SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mirtazapin Alternova 15 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 15 mg mirtazapine.

Excipient with known effect: Each tablet contains 99 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

Yellow, oblong and biconvex tablets with a scoreline. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Episodes of major depression.

4.2 Posology and method of administration

Method of administration
The tablets should be swallowed whole with an adequate amount of liquid.

Posology
Adults
The starting dose is 15 mg or 30 mg, preferably taken in the evening. The daily maintenance dose is usually between 15 mg and 45 mg pr. day.

Elderly
The recommended dose is the same as for adults. However, dose changes should be carried out with more caution and under closer supervision.

Children and adolescents under 18 years
Should not be used for treatment of children and youth under 18 years (see section 4.4), as efficacy was not demonstrated in two short-term clinical trials (see section 5.1) and because of safety concerns (see section 4.4, 4.8 and 5.1).

Renal impairment
The elimination of mirtazapine can be prolonged in patients with moderate to severe renal impairment (creatinine clearance < 40 ml/min). This should be taken into consideration when prescribing mirtazapine to this category of patients (see section 4.4).

Hepatic impairment
The clearance of mirtazapine may be decreased in patients with hepatic impairment. This should be taken into consideration when the dose is determined and when the clinical response is evaluated. This

is particularly important in patients with severe hepatic impairment, as patients with severe hepatic impairment have not been investigated (see section 4.4).

Mirtazapine can be taken once daily since the elimination half-life is 20-40 hours. The product should preferably be taken as a single dose immediately before bedtime in the beginning of the treatment. The daily dose can also be divided on two doses as a dose in the morning and a dose in the evening. The higher dose should be taken at night.

The first anti-depressive effect is usually seen within 2-4 weeks. After the optimal clinical effect has been achieved the treatment should continue for 4-6 months with the maximal dose until a gradually withdrawal of the treatment is done. To avoid withdrawal reactions the dose should gradually be lowered over a suitable time interval (see section 4.4).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Concomitant use of mirtazapine with monoamine oxidase (MAO) inhibitors (see section 4.5).

4.4 Special warnings and precautions for use

Use in children and adolescents under 18 years of age
Mirtazapin Alternova should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural developments are lacking.

Suicide/suicidal thoughts or clinical worsening
Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.
Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

With regard to the chance of suicide, in particular at the beginning of treatment, only a limited number of mirtazapine tablets should be given to the patient.

Bone marrow depression
Bone marrow depression, usually presenting as granulocytopenia or agranulocytosis, has been reported during treatment with mirtazapine.
In clinical studies with mirtazapine reversible agranulocytopenia has been reported as a rare occurrence. Agranulocytosis, which normally occurs after 4-6 weeks of treatment, has very rarely been reported in the post-marketing period. Most of the cases were reversible, but some cases were fatal.

Fatal cases mostly concerned patients aged 65 years and above. If the patient develops fever, sore throat, stomatitis or other signs indicating an infection the treatment should temporarily be discontinued until the result of the patient's blood picture is obtained.

Conditions which need supervision

Careful dosage and regular and close monitoring are necessary in patients with:

- Epilepsy and organic brain-syndrome. Clinical experience has shown that epileptic seizures rarely occur in patients in treatment with mirtazapine. However, as with other antidepressants, mirtazapine should be introduced cautiously in patients who have a history of seizures. Treatment should be discontinued in any patient who develops seizures, or where there is an increase in seizure frequency.
- Liver problems: Following a single 15 mg oral dose of mirtazapine, the clearance of mirtazapine was approximately 35 % decreased in patients with mild to moderate hepatic impairment compared to subjects with normal hepatic function. The average plasma concentration of mirtazapine was about 55 % increased.
- Kidney problems: Following a single 15 mg oral dose of mirtazapine in patients with moderate (creatinine clearance < 40 ml/min) and severe (creatinine clearance ≤ 10 ml/min) renal impairment, the clearance of mirtazapine was about 30 % and 50 % decreased respectively compared to normal subjects. The average plasma concentration of mirtazapine was about 55 % and 115 % increased respectively. No significant differences were found in patients with mild renal impairment (creatinine clearance < 80 mL/min) as compared to the control group.
- Heart diseases such as conductance disturbances, angina pectoris and recent myocardial infarct where the usual safety precautions should be taken and concomitant medication should be administered carefully.
- Low blood pressure.
- Diabetes mellitus. In patients with diabetes, antidepressants may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted and close monitoring is recommended.

Jaundice

The treatment should be discontinued if jaundice occurs.

Like with all other antidepressants, the following should be taken into account:

- Worsening of psychotic symptoms can occur when anti-depressives are administered to patients with schizophrenia or other psychotic conditions. Paranoid ideas can also be enhanced.
- The risk of suicide is sustained until full therapeutic effect is achieved and can be increased in the beginning of treatment if the restriction and lethargy is lessened before a satisfactory improvement of the condition occurs.
- Even though mirtazapine is not considered to be addictive an abrupt discontinuation of long term treatment can result in withdrawal symptoms. The majority of withdrawal reactions are mild and self-limiting. Among the various reported withdrawal symptoms, dizziness, agitation, anxiety, nausea, headache and general malaise are the most frequently reported. Even though they have been reported as withdrawal symptoms, it should be realized that these symptoms may be related to the underlying disease. As advised in section 4.2, it is recommended to discontinue treatment with mirtazapine gradually.
- When the depressive phase of a bipolar disease is treated it can change into a manic phase. Patients with a history of mania/hypomania should be closely monitored. Mirtazapine should be discontinued in any patient entering a manic phase.
- Elderly patients are often more sensitive to side effects. In clinical studies with mirtazapine there was not reported a higher frequency of side effects in elderly patients compared to other age groups. Clinical experience is however still limited.
- Serotonin syndrome can occur when selective serotonin reuptake inhibitors (SSRI) is mixed with other serotonergic drugs (see section 4.5). Symptoms of serotonin syndrome may be hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma. Caution is advised and closer clinical monitoring is required when these active substances are combined with mirtazapine. Treatment with mirtazapine should be discontinued if such events occur and supportive symptomatic treatment initiated. Post marketing experience

show that serotonin syndrome occurs very rarely with patients that are treated with mirtazapine or with mirtazapine in combination with other SSRI's (see section 4.8).
- Urinary problems such as prostate hypertrophy (even though a worsening is not to be expected, since mirtazapine have a very weak anti-cholinergic activity).
- Acute narrow-angle glaucoma and elevated intraocular pressure (also here it is a very small risk of problems during the mirtazapine treatment due to the very weak anti-cholinergic effect).
- Akathisia/psychomotor restlessness: The use of antidepressants have been associated with the development of akathisia, characterized by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Hyponatraemia
Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported very rarely with the use of mirtazapine. Caution should be exercised in patients at risk, such as elderly patients or patients concomitantly treated with medications know to cause hyponatraemia.

This product contains lactose monohydrate. Therefore it should not be used for patients with hereditary galactose intolerance, a special form of hereditary lactase deficiency (Lapp Lactase deficiency) or glucose/galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
Mirtazapine should not be given concomitantly with MAO-inhibitors or within 2 weeks after stopping treatment with MAO-inhibitors. Treatment with MAO inhibitors can be initiated about two weeks after withdrawal of mirtazapine (see section 4.3).

Mirtazapine can increase the CNS-depressant effect of alcohol. Patients should therefore be advised to avoid alcohol during the treatment with mirtazapine.

Mirtazapine may increase the sedating properties of benzodiazepines and other sedatives (notably most antipsychotics, antihistamine H1 antagonists, opioids). Caution should be exercised when these medicinal products are prescribed together with mirtazapine.

If other serotonergic drugs (e.g. SSRI, L-tryptophan, triptans, tramadol, linezolid, lithium, St. John's Wort and venlafaxine) are used concomitantly with mirtazapine there is a risk of interaction that may lead to development of serotonin associated effects (serotonergic syndrome, see section 4.4). Post marketing experience have shown that serotonergic syndrome occur very rarely in patients treated with mirtazapine in combination with SSRI's or venlafaxin. If the combination is judged to be necessary dose changes should be done carefully and under suitable monitoring of signs of beginning serotonergic overstimulation.

In patients treated with warfarin, mirtazapine dosed with 30 mg once daily caused a small but statistically significant increase in INR. Since it cannot be excluded that higher doses of mirtazapine can cause a more pronounced effect it is advisable to monitor INR in case of concurrent treatment with warfarin and mirtazapine.

Pharmacokinetic interactions
Mirtazapine is metabolised almost completely by CYP2D6 and CYP3A4 and to a small extent by CYP1A2. An interaction study with healthy volunteers showed that paroxetine, a CYP2D5-inhibitor, had no influence on the steady state pharmacokinetics of mirtazapine. Concomitant administration of the potent CYP3A4-inhibitor ketoconazol increased the peak-plasma level and AUC of mirtazapine with 40 % and 50 % respectively. Caution should be taken when mirtazapine is administered concomitantly with potent CYP3A3-inhibitors such as HIV-protease inhibitors, azole fungicides, erythromycin and nefazodone.

Phenytoin and carbamazepine, which induce CYP3A4, caused mirtazapine clearance to double, which lead to fall in plasma concentration of respectively 45 % and 60 %. When carbamazepine or another inducer of drug metabolism (e.g. rifampicin or phenytoin) is used with mirtazapine, the dose of mirtazapine may need to be increased. If the treatment with the inducer is terminated the dose of mirtazapine may need to be reduced.

The bioavailability of mirtazapine increased with more than 50 % when taken together with cimetidine (weak inhibitor of CYP1A2, CYP2D6 and CYP3A4). Caution should be exercised, and the mirtazapine dose should maybe be reduced when concomitant treatment with cimetidine or potent CYP3A4 inhibitors, HIV protease inhibitors, azole antifungals, erythromycin or nefazodone is begun and increased when the treatment with cimetidine is ended.

In vitro data suggest that mirtazapine is a very weak competitive inhibitor or CYP 1A2, 2D6 and 3A4.

In *in vitro* interaction studies mirtazapine did not influence pharmacokinetic for risperidone or paroxetine (CYP2D6 substrate), carbamazepine (CYP3A4 substrate), amitriptyline or cimetidine.

No clinical influence or changes in pharmacokinetic in man by concomitant administration of mirtazapine and lithium have been observed.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is not adequate data from use of mirtazapine tablets for pregnant women. Limited data do not indicate an increased risk of congenital malformations. Animal tests have not shown any teratogenic effects of clinical relevance, but they have shown reproductive toxicity and developmental toxicity (see section 5.3). The potential risk in humans is unknown.

Mirtazapine tablets should not be used during pregnancy unless it is strictly necessary after a thorough clinical judgement of risks and benefits. Caution should be exercised when prescribing to pregnant women. If mirtazapine is used until, or shortly before birth, postnatal monitoring of the newborn is recommended to account for possible withdrawal effects.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated the association of PPHN to mirtazapine treatment, this potential risk cannot be ruled out taking into account the related mechanism of action (increase in serotonin concentrations).

Lactation
Mirtazapine is excreted in the breast milk in sufficient degree that an effect on the nursing child is likely if therapeutic mirtazapine doses are given to breast feeding women. Mirtazapine should not be used during breast feeding. Animal studies and limited human data have shown excretion in breast milk only in very small amounts. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with mirtazapine should be made after evaluation of the benefit of breast-feeding to the child and the benefit of mirtazapine to the mother.

4.7 Effects on ability to drive and use machines

Mirtazapin can weaken the ability to concentrate and reduce alertness (particularly at the beginning of treatment). This should be considered before undertaking tasks that require concentration such as driving a car or operating dangerous machinery.

4.8 Undesirable effects

Depressed patients have a number of symptoms that are due to the disease itself. It is sometimes difficult to distinguish which are consequences of the illness itself and which are consequences of treatment with Mirtazapine.

The most commonly reported adverse reactions, occurring in more than 5 % of patients treated with mirtazapine in randomized placebo-controlled trials (see below) are somnolence, sedation, dry mouth, weight increase, increased appetite, dizziness and fatigue.
All randomized placebo-controlled trials in patients (including indications other than major depressive disorder) have been evaluated for adverse reactions. The meta-analysis considered 20 trials with a planned duration of treatment of up to 12 weeks, with 1501 patients (134 patient years) receiving doses of up to 60 mg mirtazapine and 850 patients (79 patient years) receiving placebo. Extension phases of these trials have been excluded to maintain comparability to placebo treatment.

Table 1 shows the categorized incidence of adverse reactions which occurred in the clinical trials statistically significantly more frequently during treatment with mirtazapine than with placebo, added with adverse reactions from spontaneous reporting are based on the reporting rate of these events in the clinical trials. The frequency of adverse reactions from spontaneous reporting for which no cases in the randomized placebo-controlled patient trials were observed with mirtazapine has been classified as 'not known'.

Table 1

	Very common (≥ 1/10)	Common (≥1/100 to <1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders				Acute bone marrow depression (eosinophilia granulocyto-penia, agranulocyto-sis, aplastic anaemia and thrombocyto-penia). See also Section 4.4	
Endocrine disorders					Inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	Greater appetite[1] and weight increase[1].				Hypo-natraemia
Psychiatric disorders		Abnormal dreams. Confusion. Anxiety[2, 5]. Insomnia[3, 5]	Nightmares[2]. Mania. Agitation[2]. Hallu-cinations. Psychomotor restlessness (including	Aggression.	Suicidal ideation[6]. Suicidal behaviour [6]

			akathisia, hyperkinesia)		
Nervous system disorders	Somnolence[1,4]. Sedation, especially in the first weeks of treatment[1,4]. Headache[2]	Lethargy. Dizziness. Tremor.	Paraesthesia[2]. Restless legs. Syncope	Myoclonus.	Convulsion (insults). Serotonin syndrome. Oral paraesthesia. Dysarthria
Vascular disorders		Orthostatic hypotension. Generalised or local oedema and consequent increase in weight.	Hypotension[2].		
Gastrointesti-nal disorders	Dry mouth.	Nausea[3]. Diarrhoea[2]. Vomiting[2].	Oral hypoesthesia.	Pancreatitis.	Mouth oedema. Increased salivation.
Hepatobiliary disorders				Elevated serum liver enzyme levels.	
Skin and subcutaneous tissue disorders		Exanthema[2].			Stevens-Johnsons syndrome. Dermatitis bullous. Erythema multiforme. Toxic epidermal necrolysis.
Musculoskel e-tal and connective tissue disorders		Arthralgia. Myalgia. Back pain[1]			
General disorders and administratio n site conditions		Oedema peripheral[1]. Fatigue			Somnambulism

[1] In clinical trials these events occurred statistically significantly more frequently during treatment with mirtazapine than with placebo.
[2] In clinical trials these events occurred more frequently during treatment with placebo than with mirtazapine, however not statistically significantly more frequently.
[3] In clinical trials these events occurred statistically significantly more frequently during treatment with placebo than with mirtazapine.
[4] N.B. dose reduction generally does not lead to less somnolence/sedation but can jeopardize antidepressant efficacy.
[5] Upon treatment with antidepressants in general, anxiety and insomnia (which may be symptoms of depression) can develop or become aggravation. Under mirtazapine treatment, development or aggravation of anxiety and insomnia has been reported.

6 Cases of suicidal ideation and suicidal behaviours have been reported during mirtazapine therapy or early after treatment discontinuation (see section 4.4).

In laboratory evaluations in clinical trials, transient increases in transaminases and gamma-glutamyltransferase have been observed (however associated adverse events have not been reported statistically significantly more frequently with mirtazapine than with placebo).

Paediatric population
The following adverse events were observed commonly in clinical trials in children: Weight gain, urticaria and hypertriglyceridemia (also see section 5.1).

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

Experience (although still limited) with overdose of mirtazapine alone show that the symptoms are usually mild. There have been reports of effects on the central nervous system with disorientation and longer-lasting sedation coupled with tachycardia and slight hyper- or hypotension. However, there is a possibility of more serious outcomes (including fatalities) at dosages much higher than the therapeutic dose, especially with mixed overdoses.
In the event of overdosing a stomach lavage should be performed along with appropriate symptomatic and supportive treatment of vital functions. Activated charcoal should also be considered.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group; other antidepressants, ATC code: N06AX11

5.1 Pharmacodynamic properties

Mirtazapine is a tetracyclic piperazinoazepine analogue of mirtazapine and has a chemical structure unrelated to TCA's, MAO-inhibitors or SSRI's. It is used to treat episodes of major depression. Mirtazapine is regarded as being of special clinical value for the treatment of depressed patients who are afflicted by pronounced anxiety or sleep disorders at the same time.

Mirtazapine is a pre-synaptic α_2-antagonist that enhances central noradrenergic and serotonergic neurotransmission in the central nervous system. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT_1 receptors because 5-HT_2 and 5-HT_3 receptors are blocked by mirtazapine. Both of the enantiomers of mirtazapine are thought to contribute the antidepressant effect—the S(+) enantiomer by blocking α_2 and 5-HT_2 receptors, and the R(-) enantiomer by blocking 5-HT_3 receptors. The histamine H_1-antagonistic activity of mirtazapine is responsible for whatever sedation occurs during treatment. It has practically no anticholinergic activity and there are almost no cardiovascular side effects when it is given in therapeutic doses.

Paediatric population
Two randomized, double-blind, placebo-controlled trials in children aged between 7 and 18 years with major depressive disorder (n=259) using a flexible dose for the first 4 weeks (15-45 mg mirtazapine) followed by a fixed dose (15, 30, or 45 mg mirtazapine) for another 4 weeks failed to demonstrate significant differences between mirtazapine and placebo on the primary and secondary endpoints. Significant weight gain (≥ 7 %) was observed in 48.8% of the mirtazapine treated subjects compared to 5.7% in the placebo arm. Urticaria (11.8 % vs. 6.8 %) and hypertriglyceridemia (2.9 % vs. 0 %) were also commonly observed.

5.2 Pharmacokinetic properties

Absorption
After peroral intake of mirtazapine tablets the active content of mirtazapine is absorbed swiftly and well (bioavailability ≈ 50 %), and maximal plasma levels are reached after about 2 hours.

Distribution
About 85 % of mirtazapine is bound to plasma proteins. Steady-state is reached after 3-4 days, after which there is no further accumulation mirtazapine exhibits a linear pharmacokinetic within the recommended dosage range.

Biotransformation and elimination
Mirtazapine is metabolised effectively and eliminated with the urine and faeces within a few days. Biotransformation mainly takes place via demethylation and oxidation, followed by conjugation. In vitro studies with human liver microsomes show that cytochrome P450 and the enzymes CYP2D6 and CYP1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas the CYP3A4 enzyme is considered responsible for the formation of N-demethyl and N-oxide metabolites. The demethyl metabolite is pharmacologically active and its pharmacokinetic profile does not fit the non-metabolised drug.
The average half-life is 20-40 hours. Longer half-life times up to 65 hours are occasionally seen but the half-life time is usually shorter in young men.

Special populations
The clearance of mirtazapine may be reduced in patients with kidney or liver insufficiency.

5.3 Preclinical safety data

Preclinical data show no special risks to humans based on conventional studies of safety pharmacology, toxicity of repeated dosage, genotoxicity or carcinogenicity.

Reproductive toxicity studies have shown that mirtazapine caused embryotoxicity and resulted in a lower survival rate of offspring at exposure doses equal to or a bit higher than therapeutic exposure levels.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, corn starch, hydroxypropyl cellulose, colloidal anhydrous silica, magnesium stearate.

Film coating: Hypromellose, macrogol 8000, titanium dioxide (E171), quinoline yellow (E 104), sunset yellow FCF (E110) and yellow iron oxide (E172).

6.2 Incompatibilities

Not relevant.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blisters

Pack sizes: 14, 28, 30, 56, 60, 70, 90 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not relevant.

7. MARKETING AUTHORISATION HOLDER

Alternova A/S
Lodshusvej 11
4230 Skælskør
Denmark

8. MARKETING AUTHORISATION NUMBERS

33131

9. DATE OF FIRST AUTHORISATION

14 February 2003

10. DATE OF REVISION OF THE TEXT

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