4.1 Therapeutic Uses

EXPTL Therapy: 114 patients with chronic tension headache (more than 10 days per month for at least 6 months) were treated with placebo, clomipramine or mianserin in a double blind parallel group comparison. Eighty-two patients completed the study. Headache pain was scored weekly on visual analogue scales for the 6 weeks of treatment. Observer-rating of headache was made at entry, after 3 weeks and after 6 weeks of treatment. In all groups, headache complaints decreased significantly compared to baseline. With the main parameter the decrease on both clomipramine and mianserin was significant compared to placebo. Although the trend was the same for the other parameters, the changes relative to placebo did not reach statistical significance.

Langemark M et al; Headache 30 (3): 118-21 (1990)

Mianserin is a tetracyclic compound advocated for the treatment of depressive illness and depression associated with anxiety. It combines antidepressant activity with a sedative effect and has an EEG and clinical activity profile similar to that of amitriptyline. It has an overall efficacy comparable with amitriptyline and imipramine in depressive illness, but at dosages which have achieved a similar overall clinical improvement, mianserin causes significantly fewer anticholinergic side effects than amitriptyline or imipramine and also appears less likely than these drugs to cause serious cardiotoxicity on overdosage. Mianserin also has anti-anxiety activity, but its role in treating patients with anxiety associated with primary depression has still to be clarified. Mianserin appears to be well tolerated by the elderly and by patients with cardiovascular disease, including those recovering from a recent myocardial infarction, and does not appear to antagonise the action of adrenergic neurone blocking antihypertensive drugs or affect the anticoagulant action of phenprocoumon.

Brogden RN et al; Drugs 16 (4): 273-301 (1978)

In a 6-week study the efficacy of combined treatment of imipramine plus mianserin was compared to combined treatment of desipramine plus mianserin in patients with post-stroke depression. Patients were required to have a minimum baseline total score of 15 on the 17-item Hamilton Depression Scale (HAMD). The Melancholia Scale (MES) was also used to measure severity of depressive states to show that somatic symptoms had little influence on the evaluation of depression. Out of 120 stroke patients screened, 20 patients fulfilled the inclusion criteria. The doses of the drugs were flexible, using side-effects as a guide during treatment. Both intention to treat analysis and efficacy data (excluding patients who had dropped out during the first 2 weeks of treatment) showed that imipramine (mean dose 75 mg daily) plus mianserin (mean dose 25 mg daily) was superior to desipramine (mean dose 66 mg daily) plus mianserin (27 mg daily). The MES was found to be more sensitive than the HAMD for measuring change in depressive states during treatment. The assessment of side-effects using the UKU /side effect rating scale/ scale showed good tolerance in general. The only

difference between the two treatment groups was seen in micturition disturbances, where the imipramine treated patients had most complaints after 14 days of treatment, but the symptoms disappeared despite continuous treatment.

Lauritzen L et al; Psychopharmacology (Berl) 114 (1): 119-22 (1994)

4.2 Drug Warning
Seizures were observed following the withdrawal of mianserin 60 mg/day for 2 years. To our knowledge, this is the first report of convulsions after suspension of an antidepressant. This phenomenon was observed in a young woman (with no history of epilepsy or other organic diseases that may induce seizures) 10 days after abrupt discontinuation of long-term treatment with mianserin.

De Leo D et al; Ital J Neurol Sci 9 (2): 167-9 (1988)

An alcoholic woman who was admitted to hospital for detoxification was prescribed thyroxine because of hypothyroidism and mianserin to alleviate severe depression. After several weeks' treatment she became unwell and was readmitted to hospital. Haematological examination indicated agranulocytosis. Further extensive investigations elicited no cause for this other than the mianserin, since no such disturbance has been reported for thyroxine after years of use. Thus mianserin is probably implicated in this case of agranulocytosis. Although the response may have been idiosyncratic, it highlights the need to monitor new drugs during the early phases of widespread use.[Curson DA, Hale AS; Br Med J 1 (6160): 378-9 (1979)] Full text: PMC1597989

Forty patients have been reported to the Committee on Safety of Medicines (CSM) because of convulsions occurring during treatment with mianserin, suggesting that this drug is more epileptogenic than tricyclic antidepressants. Details concerning 83% of these cases were obtained in a questionnaire study carried out in collaboration with the CSM and compared with those of a control group. ... As the CSM data do not allow for a reliable assessment of the relative epileptogenic effects of antidepressants, a comparison has been made between unpublished work on seizures occurring during treatment with imipramine and amitriptyline and published research on mianserin. Factors that might predispose to seizures include relevant family and past medical history, starting treatment, a change in dose, benzodiazepine withdrawal and concomitant treatment with other drugs that have epileptogenic properties.

Edwards JG, Glen-Bott M; Br J Clin Pharmacol 15 (Suppl 2) :299S-311S (1983)

Our report concerns 2 patients who developed delirium after an epileptic attack during mianserin treatment. In both cases the EEG showed a change with periodic sharp slow complexes similar to that seen in Creutzfeldt-Jakob disease. The symptoms subsided, however, and the EEG normalized after the antidepressant was discontinued, suggesting a noxious response to mianserin. If Creutzfeldt-Jakob-like changes in the EEG occur, the possible effect of antidepressant medication should be considered.

Koponen H et al; Neuropsychobiology 23 (3): 164-8 (1990-91)

Cardiovascular effects of the tetracyclic antidepressant drug mianserin were examined in a prospective study including ten elderly depressed patients (age 60-77 years). During 1 week on placebo and 5 weeks on mianserin, 60 mg/day, orthostatic blood pressure testing, recording of standard electrocardiogram, 24-hr electrocardiographic recording and systolic time intervals were carried out along with frequent monitoring of plasma levels of mianserin (13-57 ug/L) and the primary metabolite desmethylmianserin (7-27 ug/L). Mianserin caused a significant increase in orthostatic systolic blood pressure drop, and this correlated well with the plasma mianserin levels (rs = 0.70). There were no significant changes in supine blood pressure or in orthostatic changes in heart rate. No cardiac conduction disturbances or arrhythmias were provoked, but mianserin caused changes in systolic time intervals indicating impairment of left ventricular contractility and performance. Like tricyclic antidepressants mianserin should thus be used with caution in patients with latent or overt cardiovascular disease.

Moller M et al; Psychopharmacology (Berl) 80 (2): 174-7 (1983)

Although cardiac arrhythmias with mianserin use are unusual, life-threatening ventricular arrhythmias including polymorphous ventricular tachycardia following an over dose with an unknown amount of mianserin were associated with serum therapeutic concentration 20 to 50 times the therapeutic value. The therapeutic concentration of mianserin (plus desmethylmianserin) is 100 ng/ml and serious toxicity has been associated with concentrations above 500 mg/ml.

Ellenhorn, M.J., S. Schonwald, G. Ordog, J. Wasserberger. Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning. 2nd ed. Baltimore, MD: Williams and Wilkins, 1997., p. 630

Four cases are described in which the drug mianserin was implicated in the development of leucopenia. In one case this was accompanied by fatal aplastic anaemia. In a second, generalized bone marrow depression occurred, although leucopenia was the only clinically significant manifestation. Mianserin may depress bone marrow function and haematological surveillance is appropriate for patients taking this drug.[Adams PC et al; Postgrad Med J 59 (687): 31-3 (1983)] Full text: PMC2417361

An acute episode of symptomatic sinus bradycardia, occurred in a 50-year-old female patient after she had been given a single therapeutic dose of mianserin. Heart rate was corrected by atropine injection. Re-administration of mianserin resulted in the recurrence of bradycardia. Further examination showed no cardiac abnormalities. This case is the first report of conduction defect in a patient given therapeutic doses of mianserin.

Carcone B et al; Hum Exp Toxicol 10 (5): 383-4 (1991)

5.1 Pharmacology

Mianserin is a tetracyclic antidepressant that has antihistaminic and hypnosedative, but almost no anticholinergic, effect. It is a weak inhibitor of norepinephrine reuptake and strongly stimulates the release of norepinephrine. Interactions with serotonin receptors in the central nervous system have also been found. Its effect is usually noticeable after one to three weeks. Mianserin may cause drowsiness and hematological problems.

5.2 MeSH Pharmacological Classification
Antidepressive Agents, Second-Generation

A structurally and mechanistically diverse group of drugs that are not tricyclics or monoamine oxidase inhibitors. The most clinically important appear to act selectively on serotonergic systems, especially by inhibiting serotonin reuptake.

Serotonin Antagonists

Drugs that bind to but do not activate serotonin receptors, thereby blocking the actions of serotonin or SEROTONIN RECEPTOR AGONISTS.

Adrenergic alpha-Antagonists

Drugs that bind to but do not activate alpha-adrenergic receptors thereby blocking the actions of endogenous or exogenous adrenergic agonists. Adrenergic alpha-antagonists are used in the treatment of hypertension, vasospasm, peripheral vascular disease, shock, and pheochromocytoma.

Histamine H1 Antagonists

Drugs that selectively bind to but do not activate histamine H1 receptors, thereby blocking the actions of endogenous histamine. Included here are the classical antihistaminics that antagonize or prevent the action of histamine mainly in immediate hypersensitivity. They act in the bronchi, capillaries, and some other smooth muscles, and are used to prevent or allay motion sickness, seasonal rhinitis, and allergic dermatitis and to induce somnolence. The effects of blocking central nervous system H1 receptors are not as well understood.

5.4 Absorption, Distribution and Excretion
Absorption

Absorbed following oral administration.

A pharmacokinetic study with mianserin HCl was performed in six healthy male subjects. The subjects were treated on different occasions intravenously with a constant-rate infusion of 5 mg mianserin HCl in 1 hr, orally with a single dose of 60 mg as two tablets of 30 mg each and with 60 mg as an oral solution. The wash-out period between treatments was 1 month. Blood samples were taken at predetermined times over a period of 120 hr following dosing. The mianserin concentration in the plasma samples was determined and the results were pharmacokinetically analyzed. The intravenous data could be adequately described by a 3-compartment model and the oral data by a 2-compartment model, both with first-order transfer and elimination rate constants. The mean plasma clearance of mianserin was found to be 19 +/- 2 L/hr (mean +/- SEM), the kinetic volume of distribution 444 +/- 250 L, the steady-state volume of distribution 242 +/- 171 L and the elimination half-life 33 +/- 5 hr. The absolute bioavailability in terms of extent of absorption was 22 +/- 3% for the solution and 20 +/- 3% for the tablets. The mean peak level for the solution was 79 +/- 11 ng/mL and for the tablets 54 +/- 5 ng /mL; mean peak time for the solution was 1.1 +/- 0.2 hr and for the tablets 1.4 +/- 0.2 hr. The mean absorption half-life for the solution was 0.43 +/- 0.13 hr and for the tablets 0.39 +/- 0.11 hr.

Timmer CJ et al; Eur J Drug Metab Pharmacokinet 10 (4): 315-23 (1985)

We studied mianserin kinetics after a single (60 mg) dose in eight inpatients suffering from depression. There was a considerable interpatient variability in plasma levels. Mean peak plasma levels (+/- SEM) were 114 +/- 26 ng/ml and were reached between 1 and 3 hr. The decline of mianserin levels in plasma was biphasic. The mean elimination t 1/2 was 21.6 +/- 3.1 hr and ranged from 10.7 to 40.8 hr. The estimated first-pass loss ranged from 26% to 48% (mean, 37%) and was lower than that reported for tertiary amine tricyclic antidepressants. The mean apparent volume of distribution (15.7 +/- 2.2 L/kg; 9.7 to 28.8 L/kg) was in the range of that for imipramine but somewhat lower than for maprotiline. Apparent total body clearance ranged from 0.33 to 0.81 L/hr/kg (mean +/- SEM, 0.52 +/- 0.05 L/hr/kg) and was of the order of that after maprotiline. Our results indicate that mianserin kinetics are in most respects similar to those of tertiary amine tricyclic antidepressants (e.g., imipramine) and the tetracyclic maprotiline.

Hrdina PD et al; Clin Pharmacol Ther 33 (6): 757-62 (1983)

5.5 Metabolism/Metabolites
Metabolism

Hepatic.

Mianserin metabolism was studied in female humans, rabbits, and rats. ... In human females, unchanged mianserin, 8-hydroxymianserin and mianserin-2-oxide were isolated and identified in urine. The two metabolites were over 60 percent of the total urinary radioactivity; conjugated and unconjugated mianserin accounted for approximately 35 percent. In rabbits, mianserin was metabolized largely as 8-hydroxymianserin and an unidentified ester of 8-hydroxymianserin; only about 2.4 percent was unchanged mianserin. Small amounts of 2-formyldesmethylmianserin were isolated. The principal metabolite in rats was 8-hydroxydesmethylmianserin. Rats metabolized mianserin principally to 8-hydroxy compounds and to a lesser extent to demethylated metabolites. The authors conclude that mianserin is metabolized by three main pathways: 8-hydroxylation, demethylation, and 2-oxide formation. /Mianserin HCl/

De Jongh GD Drug Metabolism and Disposition 9 (1): 48-53 (1981)

To measure steady-state plasma concentrations of mianserin and its major active metabolite, desmethylmianserin, and to analyze the effects of various clinical factors on these plasma concentrations, steady-state plasma concentrations of mianserin and desmethylmianserin were measured in 76 depressed patients, ages 20-70 yr, receiving 30 mg/day mianserin at bedtime for 3 wk with doses increased up to 60 mg/day if needed. There were considerable interindividual variations in the steady-state plasma concentrations of these compounds; the plasma concentrations of mianserin plus desmethylmianserin were within the therapeutic range in only 43% of the patients. With advancing age, the plasma concentrations of mianserin increased significantly, while those of mianserin plus desmethylmianserin remained unchanged. Sex, smoking, and coadministration of benzodiazepines did not affect the drug's metabolism. There was no evidence that the kinetics of these compounds were nonlinear with increasing doses.

Otani K et al; Ther. Drug Monit 15 (2): 113-7 (1983)

5.6 Biological Half-Life
10-17 hours

The pharmacokinetics of mianserin hydrochloride have been determined in eight normal healthy volunteers, mean age 27, and 14 elderly patients, mean age 76. Mianserin was administered to volunteers by intravenous infusion (0.011 mg/kg/min for 15 min) and, on another occasion, by mouth, in a single dose of 30 mg. Elderly patients received a single oral dose of 40-60 mg. The terminal elimination half-life was significantly prolonged in the elderly. In young subjects it was 9.6 +/- 1.9 (s.d.) hr. In the elderly it was 27 +/- 13.1 (s.d.) hr. Apparent oral clearance was significantly reduced in the elderly. In young subjects it was 87.1 +/- 32 (s.d.) hr. In the elderly, it was 38.1 +/- 14.8 (s.d.) hr. These kinetic differences may have an important bearing on the sedative effects of mianserin.

Shami M et al; Br J Clin Pharmacol 15 (Suppl 2): 313S-322S (1983)

5.7 Mechanism of Action

Mianserin's mechanism of therapeutic action is not well understood, although it apparently blocks alpha-adrenergic, histamine H1, and some types of serotonin receptors.