

**Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006,
as amended**

**Catapressan/Dixarit
Clonidine hydrochloride**

NL/H/0017/pdWS/001

| | |
|--|-----------------|
| Rapporteur: | The Netherlands |
| Finalisation procedure (day 120): | 12 January 2011 |
| Date of finalisation of PAR | 31 March 2011 |

ADMINISTRATIVE INFORMATION

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| Invented name of the medicinal product(s): | See section VI |
| INN (or common name) of the active substance(s): | Clonidine hydrochloride |
| MAH (s): | See section VI |
| Pharmaco-therapeutic group (ATC Code): | N02CX02 |
| Pharmaceutical form(s) and strength(s): | Different strengths and pharmaceutical forms |

I. EXECUTIVE SUMMARY

The MAH of the innovator, Boehringer Ingelheim International GmbH and also on behalf of several other MAHs, has submitted 12 studies.

The MAH has concluded that review and evaluation of these studies provides no evidence in support for a therapeutic indication or a recommendation on posology in children.

SmPC changes are proposed in sections 4.2 and 5.1.

II. RECOMMENDATION¹

Based on the review of the presented paediatric data in the day 70 preliminary PdAR the rapporteur concluded the data from the submitted studies did not justify new indications but focused on wording for dosage recommendation and specific safety information related to paediatric patients in the SmPC. The response from the MAH was received in September 2010 and included the MAH's response to the comments raised in the Preliminary Paediatric Assessment Report and by the CMS. At the end of the procedure, text proposals for section 4.2 and 5.1 for the SmPC were agreed upon.

Overall, it can be concluded that the safety and efficacy of clonidine in children and adolescents have not been established.

In section 4.2, it should be mentioned that the use of clonidine is not recommended in children and adolescents below the age of 18 years.

In section 5.1, a brief information about the outcome of the main clinical studies should be provided.

III. INTRODUCTION

Clonidine hydrochloride is a partial agonist of the α_2 -adrenergic receptors. It is a central antihypertensive medicinal product which acts by reducing the vasoconstrictive and vasodilatative stimuli in the body. It is also used for reduction of withdrawal symptoms during opioid detoxification.

Clonidine has been registered in different EU countries since the 1966 (1971 in the Netherlands).

In the European Union, clonidine is available as tablets (containing 0.025, 0.1, 0.15 or 0.3 mg of clonidine hydrochloride), ampules for injection or intravenous infusion (containing 0.15 mg/ml or 0.75 mg/5 ml of clonidine hydrochloride) and as transdermal therapeutic system (containing 2.5 mg and 5 mg of clonidine per plaster). Approved indications are menopausal flushing, hypertension, withdrawal symptoms after stopping treatment with opiates.

In addition, clonidine is also used in basic therapy and prophylactic treatment of migraine or recurrent vascular headaches and is available for this purpose in the form of sugar-coated tablets (containing 0.025 mg of clonidine hydrochloride).

Clonidine is used off-label to treat psychiatric disorders including stress, sleep disturbances, and hyper arousal caused by post-traumatic stress disorder, borderline personality disorder, and other anxiety disorders. Other off label use is to relief symptoms of alcohol and opiate withdrawal, smoking secession, posttherapeutic neuralgia. In addition clonidine has been studied for treatment of ADHD and Tourette's syndrome.

In accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use, for the current procedure the 12 studies have been submitted. The MAH of the innovator, Boehringer Ingelheim International GmbH, has submitted the studies also on behalf of other MAHs, namely:

- Boehringer Ingelheim RCV GmbH & Co. KG (Austria)
- SCS Boehringer Ingelheim Comm.V (Belgium and Luxembourg)
- Boehringer Ingelheim France S.A.S. (France)
- Boehringer Ingelheim Pharma GmbH & Co. KG (Germany)
- Boehringer Ingelheim Italia S.p.A. (Italy)
- Boehringer Ingelheim B.V. (Netherlands)
- Unifarma Lda. (Portugal)
- Boehringer Ingelheim Limited (Great Britain)
- Boehringer Ingelheim Ellas AE (Greece)
- Laboratorios Fher S.A. (Spain)

The MAH has concluded that review and evaluation of these studies provides no evidence in support for a therapeutic indication or a recommendation on posology in children.

The details of these studies will be discussed under section IV.3 Clinical aspects.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

Tablets, intravenous injection

IV.2 Non-clinical aspects

Not applicable

IV.3 Clinical aspects

1.Introduction

The MAH submitted reports for the following studies:

U79-0288, Open label, pilot trial on the use of clonidine for paediatric hypertension

U85-0798: The use of clonidin monotherapy in adolescent hypertension

U85-0838: Randomized, comparative trial on the effects of clonidine compared to hydrochlorothiazide in hypertensive adolescents

U86-0170: Double-blind comparative trial of clonidine and propranolol in adolescent hypertension

U87-0271: Open label, pilot study on the use of clonidine in adolescent hypertensive latin males

U89-0198: Randomized, double-blind, placebo controlled trial of clonidine and hydralazine in pregnant women with mild to moderate hypertension

U91-0018: Clonidine treatment of Tourette's syndrome

U91-0711: A controlled trial investigating the effects of clonidine in children with attention-deficit hyperactivity disorder

U93-0224: Pharmacokinetics and hemodynamic response after an intravenous bolus injection of clonidine in children

U96-0295: Investigation of dose-dependent efficacy of clonidine after addition to bupivacain for caudal block in children

U97-0073: Clonidine medication for children who stutter: A double-blind cross-over pilot study

U02-1350: Spina anaesthesia and clonidin in premature infants preventing postoperative apnoea

2 Clinical studies

Studies in hypertension:

Study U79-0288

Open label, pilot trial on the use of clonidine for pediatric hypertension

- **Study dates:** 1979
- **Study objective:**
To assess the safety and efficacy of clonidine tablets in children with chronic hypertension.
- **Study design:** An open-label, pilot study, 12-26 weeks
- **Study population /Sample size**
Nine patients (6 males and 3 females) (one patient > 18 years of age) in the age range between 7 to 24 years. Two patients were excluded from the analysis: one patient was 24 years, the second discontinued due to transplant nephrectomy.
- **Treatments**
A dose range of 0.1 to 0.8 mg daily was administered for up to 26 weeks.
- **Outcomes/endpoints**
Reduction in supine blood pressure after 3-4 weeks and after 8-10 weeks.
- **Results**
Statistically significant reduction in systolic and diastolic blood pressure ($p < 0.01$ and $p = 0.03$ respectively).
No data on safety was presented in the-report of the study.
- **Conclusion MAH**
There was a statistically significant effect on the reduction in systolic and diastolic blood pressure by the end of the study.

Assessor's comments

Due to the open label and small number of subjects in this study no conclusions about efficacy could be made. Moreover there is no data on safety which might be useful in this case.

Study U85-0798

The use of clonidine monotherapy in adolescent hypertension

- **Study dates:** not specified
- **Study objective:**

To compare efficacy of clonidine 0.1mg BID with hydrochlorthiazide (HTZ) 25 mg BID

- **Study design:** Randomized, active controlled study

- **Study population /Sample size**

30 hypertensive adolescents in the age range between 13 to 19 years (15 in each treatment arm).

- **Treatments**

Clonidine 0.1mg BID versus hydrochlorthiazide (HTZ) 25 mg BID for 12 weeks and later increased to 0.2 mg BID clonidine or 50 mg BID HTZ for another 12 weeks. Total treatment period was 24 weeks.

- **Outcomes/endpoints**

Reduction in casual blood pressure and blood chemistry measured every 2 weeks.

- **Results**

Clonidine (high dose) has reached treatment goals (significant reduction in systolic, diastolic blood pressure and heart rate) in 87% of the patients, while for HTZ this goal was achieved only in 40% of the patients.

TABLE 2 Blood Pressure and Chemistry Change with Therapy

| | | | |
|-----------------------------------|--------------|--------------|--------------|
| Systolic Pressure change in mmHg | | Low Dose | High Dose |
| Clonidine | | -10+ | -10* |
| HCTZ | | - 6+ | - 9** |
| Diastolic Pressure change in mmHg | | | |
| Clonidine | | - 7** | - 8*** |
| HCTZ | | - 3 | - 4 |
| Heart Rate change in mmHg | | | |
| Clonidine | | -10** | -10** |
| HCTZ | | - 2 | + 1 |
| Chemistries | Pretreatment | Low Dose | High Dose |
| Uric Acid mg/dl | | | |
| Clonidine | 6.5 ± 1.2 | 6.7 ± 1.2 | 6.8 ± 1.3 |
| HCTZ | 6.0 ± 1.1 | *7.0 ± 1.2 | *7.0 ± 1.2 |
| Potassium mEq/L | | | |
| Clonidine | 4.3 ± .3 | 4.3 ± .3 | 4.1 ± .3 |
| HCTZ | 4.3 ± .3 | ***3.5 ± .4 | ***3.5 ± .4 |
| Chloride mEq/L | | | |
| Clonidine | 106 ± 2.2 | 105 ± 2.1 | 105 ± 2.0 |
| HCTZ | 107 ± 1.6 | ***102 ± 3.4 | ***101 ± 3.9 |
| CO ₂ mEq/L | | | |
| Clonidine | 25.2 ± 2.2 | 26.1 ± 2.2 | 24.6 ± 2.0 |
| HCTZ | 24.7 ± 1.8 | **27.7 ± 3.1 | **26.2 ± 3.1 |

VALUES ARE MEAN ± STANDARD DEVIATION

HCTZ = HYDROCHLOROTHIAZIDE

+ = P < .05 * = P < .02

** = P < .01 *** = P < .001

Adverse events were reported in the clonidine group were drowsiness and dry mouth. In the HTZ group 14/15 subjects had reduction in serum potassium, of which four patients required potassium supplementation. No other significant changes in blood chemistry were observed in the clonidine group.

Assessor's comments

Despite the limited number of patients in this study it can be concluded that, with respect to efficacy both drugs have shown an effect on hypertension.

The safety profile of the two products is different, with asymptomatic hypokaliemia as major issue for HTZ, and drowsiness and dry mouth for clonidine. The AEs of clonidine are well known, but these are a concern when clonidine is used in children, because of possible influence on school performance and other daily activities.

Study U85-0838

Randomized, comparative trial on the effects of clonidine compared to hydro-chlorothiazide in hypertensive adolescents

- **Study dates:** 1984
- **Study objective:**
To compare efficacy of clonidine 0.1mg BID with hydrochlorothiazide (HTZ) 25 mg BID
- **Study design:** Randomized, placebo controlled study, 24 weeks
- **Study population /Sample size**
30 hypertensive adolescents in the age range between 13 to 19 years.
- **Treatments**
Clonidine 0.1mg BID versus hydrochlorothiazide (HTZ) 25 mg BID for 12 weeks later increased if necessary to clonidine 0.2mg BID versus HTZ 50 mg BID for another 12 weeks.
- **Outcomes/endpoints**
Three patients did not complete the study – one was lost to follow up and 2 – due to noncompliance.
- **Results**
The main results are presented in the table below:

Significance of Mean Changes from Baseline

| | Significance of Mean Changes from Baseline | | | |
|---|---|------------|---------------------|-----------|
| | CATAPRES® | | Hydrochlorothiazide | |
| | Low-dose | High-dose | Low-dose | High-dose |
| <u>Resting Parameters</u> | | | | |
| Systolic Blood Pressure | ↓(p<0.05) | ↓(p<0.025) | ↓(p<0.05) | ↓(p<0.01) |
| Diastolic Blood Pressure | ↓(p<0.01) | ↓(p<0.001) | NS | NS |
| Pulse | ↓(p<0.01) | ↓(p<0.01) | NS | NS |
| Norepinephrine Levels | ↓* | --- | ↑* | --- |
| <u>Response to Mental Stress Testing</u> | | | | |
| Systolic Blood Pressure | NS | --- | NS | --- |
| Diastolic Blood Pressure | ↓(p<0.01) | --- | NS | --- |
| Pulse | ↓(p<0.01) | --- | NS | --- |
| Norepinephrine Levels | ↓# | --- | ↑# | --- |

At the end of the first 3 months 5 out of the 15 patients were controlled with the low dose, while for the other 10 the dosage was increased.

AEs which were considered as possibly or probably related to the drug were observed in 12/17 patients in the clonidine group versus 12/16 patients in the HTZ group. The most common AE in the clonidine group was drowsiness (9 patients).

Conclusion MAH

Clonidine therapy was significantly superior in blood pressure control compared to HTZ treatment.

Assessor's comments

In this study clonidine induces a significant decrease in blood pressure as compared to baseline, while HTZ did not show statistically significant reduction in blood pressure (except for systolic blood pressure). However the rate of reduction is relevant in the assessment of clinical benefit; the applicant should give data on the absolute reduction in blood pressure. Whether the difference in treatment effect between clonidine and HTZ is statistically significant is another question. Since in other studies the results for clonidine and HTZ are similar, the conclusions of the MAH should be taken with caution, since the assay sensitivity of the study is questioned and a placebo arm is missing. In line with earlier remarks the absolute reductions should be given and statistically analysed comparing HTZ and clonidine. With regard to safety drowsiness is reported as most common AE, which is similar to other studies.

Study U86-0170

Double-blind comparative trial of clonidine and propranolol in adolescent hypertension

- Study dates: 1985

- **Study objective:**

To compare efficacy of clonidine 0.1mg BID with propranolol 80 mg BID

- **Study design:** Randomized, double blind, parallel active controlled study, 6 months.

- **Study population /Sample size**

32 adolescents in the age range between 12 to 19 years. 29 patients completed the study.

- **Treatments**

Clonidine 0.1mg BID (8 weeks) versus propranolol 40 mg BID (8 weeks), followed by clonidine 0.2mg BID (8 weeks) versus propranolol 80 mg BID (8 weeks). For patients with unsatisfactory reduction in blood pressure, hydrochlorthiazide (25mg/BID) was added to existing therapy.

- **Outcomes/endpoints**

Assessments at week 8, 16, 24 of therapy on blood pressure reduction, cardiovascular response to mental stress, and exercise performance.

- **Results and discussion**

Significant reduction in systolic and diastolic blood pressure was achieved with clonidine and with propranolol ($p < 0.01$). Effective blood pressure control was achieved in 40% of patients on HTZ, 65% on propranolol and 85% on clonidine.

3 patients dropped out – 2 for non-compliance and 1 for unknown reasons.

Five out of the 16 patients in the clonidine arm reported AEs, which were dizziness, fatigue, headache, insomnia, dry mouth.

- **Conclusion MAH**

Adolescents requiring blood pressure control a single agent may be sufficient in most cases. Blood pressure control may be improved by switching to another agent instead of addition of a second agent.

Assessor's comments

Despite the limited number of patients in this study it seems that clonidine is as efficacious in blood pressure reduction as propranolol. However the definition of “significant benefit” should be given. The safety profile for clonidine used in adolescents does not raise new concerns.

Study U87-0271

Open label, pilot study on the use of clonidine in adolescent hypertensive Latin males

- **Study dates:** 1986

- **Study objective:** To study effectiveness and tolerability of clonidine in hypertensive Latin males

- **Study design:** Open label, 4 weeks

- **Study population /Sample size**

8 male patients of Latin ethnicity in the age range between 15 to 18 years. Two patients dropped out due to non compliance.

- **Treatments**

Clonidine 0.1mg BID for 4weeks. Patients with unsatisfactory response were up titrated to 0.2 mg BID.

- **Results**

The six patients who completed the study were controlled with 0.1 mg clonidine BID. Mean systolic blood pressure decreased with 24 ± 11.8 mm Hg and diastolic blood pressure by 15 ± 8.9 mm Hg from baseline.

Four patients in the clonidine group reported AEs which were headache, dry mouth, flu-like symptoms, pyrexia. None of the subjects withdrew from the study due to adverse events or lack of efficacy.

- **Conclusion MAH**

A clinically meaningful reduction in systolic and diastolic blood pressure was noted at end of study.

Assessor's comments

The safety profile for clonidine used in Latin male adolescents does not raise new concerns. Due to the limited number of cases no conclusions on efficacy can be made.

Study U89-0198

Management of Mild to Moderate Hypertension in Pregnancy – A clinical trial of the use of antihypertensive drug therapy

- **Study dates:** 1985 - 1988

- **Study design:** Randomized, double-blind, placebo controlled trial of clonidine or clonidine + hydralazine in pregnant women with mild to moderate hypertension

- **Study population /Sample size**

52 patients in pregnant women (not less than 28 weeks and not more than 34 weeks of gestation) with mild to moderate hypertension.

- **Treatments**

The following total daily doses divided in four intakes were applied:

- a. Clonidine 200 mg
- b. Clonidine 400 mg
- c. Clonidine 400 mg + hydralazine 50 mg
- d. Clonidine 600 mg + hydralazine 100 mg
- e. Clonidine 800 mg + hydralazine 100 mg
- f. Clonidine 800 mg + hydralazine 200 mg

Patients started at regimen **a** and were up titrated to regimen **f** if necessary until blood pressure control was achieved.

- **Results**

Eight patients in the placebo group and one in the clonidine arm were withdrawn because of maternal deterioration.

Analysis on ITT showed significant increase in premature delivery for complications in the placebo group ($p < 0.05$). Neonatal respiratory distress (6 cases) and maternal proteinuria were observed in the placebo group.

- **Conclusion MAH**

In the placebo group a significant increase in premature delivery for complications was noted. There were no perinatal deaths and no adverse neonatal effects of the treatment.

Assessor's comments

The results confirm that early control of pre-eclampsia is related to better outcome in terms of premature delivery and neonatal complications. For the scope of the art. 45 procedure this study is not considered relevant.

Studies in off-label indications:

Study U91-0018

Clonidine treatment of Tourette's syndrome

- **Study dates:** 1990
- **Study design:** Randomized, double blind, placebo controlled study for 12 weeks.
- **Study population /Sample size**
47 patients with Tourette's syndrome aged 7 to 48 years. 40 patients completed the study.
- **Treatments**
Clonidine 3 – 5 $\mu\text{g}/\text{kg}/\text{day}$ versus placebo.

- **Results**

Four subjects in the placebo groups dropped out, 2 due to symptom exacerbation, 1 because of non-compliance, and 1 due to parents' consent withdrawal.

Of the 40 patients who completed the study, 9 were older than 18 years.

Efficacy was measured using clinicians-, parents- and self-rating scales. On the TSGS total score patients in the clonidine arm showed 26% improvement from baseline versus 11% in the placebo ($p = 0.05$). In addition a few other (but not all) efficacy measures showed statistically significant difference from placebo: on the TS global scale the motor tics ($p=0.008$); on the TS-CGI ($p=0.01$); motor tics on videotape counts ($p=0.03$).

On the parental and self-rating scales the only statistically significant difference was observed for the rating of motor tics ($p=0.004$). On the rest of the items clonidine was not statistically significant better than placebo.

The most common side effects with clonidine were sedation and/or fatigue (90%), dry mouth (57%), faintness and/or dizziness (43%) and irritability (33%). Three cases with sedation and/or irritability and sedation were considered to be of moderate severity and required reduction of the clonidine dose.

- **Conclusion MAH**

Oral clonidine at dose 3 to 5 $\mu\text{g}/\text{kg}/\text{day}$ is more effective than placebo in the treatment of TS, mainly is reducing motor tics.

Assessor's comments

The results from this study give an indication for possible effectiveness of clonidine in patients with Tourette syndrome, particularly in reduction of motor tics and tics noticeable to others. This however is not considered sufficient evidence for obtaining an indication and the MAH has not requested one. The safety profile does not raise new safety issues.

Study U91-0711

A controlled trial investigating the effects of clonidine in children with attention-deficit hyperactivity disorder

- **Study dates:** 1989-1990
- **Study design:** Double blind, placebo and active controlled, 8 weeks
- **Study population /Sample size**
109 patients (aged 6 to 15 years) with attention deficit hyperactivity disorder (ADHD) according to DSM-III-R. In addition patients were split into three treatment groups:
 1. ADHD and Pervasive developmental disorder (n=5)
 2. ADHD and Tic disorders but no Pervasive developmental disorder (n=32)
 3. Attention deficit hyperactivity disorder without Pervasive developmental disorder or Tic disorder (n=72) ADHD?

- **Treatments**

Patients from group 1 and 2 were randomised either to clonidine or placebo. Patients from group 3 (pure ADHD) were randomized to clonidine 4 µg/kg/day or methylphenidate 0.6 mg/kg/day or placebo for 8 weeks.

- **Results**

108 patients completed the study, one patient in the placebo dropped out due to deterioration of symptoms.

The analysis was performed on the ITT population.

At baseline, week 3, 5, and 7 the primary efficacy measurements were with the use of the following scales:

Parent and teacher version of the Groninger behaviour observation hyperactivity scale;
Parent and teacher visual analogue score on three problem behaviours selected a priori
Parent and teacher global clinical impression score

A patient was determined as responder if the subject showed clinically significant improvement in clinical condition according to global impression of parent and/or teacher. Following this definition the data on “responders” is presented in the table below:

Treatment groups: responders (%)

1. Pervasive Developmental Disorder (n=5):
 Clonidine (n=2): 0%
 Placebo (n=3): 0%

2. Tic Disorders (n=32):
 Clonidine (n=16): 25%
 Placebo (n=16): 31%
 (comparison clonidine-placebo: Fisher p=1 n.s.)

3. No PDD or tics (n=72):
 Clonidine (n=24): 50%
 Placebo (n=24): 13%
 Methylphenidate (n=24): 50%
 (comparison clonidine-placebo, and methylphenidate-placebo:
 χ^2 p=0.013).

- **Safety results**

The most common side effect reported was drowsiness - 54% in the clonidine group. In the methylphenidate group 59% of the patients reported “annoying side effects” but it is not specified which AEs.

- **Conclusion MAH**

CONCLUSION

(1) Clinicians poorly agreed on the existence of emotional problems in children with ADHD. Possibly, emotional problems are easily overlooked in these children.

(2) Only 36% of the ADHD subjects showed minor neurological dysfunction or was neurologically abnormal.

(3) Of the ADHD children with an IQ in the normal range 56% had a specific arithmetic and/or language problem.

(4) With the global judgement of parents and teacher as criterium for respondership, clonidine was found more effective than placebo in ADHD patients without tics, and equally effective as methylphenidate.

Repeated measurements analysis of rating scale scores showed:
(a) clonidine as well as methylphenidate ameliorated hyperactivity in ADHD patients without tics, both at home and at school;

(b) clonidine was less effective in ADHD patients with tics than in ADHD patients without tics;

(c) in ADHD patients without tics the effect of clonidine was as large as the effect of methylphenidate. Clonidine made ADHD patients with tics more extravert at school. ADHD patients without tics became better oriented to a task in the school situation, both on clonidine and on methylphenidate.

(5) On clonidine not less than 53% of the patients had side effects after 7 weeks of treatment. Mostly side effects were "acceptable" and consisted of drowsiness. Methylphenidate, after 7 weeks of treatment, gave side effects in 59% of the patients. On methylphenidate more "annoying" side effects were seen than on clonidine.

(6) Employing cluster analysis we found no correlation between behavioral profiles and a favourable response to clonidine or methylphenidate.

(7) ADHD patients excreted less MHPG than controls. However, we found no effect of clonidine or methylphenidate on MHPG excretion, and MHPG excretion had no predictive value as to a favourable drug response in the study subjects.

Assessor's comments

The results from this study give some indication for possible effectiveness of clonidine in patients with ADHD, but not ADHD + pervasive developmental disorder or ADHD + tics. However due to the heterogeneity of the patient population, the lack of data on standard measurement scales for ADHD (only CGI is presented), and lack of convincing results for efficacy of clonidine on all clinically relevant aspects of this condition, this study does not provide sufficient evidence for obtaining an indication and the MAH has not requested one. The improvements noted can also be induced merely due to inclusion of patients in the clinical trial. The MAH should have provided details on the definition of clinically significant improvement and indicated in which domains / items of the test improvements were noted. The safety profile does not raise new safety issues.

Study U93-0224

Pharmacokinetics and hemodynamic response after an intravenous bolus injection of clonidine in children

- **Study dates:** not reported
- **Study design:** A pharmacokinetic and hemodynamic study of intravenous bolus injection of clonidine (2.5 µg/kg body weight) in paediatric patients during general anaesthesia
- **Study population /Sample size**
12 children (mean age 31 months)
- **Treatments**
Clonidine 2.5 µg/kg body weight intravenously during general anaesthesia
- **Results**
A significant reduction in mean arterial blood pressure by 26.3% compared to baseline was observed (p=0.0032). The time for 75% of the expected blood pressure reduction was 21.3 minutes. There was a small decrease in heart rate 127 to 119 bpm (p=0.006) was observed after the bolus injection, where after the heart rate returned back to baseline.

Besides reduction in mean arterial blood pressure and reduction in heart rate no other side effects were reported.

- **Conclusion MAH**

The use of clonidine as a premedicant or adjunct to general anesthesia in children appears to be appropriate from both a pharmacokinetic and hemodynamic standpoint.

Assessor's comments

This study provides some data about pharmacodynamic changes in children when given a bolus of clonidine during general anaesthesia. With respect to age the age ranges should have been given as well with an analysis of the PK/PD correlation in different age categories. Because of the small number of subjects and open label character, these data have a historical rather than scientific value at present. Therefore this study will not be discussed further.

Study U96-0295

Investigation of dose-dependent efficacy of clonidine after addition to bupivacaine for caudal block in children

- **Study dates:** 1992-1994
- **Study design:** double-blind study in children undergoing inguinal hernia repair under local caudal anaesthesia using a mixture of bupivacaine and clonidine
- **Study population /Sample size**
24 children (mean age 38 months)
- **Treatments**
Patients were randomly assigned to one of the following groups:

B-group 0.75 ml/kg bupivacaine 0.25%

BE-group 0.75 ml/kg bupivacaine 0.25% + 3.75 µg/kg epinephrine
BC-group 0.75 ml/kg bupivacaine 0.25% + 2 µg/kg clonidine

- **Results**

Hemodynamic parameters remained stable after treatment. Sedation score at 15 min and SPC at 15, 90 and 270 min after anaesthesia were significantly lower in the BC group compared to the B- and BA-group.

No side effects were reported.

- **Conclusion MAH**

Clonidine added to local anesthetics in caudal block provides improved postoperative analgesia with rapid onset and prolonged duration. The hemodynamic response in children seems less pronounced than that in adults.

Assessor's comments

Similarly to the previous study, this trial also provides some data about the application of clonidine in combination with bupivacaine in local caudal anaesthesia. In such study more endpoint should have been measured, but such data is not available. The CI intervals of the results of the sedation score should have been reported, but are not available. The number of patients per arm (n=8) is too low to draw definite conclusions. Therefore this study will not be discussed further.

Study U97-0073

Clonidine medication for children who stutter: A double-blind cross-over pilot study

- **Study dates:** 1989-1992
- **Study design:** double blind, placebo-controlled crossover study in children with stuttering disorder
- **Study population /Sample size**
25 children aged 6 to 13 years with stuttering disorder
- **Treatments**
Clonidine 4 µg/ kg body weight per day vs placebo – total trial duration – 28 weeks.

The trial design is presented below. Clonidine was up- and down-titrated gradually in the beginning and end of the treatment phase.

- **Conclusion MAH**

For unknown reasons no case report forms were completed at that time and no further data are available. The lack of data from this study prevails to derive findings for relevant conclusions regarding the use of clonidine as an adjunct to spinal anaesthesia.

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|----------------------------|
| Assessor's comments |
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|---|
| No conclusions can be made from this study. |
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V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

For this procedure the MAH has presented 6 clinical studies for the efficacy and tolerability of clonidine in treatment of hypertension (5 in children and adolescents and one in pregnant women) and 6 of other conditions, for which clonidine does not have an indication such as ADHD, Tourette's syndrome, stuttering disorder, caudal anaesthesia. Generally speaking the studies were performed years ago, the study protocols are incomplete and are not in accordance with the current standards for clinical research. Therefore it is not possible to make firm conclusions about efficacy and safety of the application of clonidine in paediatric patients with different clinical conditions.

With respect to efficacy as an antihypertensive medicine, the data in general confirms the properties of clonidine in reduction of systolic and diastolic blood pressure. The most commonly reported AEs were drowsiness, dizziness, dry mouth, headache and insomnia which are compatible with the known adverse events profile of clonidine. Whether these events are acceptable for children is questioned. No serious AEs have been identified in the presented studies. These AEs are mentioned in the current SPC (of clonidine HCl), however it would be recommended to adjust this to the format according to the SPC guideline (with presentation of frequencies and MeDRA terms).

With respect to the possible application of clonidine for treatment of various other conditions, the data is considered insufficient and therefore no indications can be granted and are not requested by the MAH.

In addition, brief information about the outcome of the main clinical studies in 5.1. should be provided, as this will show that the efficacy and safety in children has not been established.

➤ Recommendation

The following text proposals are agreed upon:

4.2.

There is insufficient evidence for the application of clonidine in children and adolescents younger than 18 years. Therefore the use of clonidine is not recommended in paediatric subjects under 18 years.

5.1.

The efficacy of clonidine in the treatment of hypertension has been investigated in five clinical studies in paediatric patients. The efficacy data confirms the properties of clonidine in reduction of systolic and diastolic blood pressure. However, due to limited data and methodological insufficiencies, no definitive conclusion can be drawn on the use of clonidine for hypertensive children.

The efficacy of clonidine has also been investigated in a few clinical studies with paediatric patients with ADHD, Tourette syndrome and stuttering. The efficacy of clonidine in these conditions has not been demonstrated.

There were also two small paediatric studies in migraine, neither of which demonstrated efficacy.

In the paediatric studies the most frequent adverse events were drowsiness, dry mouth, headache, dizziness and insomnia. These adverse events might have serious impact on daily functioning in paediatric patients.

Overall, the safety and efficacy of clonidine in children and adolescents have not been established.(see section 4.2).

A type IB variation to be submitted by day 270 of the procedure

Furthermore, the applicant has committed to update national SmPCs if needed with respect to the following items:

- section 4.8 of national SmPC (Presentation of ADRs with frequencies and using MEDRA terms)
- to include a warning on the rebound effect in section 4.4.

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

| Country | Tradename | MA Number | MAH | Strength | Dosage form |
|---------|---|----------------|--------------------------|--------------|----------------------|
| AUSTRIA | CATAPRESAN 0,15 MG/ML AMPULLEN | 13873 | BI RCV AT | 0.15 mg/ml | ampoule |
| AUSTRIA | CATAPRESAN 0,150 MG TABLETTEN | 13874 | BI RCV AT | 0.15 mg | tablets |
| BELGIUM | DIXARIT | 205 IS 17 F 3 | BI BE | 0.025 mg | sugar-coated tablets |
| BELGIUM | CATAPRESSAN 150 MCG/1 ML SOLUTION INJECTABLE/SOLUTION POUR PERFUSION | 205 IS 37 F 12 | BI BE | 0.15 mg/ml | ampoule |
| BELGIUM | CATAPRESSAN | 205 IS 8 F 3 | BI BE | 0.15 mg | tablets |
| DENMARK | CATAPRESAN | 06158-1972 | BI International GmbH DE | 0.025 mg | sugar-coated tablets |
| FINLAND | CATAPRESAN 150 MIKROG/ML INJEKTIONESTE | 5248 | BI International GmbH DE | 0.15 mg/ml | ampoule |
| FINLAND | CATAPRESAN 150 MIKROG TABLETTI | 5038 | BI International GmbH DE | 0.15 mg | tablets |
| FRANCE | CATAPRESSAN | 325 553 - 9 | BI SAS FR | 0.15 mg/ml | ampoule |
| FRANCE | CATAPRESSAN | 330 063 - 6 | BI SAS FR | 0.15 mg/ml | ampoule |
| FRANCE | CATAPRESSAN | 339 931 - 0 | BI SAS FR | 0.15 mg/ml | ampoule |
| FRANCE | CATAPRESSAN | 355 131 - 5 | BI SAS FR | 0.15 mg/ml | ampoule |
| FRANCE | CATAPRESSAN | 355 132 - 1 | BI SAS FR | 0.15 mg/ml | ampoule |
| FRANCE | CATAPRESSAN | 355 133 - 8 | BI SAS FR | 0.15 mg/ml | ampoule |
| FRANCE | CATAPRESSAN | 311 812.7 | BI SAS FR | 0.15 mg | tablets |
| FRANCE | CATAPRESSAN | 311 824.5 | BI SAS FR | 0.15 mg | tablets |
| FRANCE | CATAPRESSAN | 359 406.9 | BI SAS FR | 0.15 mg | tablets |
| FRANCE | CATAPRESSAN | 553 001.0 | BI SAS FR | 0.15 mg | tablets |
| FRANCE | CATAPRESSAN | 555 078.0 | BI SAS FR | 0.15 mg | tablets |
| FRANCE | CATAPRESSAN | 559 552.9 | BI SAS FR | 0.15 mg | tablets |
| GERMANY | PARACEFAN I.V. 0,75 MG | 33999.00.00 | BI DE | 0.75 mg/5 ml | ampoule |
| GERMANY | CATAPRESAN | 6191514.00.01 | BI DE | 0.15 mg/ml | ampoule |
| GERMANY | PARACEFAN I.V. 0,15 MG | 5252.00.01 | BI DE | 0.15 mg/ml | ampoule |
| GERMANY | CATAPRESAN 150 | 6191514.01.00 | BI DE | 0.15 mg | tablets |
| GERMANY | CATAPRESAN 300 | 6191514.02.00 | BI DE | 0.3 mg | tablets |
| GREECE | CATAPRESAN | 8501 | BI GR | 0.15 mg | tablets |
| ICELAND | CATAPRESAN | 711482 | BI International GmbH DE | 0.025 mg | sugar-coated tablets |
| IRELAND | DIXARIT | 7/32/1 | BIL GB | 0.025 mg | sugar-coated tablets |

| Country | Tradename | MA Number | MAH | Strength | Dosage form |
|----------------|---|-----------------|--------------------------|-------------|------------------------------------|
| IRELAND | CATAPRES AMPOULES | 7/14/3 | BIL GB | 0.15 mg/ml | ampoule |
| IRELAND | CATAPRES TABLETS 0.1 MG | PA 7/14/1 | BIL GB | 0.1 mg | tablets |
| IRELAND | CATAPRES | PA 7/14/2 | BIL GB | 0.3 mg | tablets |
| ITALY | CATAPRESAN 150 MCG/ML SOLUZIONE INIETTABILE | 021502036 | BI IT | 0.15 mg/ml | ampoule |
| ITALY | CATAPRESA | 27393014 | BI IT | 2.5mg/paste | transdermal therapeutic systems |
| ITALY | CATAPRESA | 27393026 | BI IT | 5mg/paste | transdermal therapeutic systems |
| ITALY | CATAPRESAN 300 MCG COMPRESSE | 021502024 | BI IT | 0.3 mg | tablets |
| LUXEMBOURG | DIXARIT | 0632/02/12/7851 | BI BE | 0.025 mg | sugar-coated tablets |
| LUXEMBOURG | CATAPRESSAN 150 MCG/1 ML SOLUTION INJECTABLE/SOLUTION POUR PERFUSION | 0632/00/10/6812 | BI BE | 0.15 mg/ml | ampoule |
| LUXEMBOURG | CATAPRESSAN | 0632/00/10/6813 | BI BE | 0.15 mg | tablets |
| NETHERLANDS | DIXARIT | RVG 06757 | BI NL | 0.025 mg | sugar-coated tablets |
| NETHERLANDS | CATAPRESAN INJECTIEVLOEISTOF 0,150 MG/ML | RVG 06055 | BI NL | 0.15 mg/ml | ampoule |
| NORWAY | CATAPRESAN | 5818 | BI International GmbH DE | 0.025 mg | sugar-coated tablets |
| PORTUGAL | CATAPRESAN | 9200618 | Unifarma PT | 0.15 mg | tablets |
| PORTUGAL | CATAPRESAN | 9200626 | Unifarma PT | 0.15 mg | tablets |
| SPAIN | CATAPRESAN | 50.669 | Fher ES | 0.15 mg | tablets |
| SWEDEN | CATAPRESAN | 8478 | BI International GmbH DE | 0.15 mg/ml | ampoule |
| UNITED KINGDOM | CATAPRES AMPOULES | PL 00015/5008R | BIL GB | 0.15 mg/ml | ampoule |
| UNITED KINGDOM | CATAPRES TABLETS 0.1 MG | PL 00015/5009R | BIL GB | 0.1 mg | tablets |
| UNITED KINGDOM | CATAPRES TABLETS 0.3 MG | PL 00015/5041R | BIL GB | 0.3 mg | tablets |