized carefully (see section 4.4).

Elderly patients
It is recommended to reduce the dose in elderly patients.

Patients with renal and hepatic impairment or in bad general conditions
It is recommended to reduce the dose in patients with renal impairment or severe chronic liver disorders or in bad general conditions.

Paediatric population
The safety and efficacy of levomethadone in children and adolescents under 18 years have not been established.
Levomethadone Molteni is contraindicated in children and adolescents under 18 years (see section 4.3).

Method of administration

Levomethadone Molteni is for oral use only.
The prescribed dose is usually diluted with water or fruit juice (e.g. orange juice, raspberry syrup).

The solution contained in the 100 ml bottle can be withdrawn via the luer lock using a graduated

commercially available disposable syringe. The syringe without needle is mounted on the luer lock. The bottle with the syringe attached is then turned upside down so that the desired amount of solution can be sucked into the syringe. Prior to separating the syringe from the bottle the bottle should be brought back into an upright position to avoid the leakage of solution. Also, the bottle must be kept in its upright position in case any excess amount of solution withdrawn shall be filled back into the bottle. Otherwise the solution may leak from the exhaust valve of the luer lock.

From the 500 ml or the 1000 ml bottle, the solution can be withdrawn at the dispensing site using e.g. a commercially available calibrated dispenser.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- Concurrent administration with MAO inhibitors or within 2 weeks of discontinuation of treatment with them.
- During the treatment with levomethadone, narcotic antagonists or other agonists/antagonists (e.g. pentazocine and buprenorphine) must not be administered, except for the treatment of overdose.
- Respiratory depression
- Obstructive airways disease.
- Patients dependent on non-opioid drugs.
- Children and adolescents under 18 years.

4.4 Special warnings and precautions for use

Careful evaluation of the indication and special medical monitoring are necessary in case of:

- Pregnancy and lactation (see section 4.6).
- Reduced consciousness.
- Concomitant use of medicinal products or substances that depress the central nervous system and the respiration respectively.
- Pathological states in which respiratory depression needs to be avoided.
- Moderate to severe disorders of the respiratory centre and the respiratory function.
- Increased intracranial pressure.
- Hypotension in case of hypovolemia.
- Prostatic hypertrophy with urinary retention.
- Pancreatitis.
- Biliary disorders.
- Obstructive and inflammatory intestinal diseases.
- Pheochromocytoma.
- Hypothyroidism.
- Known or suspected prolongation of the QT interval or electrolyte imbalance, in particular hypopotassemia.
- Bradycardia.
- Therapy with class I and class III antiarrhythmics.

Levomethadone should be used with caution in patients with asthma, chronic obstructive pulmonary disease or cor pulmonale and in individuals with a substantially decreased respiratory reserve, pre-existing impairment of the respiratory function, hypoxia or hypercapnia. Even the usual therapeutic doses of

narcotics may reduce the respiratory drive in these patients while in parallel the respiratory resistance can increase to the point of apnoea. In patients especially prone to such atopic phenomena an exacerbation of pre-existing asthma, skin rash and altered blood count (eosinophilia) can occur.

The effect of narcotics leading to respiratory depression and their ability to increase the pressure of the cerebrospinal fluid, may be significantly enhanced in case of pre-existing increased intracranial pressure. Considering the therapeutic profile of levomethadone as μ-agonist the active substance should be used with extreme caution and it should be used only if strictly necessary for the treatment of such patients.

Concomitant use of Levomethadone Molteni and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Levomethadone Molteni concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

The use of levomethadone may cause addiction. The discontinuation after either repeated administration and/or in case of opioid addiction or the use of an opioid antagonist cause the onset of a withdrawal syndrome.

Levomethadone Molteni is intended for oral use only. The abuse by intravenous administration of Levomethadone Molteni may have serious undesirable effects such as sepsis, phlebitis or pulmonary embolisms.

The abuse of narcotics and drugs during the substitution therapy may lead to life threatening events and it must absolutely be avoided.

Extreme caution must be taken in the following cases:

- Severe risk patients
  Suicide attempts with opiates, especially combined with tricyclic antidepressants, alcohol and other substances affecting the central nervous system, are part of the clinical features of addiction. Therefore individual evaluation and a treatment schedule possibly including a period of hospitalization should be considered for patients who, despite an appropriate pharmacotherapeutic intervention continue with uncontrolled drug intake and show persistent, highly harmful behavior.

- Acute abdominal conditions
  As with μ-agonists, in general, the use of levomethadone might confound the diagnosis or clinical course in patients with acute abdominal disorders. For this reason patients with symptoms of acute abdomen, receiving substitution therapy, should be closely monitored until the exact diagnosis is established.

- Cardiac arrhythmias
  Cases of QT prolongation and torsade de pointes have been reported during treatment with methadone, particularly at high doses (>100 mg/day) and levomethadone. In patients, for whom the potential benefits of a treatment with levomethadone outweigh the risk of tachycardia, an ECG should

be done before starting the treatment and two weeks after the start, to assess and quantify the effect of levomethadone on the QT interval. Likewise, it is advisable to perform an ECG before increasing the dose.

Moreover, urine samples must be regularly controlled, in order to detect a possible concomitant consumption of narcotics.

When using levomethadone, it is important to consider that levomethadone is about twice as active as the methadone racemate (see also section 4.2).

The use of Levomethadone Molteni may lead to positive results of doping tests. Moreover, the use of Levomethadone Molteni as a doping substance may seriously harm the health of the subject.

Levomethadone Molteni contains the excipient methyl parahydroxybenzoate (E218) which may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

In case of concomitant use of levomethadone with other medicinal products or substances the following interactions need to be considered:

An increase of the depressing effect on the central nervous system and of the respiratory depression may be observed in case of combined use with medicinal products or other substances such as:
- Centrally acting analgesics (also other opioids)
- Alcohol
- Phenothiazine derivatives
- Barbiturates and other hypnotic drugs and narcotics respectively
- Tricyclic antidepressants
- Sedative medicines such as benzodiazepines or related drugs: the concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

In case of medication with MAO inhibitors within 14 days before the use of opioids (pethidine), life threatening effects on the central nervous system, respiration and circulation associated with depressive or excitatory symptoms have been reported. Such reactions cannot be excluded when using levomethadone.

The effect of levomethadone can be enhanced by antihypertensive active substances such as:
- Reserpine
- Clonidine
- Urapidil
- Prazosin

An increase of the plasma concentration of levomethadone and a prolongation of the effects may occur with medicinal products and substances that inhibit the enzymatic metabolism of levomethadone in the liver (cytochrome P450 system) such as:
- Cimetidine
- Antimycotics

- Antiarrhythmics
- Contraceptives

A decrease of the plasma concentration of levomethadone and a shorter duration of action may occur with medicinal products and substances that enhance the enzymatic metabolism of levomethadone in the liver such as:
- Carbamazepine
- Phenobarbital
- Phenytoin
- Rifampicin
- Flunitrazepam

Eventually, this can cause withdrawal symptoms.

In heroin addicted patients or in patients undergoing substitution with methadone, Pentazocine and Buprenorphine may cause withdrawal phenomena (see also section 4.3). Buprenorphine must not be used earlier than 20 hours from the discontinuation of Levomethadone Molteni.

4.6 Fertility, pregnancy and lactation

Pregnancy

Levomethadone crosses the placenta barrier. During pregnancy, levomethadone should be used only when strictly needed and under medical supervision. The chronic administration during pregnancy may cause tolerance and addiction also in the foetus and, after delivery, withdrawal phenomena in the newborn.

In some rare cases, the use in opioid addicted pregnant and breastfeeding patients may be indicated in order to avoid greater damages to the mother and the child.

In case of opioid addicted mothers, the child should be monitored closely for the onset of a withdrawal situation and, for instance, after the weaning or the abstinence of the mother.

During pregnancy the maximum dose of 10 mg of levomethadone per day should not be exceeded if possible; however, a sufficient substitution, adjusted individually, should be considered. It may be advisable to divide the daily dose, in order to avoid peak plasma concentrations in the interest of the fetus. The reduction of the dose or the withdrawal during pregnancy should be carried out always under strict medical control of the pregnant woman and after a careful assessment of all risks. The withdrawal of the newborn should be carried out in a paediatric intensive care unit, as the treatment with Levomethadone Molteni may lead to tolerance and addiction in the foetus and to withdrawal symptoms in the newborn.

Breast-feeding

Levomethadone is excreted in human milk. In case of substitution therapy with levomethadone, breastfeeding is generally not recommended since the effects on the breastfed newborns have not been studied thoroughly. At doses up to 30 mg a day, the level of levomethadone in the human milk is low; therefore, the mother can breastfeed the newborn if medical supervision of both mother and newborn is ensured. Considering the amounts of milk taken from a newborn infant younger than 3 months the quantity of active substance ingested is below the pharmacologically active dose. During the first 3 months after the childbirth, the dosage of levomethadone should be reduced in breastfeeding mothers in order to avoid effects on the newborn resulting from gradually increasing milk quantities consumed.

4.7 Effects on ability to drive and use machines

Levomethadone Molteni has major influence on the ability to drive and use machines, as it may cause drowsiness and reduce alertness.

Patients should not drive or use machines while taking Levomethadone Molteni. The time after which such activities may be safely resumed is extremely patient-dependent and must be decided by the physician.

4.8 Undesirable effects

Often, at the beginning of a substitution treatment there are opioid withdrawal symptoms such as anxiety, anorexia, uncoordinated and quick movements, intestinal cramps, depression, diarrhoea, vomiting, fever, alternate shivering and hot flushes, yawning, goose flesh, loss of weight, tachycardia, running nose, sneeze, miosis, irritability, drowsiness, diffuse pain, weakness, excessive sweating, increased lachrymation, nausea, restlessness, abdominal cramps and tremor.

The incidence of the undesirable effects is classified as follows:

Very common	(≥ 1/10)
Common	(≥ 1/100 to < 1/10)
Uncommon	(≥ 1/1000 to < 1/100)
Rare	(≥ 1/10.000 to < 1/1000)
Very rare	(< 1/10.000)
Not known	(cannot be estimated from the available data)

System organ class (MedDRA)	**Frequency**	**Adverse event**
Metabolism and nutrition disorders	Uncommon to common	Lack of appetite.
Nervous system disorders	Uncommon to common	Dizziness, sedation, confusion, disorientation, headaches, insomnia, restlessness, decreased libido and/or potency, euphoria, dysphoria.
Eye disorders	Uncommon to common	Visual disturbance.
Cardiac disorders	Uncommon to common	Palpitation, bradycardia.
	Rare to very rare	Cardiac arrhythmias (syncopes), cardiac arrest.
Vascular disorders	Rare to very rare	Orthostatic hypotension, impaired circulatory function, shock, seeping haemorrhage.
Respiratory, thoracic and mediastinal disorders	Uncommon to common	Respiratory depression.

System organ class (MedDRA)	Frequency	Adverse event
	Rare to very rare	Respiratory arrest.
Gastrointestinal disorders	Uncommon to common	Vomiting, nausea, dry mouth, constipation.
Hepatobiliary disorders	Uncommon to common	Biliary spasm
Skin and subcutaneous tissue disorders	Uncommon to common	Nettle rash and other types of skin rash, pruritus.
Renal and urinary disorders	Uncommon to common	Reduced urine volume, difficulty to urinate.
General disorders and administration site conditions	Uncommon to common	Excessive sweating, faintness, weakness, oedema.
	Rare to very rare	Flush.

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 listed in Appendix V.

4.9 Overdose

Especially in subjects who are non-tolerant to opioids (children in particular), dangerous intoxications may occur also in case of doses lower than the ones given in the substitution therapy: in children up to 5 years this can happen starting from about 0.5 mg of levomethadone, in older children starting from about 1.5 mg and in adults non-tolerant to opioids starting from about 10 mg.

A dose reduction is recommended if patients show signs and symptoms of excessive levomethadone effects that are characterised by disorders such as: "feeling funny", impaired concentration capability, drowsiness and possibly dizziness when standing.

Moreover overdoses are characterized by respiratory depression (Cheyne-Stokes respiration, cyanosis), excessive drowsiness with tendency to reduced consciousness and even coma, miosis, relaxation of the skeletal muscles, cold and moist skin and sometimes bradycardia and hypotension. Massive intoxications may cause respiratory arrest, circulatory failure, cardiac arrest and death.

Prompt intervention of emergency medicine or intensive care medicine is mandatory (e.g. intubation and ventilation). For treatment of symptoms of intoxication specific opioid antagonists (e.g. naloxone) can be used. The dose of the individual opioid antagonists varies. In particular it is important to take into account that levomethadone may have long lasting depressive action on the respiration (up to 75 hours), while the opioid antagonists have a much shorter action (1 to 3 hours). Therefore, once the antagonistic effects ease off reinjections may be necessary. Measures to prevent the loss of temperature and to substitute the

vascular volume may be necessary.

In case of oral levomethadone intoxication, a gastric lavage may be performed only after administration of an antagonist. Protection of the respiratory ways through intubation both in case of gastric lavage and before the administration of the antagonists (onset of vomiting is possible) is particularly important. In the treatment of the intoxications alcohol, barbiturates, bemegride, phenothiazine and scopolamine must not be used.

Levomethadone is not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other nervous system drugs; drugs used in addictive disorders; drugs used in opioid dependence
ATC code: N07BC05

Levomethadone hydrochloride is a synthetic opioid, a basic diphenylmethane derivative structurally derived from morphine.

Levomethadone is the R(-)enantiomer of methadone. The S(+)enantiomer has only 1/50 of the analgesic effect of the R(-)enantiomer. The clinical effects of levomethadone in the treatment of opiate/opioid addiction are based on two mechanisms: on the one hand levomethadone, as a synthetic opioid agonist produces morphine-like effects that suppress withdrawal symptoms in opiate/opioid addicted subjects. On the other hand, depending on the dose and the duration of the substitution therapy the chronic use of oral levomethadone can lead to tolerance that blocks the effect of parenterally administered opiates subjectively experienced as euphorigenic.

The effect in the substitution therapy starts after 1-2 hours from the oral administration and in case of a single administration lasts from 6 to 8 hours. After repeated dosing the duration of the effect is prolonged up to 22 to 48 hours, due to the pharmacokinetic balance so that a once daily administration is sufficient.

Levomethadone, being an opioid agonist, induces a long lasting respiratory depression that reaches its peak after 4 hours and may last up to 75 hours. Besides the typical effects of the opioids, such as sedation, euphoria and miosis, levomethadone has other pharmacological effects such as bradycardia, increase of the blood pressure, bronchial constriction and anti-diuresis. The long term consumption of levomethadone causes addiction, similar to the one from heroin and morphine.

5.2 Pharmacokinetic properties

Absorption

Levomethadone is rapidly absorbed after oral administration. The absolute bioavailability after oral administration is on average about 82%.

In case of an oral daily dosage of 30 mg, the steady state of levomethadone plasma levels is reached in 4-5

days.

Distribution

The substance has a relatively large volume of distribution of 3-4 l/kg. This means that the strongly lipophilic substance accumulates in considerable amounts in the peripheral tissues, in fat, muscles and skin. About 85% is bound to serum protein predominantly to acid alfa-glycoprotein and albumin.

Biotransformation

So far 32 metabolites of methadone have been identified. 2 pharmacologically active metabolites account for only 2% of the administered dose. Methadone and its metabolites accumulate mainly in lungs, liver, kidney, spleen and muscles.

Elimination

The elimination of methadone and its metabolites takes place in the kidney and in the biles. The elimination via kidneys which strongly depends on the pH value is the main route in case of high dosages; in case of administrations exceeding 160 mg, about 60% is excreted as unchanged methadone. 10 to 45% of the total recovered amount is excreted in the bile.

The terminal plasma half life is subject to considerable individual variability (between 14 and 55 hours). It increases with the duration of therapy, in the elderly and in case of chronic liver diseases.

Levomethadone is not dialysable. However in case of anuria there is no risk of accumulation as at that point the elimination takes place only via the feces.

Special populations

Levomethadone is excreted in human milk and crosses the placenta barrier. The concentration in the blood of the umbilical cord is lower than the plasma concentration of the mother. There is no correlation between the concentration in maternal plasma / blood of the umbilical cord and the levels found in the amniotic fluid.

5.3 Preclinical safety data

In case of acute intoxication, death occurs due to respiratory arrest. The LD_{50} values of levomethadone after intravenous administration are between 13.6 and 28.7 mg/kg in mice and 8.7 mg/kg in rats.

For acute toxicity in humans see section 4.9.

In preclinical studies the main target organs following subchronic and chronic administration are the respiratory system (respiratory depression) and the liver (increased SGTP activity, hypertrophy of the liver cells, eosinophilic cytoplasmic changes).

Mutagenic and carcinogenic potential
In-vitro and in-vivo investigations carried out on the genotoxicity of methadone have shown contradicting results indicating a slight clastogenic potential. Currently, a risk for the clinical use cannot be deduced. Long term studies carried out in rats and mice have not shown evidence of carcinogenic potential.

Toxicity to reproduction
Levomethadone has not been sufficiently studied. Information on D,L methadone can be referred to for the evaluation. The impairment of the sexual function in male patients taking D,L methadone is a known undesirable effect of the substance. In 29 male patients undergoing substitution therapy with methadone the sexual function was evidently impaired. Their volume of the ejaculation and the secretion of the seminal vesicle and the prostate were reduced by more than 50% compared to 16 heroin addicted subjects and 43 subjects of the control group.

In rats, a 5 days administration of a methadone daily dose of 20 mg/kg resulted in a loss of weight of the prostate, seminal vesicle and testes. In the offspring of males treated with methadone (up to 38 mg/kg per day) there was an increased neonatal mortality (up to 74%).

A number of studies in humans has shown that the use of methadone during pregnancy does not imply an evident increase of congenital anomalies and does not affect the childbirth. The children of mothers undergoing a substitution therapy with methadone showed a relatively lower weight at birth and a smaller cranial circumference compared with children that have not been exposed to drugs. Withdrawal symptoms occurred in 56 of 92 newborns of mothers treated with methadone. Furthermore, a greater incidence of otitis media was observed as well as neurological findings with hearing disorders, retardation in the intellective and motor development and eye anomalies. There is a suspect of a relation with an increase of SIDS (Sudden Infant Death Syndrome).

The offspring of methadone addicted female rats have shown a retardation in the postnatal cerebral growth, lower body weight and greater neonatal mortality. The oral administration of methadone to rats between day 14 and day 19 of gestation implied a significant drop of the testosterone blood levels in male offspring (antagonisation with naloxone is possible).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate (E218)
Betaine hydrochloride
Glycerol
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

The solution should be used within 12 weeks of first opening.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Amber coloured 100-ml bottle (type III glass), closed with a tamper-evident child-proof screw cap (PP) and provided with an insert (PE) having a conical fitting for Luer-lock syringes. Pack with one 100-ml bottle or bundle pack with 3 x 100-ml bottles.

Amber coloured 500-ml bottle (type III glass), closed with a tamper-evident child-proof screw (PP) cap. Pack with one 500-ml bottle.

Amber coloured 1000-ml bottle (type III glass), closed with a tamper-evident child-proof screw (PP) cap. Pack with one 1000-ml bottle.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

L. Molteni & C. dei F.lli Alitti Società di Esercizio S.p.A.
Strada Statale 67, Località Granatieri
50018 Scandicci (Firenze)
Italy

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

July 2018