

**Rapporteur's
Public Assessment Report
for paediatric data in EU Worksharing procedure**

**Mianserin
(Tolvon)**

UK/H/0019/pdWS/001

**Marketing Authorisation Holder(s):
N. V. Organon**

Rapporteur:		UK
Start of the procedure:	(Day 0)	26 February 2010
PPdAR:	(Day 70)	07 May 2010
Date re-start procedure:	(Day 90)	Not applicable
Date of Finalisation procedure:	(Day 120)	26 May 2010
Date of PAR:		26 May 2010

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Tolvon
INN (or common name) of the active substance(s):	Mianserin
MAH (s):	N. V. Organon
Pharmaco-therapeutic group (ATC Code):	N06AX03 – Antidepressants, block of adrenergic receptors (NaSSA)
Pharmaceutical form(s) and strength(s):	Tablet 10mg and 30mg

INDEX

1	Executive Summary And Recommendation.....	4
2	Introduction	4
3	Scientific Discussion	5
3.1	Non-Clinical Aspects	5
3.2	Clinical Aspects.....	5
3.2.1	Introduction	5
3.2.2	Clinical Studies	5
3.2.3	Evidence From Literature:	5
3.2.4	Discussion On Clinical Aspects	7
4	Rapporteur’s Overall Conclusion And Recommendation	7
4.1	Overall Conclusion	7
4.2	Recommendation	7

1 EXECUTIVE SUMMARY AND RECOMMENDATION

This is an entirely bibliographic submission of paediatric data for mianserin in accordance with Article 45 EC Regulation No 1901/2006 as amended. The MAH considers no changes to the product information are necessary.

The data reported from literature are case reports, abstracts or open-label studies. They do not identify any new safety concerns and do not warrant being included in the product information. The Rapporteur considers that the applicant has fulfilled their obligation under article 45 of the Paediatric.

2 INTRODUCTION

MIANSERIN

Mianserin is a tetracyclic antidepressant with alpha 1 and 2, 5-HT 2A and 2C and histamine 1 antagonist properties. It was first licensed in the 1970s via national application procedures. No European harmonization referral has taken place. The brand leader (Tolvon/Bovidon) is not licensed in the UK any more.

SUBMISSION

On 22nd February 2009 Organon submitted a clinical overview and referenced publications, stating that neither studies in juvenile animals nor clinical trials in paediatric patients had been conducted by themselves.

Based on the available data and in view of the fact that the product information contains wording in line with that adopted in the article 31 referral EMEA/H/A-31/651 following the SSRI-review, the MAH considers no changes to the product information are necessary. The relevant wording is as follows:

4.2 Children and adolescents under the age of 18 years

Mianserin should not be used in children and adolescents under the age of 18 years (see section 4.4).

4.4 Use in children and adolescents under 18 years of age

Mianserin 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 development 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 antidepressants 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 therapy with antidepressants 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.

4.8 Undesirable effects

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

3 SCIENTIFIC DISCUSSION

3.1 Non-Clinical aspects

The applicant states that they have not conducted any studies juvenile animal studies.

3.2 Clinical aspects

3.2.1 Introduction

The submission is entirely bibliographic.

3.2.2 Clinical studies

The applicant states that they have not conducted any studies in the paediatric population.

3.2.3 Evidence from literature:

The following publications were referenced in the Clinical Overview:

1 Chabrol H, Netter JC, Carriere JP. Benign intra-cranial hypertension in a child treated with mianserin. Arch. Fr. Pediatr. 1982;39:650.

2 Echizenya M et al. A case of bizarre behaviour after administration of hypnotic agent. The 32nd annual meeting of Japanese Society of Sleep Research (7-9 November, 2007).

3 Inoue Y, A case of Neuroleptic Malignant Syndrome with an abnormal signal in the cerebral peduncle revealed by head magnetic resonance imaging (MRI). Journal of Japanese association for acute medicine. The 37th annual meeting of Japanese association for acute medicine, 29-31 OCT 2009.

4 Mouren MC, Denis HP, Dugas M. Treatment of depression in children and adolescents with a new non-tricyclic molecule: mianserin. Neuropsychiatr. Enfant Adolesc. 1983 Oct;31(10):485-90

5 Dugas M, Mouren MC, Halfon O, Moron P. Treatment of childhood and adolescent depression with mianserin. Acta Psychiatr. Scand. Suppl. 1985;320:48-53

6 Winsberg BG, Camp-Bruno JA, Vink J, Timmer CJ, Sverd J. Mianserin pharmacokinetics and behavior in hyperkinetic children. J. Clin. Psychopharmacol. 1987 Jun;7(3):143-7

7 Langer DH, Rapoport JL, Ebert MH, Lake CR, Nee LE. Pilot trial of mianserin hydrochloride for childhood hyperactivity. In: Greenhill, LL; Shopsin, B (Eds). The psychobiology of childhood; A Profile of current issues. Lancaster, MTP, 1984. P.197-210.

8 Winsberg B, Suckow R, Cooper T, Camp J, Dunbar G, Vink J. Pharmacokinetics of mianserin and its desmethyl metabolite in children and adults. In: Congress of the colloquium internationale neuro-psychopharmacologicum; Florence, June 19-23, 1984; Book of abstracts. S.L., S.N., 1984. P.190, Abstract No. P74.

9 Propper L, Hrdlicka M, Bares M, Kajlikova M, Goetz M, Lorenc J, Koutek J. Mianserin in the treatment of depression and anxiety in childhood and adolescence. Ceska Slov Psychiatr 2000;96:376-80.

10 Newman B, Crome P. The clinical toxicology of mianserin hydrochloride. Vet. Hum. Toxicol. 21, Suppl., 60-63 1979

11 Chand S, Crome P, Dawling S. One hundred cases of acute intoxication with mianserin hydrochloride. Pharmacopsychiatrie 14, 15-17 1981

The MAH states that the identified publications do not point to significant safety concerns that would be specific to this age category or requiring warnings other than the ones currently present in the labelling of mianserin, but does not discuss any of the publications.

Assessor's comment:

Search criteria and searched databases are not identified in the report.

There are some limited paediatric PK data (ref 6 and 8). Winsberg et al (6) states that prepubescent children with hyperkinetic behaviour disorder have a significantly faster elimination half life and a smaller apparent volume of distribution than adults. The author notes akathisia, excitability, confusion, sedation, insomnia, migraine, tachycardia, bradycardia and minor ECG changes as possible side effects in the sample of six hyperkinetic children with an IQ range of 40 to 90. In a different publication the same author reports absence of any PK differences in children and adults (8).

Two publications (10 and 11) review cases of mianserin poisoning reported to the London National Poisons Information Centre. Only one of these publications includes specific information on children. Of five children under the age of 5 years, each having taken less than 50mg mianserin, 3 were reported as drowsy and 2 had no symptoms.

Mouren MC et al (4) report results partial and preliminary results from an open-label pilot study in 72 paediatric subjects aged 8 to 19 years with depression who were treated with mianserin at a dose of 1mg/kg for those < 13 years and 50-60mg/kg for adolescents for 1 to 16 months (median 3 months). Diagnostic criteria used for establishing the diagnosis are not stated, and only about half of the children were assessed by CDRS. 16% of subjects received concomitant psychoactive drugs. In 72% of subjects there was 'very good efficacy'. Treatment had to be discontinued because of side effects in 14% of subjects and because of lack of efficacy in another 14%. Individual patients experienced anticholinergic side effects (n=4), Somnolence led to treatment discontinuation in 5 cases, and was mild in 17 cases. One patient gained 10kg in 3 months. The authors state that there was no relationship between side effects, age and/or gender.

Dugas M et al (5) report results from another open-label uncontrolled pilot trial in 110 depressed children aged 8 to 19 years. For inclusion, children had to have a CDRS score of at least 30. Treatment duration was 7 – 167 days. The authors state that efficacy was noticeable by the end of the first week and maintained throughout the 60 day study period (sic). Side effects did not appear to be age- or sex-related. Reported side effects are drowsiness (causing discontinuation in 2 cases), weight gain (up to 11kg in 3 months), 'very rare' anticholinergic effects, and a single report of insomnia with agitation and seizures. The authors state they believe that mianserin contributed to the development of seizures in a teenager whose EEG abnormalities had already existed prior to treatment.

Propper L (9) reports results from a retrospective evaluation of effectiveness of 30 – 90mg mianserin in the treatment of 'depressive stage' and anxiety states in 13 patients aged 13 to 18 years. The translation of this Czech article notes that mianserin was well tolerated in all cases.

Langer H et al (7) report lack of efficacy of mianserin at doses up to 60mg/day in five hyperactive boys aged 6-12 years and state that drowsiness, orthostatic hypotension and tachycardia caused serious clinical concern, even at doses as low as 10-20mg.

Chabrol H et al(1) reports a case of intracranial hypertension in a 5 year old child following administration of 10mg mianserin.

Inoue Y (3) reports a case of 'malignant syndrome' in a 17-year old boy following medication with mianserin, sertraline, risperidone and Phenobarbital.

Echizenya M et al. (2) report bizarre behaviour such as crying, laughing, dancing and uttering a strange sound in a 14-year old girl with non-24-hour sleep-wake syndrome being treated with triazolam, brotizolam and mianserin.

The data reported from literature are case reports, abstracts or open-label studies, do not identify any new safety concerns and do not warrant being included in the product information.

3.2.4 Discussion on clinical aspects

The submission is entirely bibliographic and consists of published case reports, abstracts or open-label studies. No new safety signals were identified. On the basis of the submitted evidence, the Rapporteur considers that no changes to the product information are required.

4 RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

4.1 Overall conclusion

The submitted data do not warrant inclusion in the product information.

4.2 Recommendation

The Rapporteur considers that the applicant has fulfilled their obligation under article 45 of the Paediatric Regulation. The submitted data do not warrant inclusion in the product information.