

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

**Isradipine
Lomir, ICAZ**

UK/W/027/pdWS/001

Rapporteur:	UK
Finalisation procedure (day 120):	20 June 2011
Date of finalisation of PAR	25 June 2011

ADMINISTRATIVE INFORMATION

Invented name of the medicinal products:	Lomir, ICAZ
INN (or common name) of the active substance:	Isradipine
MAH (s):	Daiichi Sankyo Portugal Lda., Daiichi Sankyo Italia SpA, Daiichi Sankyo Belgium N.V.-S.A., Daiichi Sankyo France SAS
Pharmaco-therapeutic group (ATC Code):	C08C A03
Pharmaceutical form(s) and strength(s):	2.5 mg tablets 2.5 and 5.0 mg SRO capsules

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I. EXECUTIVE SUMMARY

This is an assessment of data for isradipine, as part of the Article 45 EU worksharing procedure for assessment of paediatric studies completed before the Paediatric Regulation entered into force 26 Jan 2007. The UK is Rapporteur for this procedure.

Isradipine is a calcium channel blocker of the dihydropyridine class with a selective activity in the voltage gated calcium channels (L-type or “long-acting”). It is prescribed for the treatment of essential hypertension. It does not have an approved paediatric posology in any country, and the extent of its off-label use is unknown. It is available in 2.5 mg tablets and 2.5 and 5.0 mg slow release capsules.

Isradipine was first authorised in Europe in 1989 via a National procedure and is currently being marketed in all EU countries. Novartis is currently the Marketing Authorization Holder in 34 countries and Daiichi Sankyo is MAH in 5 countries. The submission of data under this Article 45 procedure is made by Daiichi Sankyo and the applicant stated that “the implication of the available information and data does not allow to recommend the use of isradipine in children for high blood pressure treatment.”

The current submission includes: three literature retrospective paediatric studies, a PSUR covering the period February 2007 to January 2010 and a brief clinical overview.

The Rapporteur is of the opinion that the applicant’s position is acceptable and no fundamental changes to the SmPC are required as a result of this submission. This opinion is endorsed by concerned MSs after circulation of PPdAR. There is no List of Questions and the Rapporteur and all concerned members of state agree that no further action is required.

Summary of outcome

- No change unless current SmPC lacking paediatric information
- Change
- New study data: <section(s) xxxx, xxxx>
- New safety information: <section(s) xxxx, xxxx>
- Paediatric information clarified: section 4.2 to be implemented Nationally, only if the current SmPC are lacking paediatric information
- New indication: <section(s) xxxx, xxxx>

II. RECOMMENDATION

No further action required.

Proposed SmPC/PIL changes

If the current SmPC and PIL are lacking paediatric information; the following proposed text should be implemented nationally.

SmPC- Section 4.2

Paediatric population

The safety and efficacy of isradipine in children have not been established. No data are available.

PIL- Chapter 3

Use in children

<Product name> tablets/capsules are not recommended for children.

III. INTRODUCTION

On 13 August 2010, the MAH Daiichi Sankyo submitted three literature based completed paediatric retrospective studies for isradipine, in accordance with Article 45 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview and a PSUR covering the period February 2007 to January 2010 have also been provided. The MAH stated that the submitted paediatric studies do not influence the benefit risk for isradipine and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

Product characteristics

Isradipine is a dihydropyridine calcium antagonist with a higher affinity for calcium channels in arterial smooth muscle than for those in the myocardium. Thus it produces vasodilatation of peripheral coronary and cerebral arteries without notably depressing cardiac function. As a result of the vasodilatation of peripheral arteries, the arterial blood pressure is lowered; the attending after-load reduction improves myocardial contractility and increases cardiac output, while myocardial oxygen consumption decreases. In adults isradipine is indicated for treatment of essential hypertension with recommended therapeutic dose range of 2.5-5 mg twice daily. Currently, isradipine is not recommended in the European Union for use in children or adolescents below the age of eighteen due to insufficient data on safety and efficacy.

Paediatric hypertension

Hypertension is an important risk factor for cardiovascular morbidity and mortality and occurs in 1 to 9% of children and adolescents. In younger children, hypertension is generally secondary to

renal or renovascular disease. The most common cause of paediatric hypertension, accounting for between 60 and 70% of cases is renal disease, including hereditary kidney disorders, renal hypo- or dysplasia and acquired glomerulopathies. Other causes include diabetes mellitus, cardiac pathologies, coarctation of the aorta, and endocrine disease such as pheochromocytoma and hyperthyroidism. Essential hypertension is rare in infants and young schoolchildren, but is frequent in adolescents. Its increasing prevalence during childhood parallels that of obesity. In adolescents, essential hypertension is more prominent, especially in association with obesity.

Hypertension in children is defined as diastolic and/or systolic blood pressure (BP) greater than the 95th percentile for gender, age and height, measured on at least 3 occasions. The treatment goal is generally to reduce BP to below the 95th percentile, although in some cases, e.g. children with nephropathy, a lower target may be desired.

Acceptable drug classes for use in children include ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, and diuretics. There are currently a few drugs approved for the treatment of hypertension in children, but often the use of antihypertensives in this age group is off-label.

IV.1 Information on the pharmaceutical formulation used in the studies

Isradipine was administered either as commercially available 2.5- or 5-mg immediate-release capsules or as a 1.0 mg/ml extemporaneous compounded preparation.

IV.2 Clinical aspects

1. Introduction

The MAH submitted the following papers:

- JT Flynn & SJ Warwick. Isradipine treatment of hypertension in children: a single-centre experience. *Pediate Nephrol* (2002) 17: 748-753.
- CE Johnson, PA Jacobson & MH Song. Isradipine therapy in hypertensive paediatric patients. *The Annals of Pharmacotherapy* (1997) Vol. 31, 704-707.
- LM. Strauser, T Groshong, & JD Tobias. Initial experience with isradipine for the treatment of hypertension in children. *Southern Medical Journal* (2000) Vol. 93, No.3: 287-293.
- PSUR covering the period of February 2007 to January 2010.
- A brief clinical overview evaluating the available literature.

IV.2 Non-clinical aspects

No non-clinical studies on juvenile animals were submitted by the applicant.

IV.3 Clinical Aspects

IV.3.1 Isradipine treatment of hypertension in children: a single-centre experience.

JT Flynn & SJ Warwick 2002

➤ Description

Retrospective, un-controlled study in which data were collected by review of patient's medical records. Efficacy of isradipine in lowering blood pressure was measured by comparing with the baseline values.

➤ Methods

- Objective(s)

- To determine the effects of isradipine treatment in hospitalized paediatric patients.

- To determine whether there was a dose-response relationship between isradipine dose and the change in BP.

- Study design

Demographic information collected included patient's age, weight, underlying diagnosis, and treatment with other antihypertensive medications prior to use of isradipine. Vital signs, including systolic BP, diastolic BP, and heart rate were recorded from inpatient nursing flow sheets and outpatient clinic records. Isradipine dose and formulation, use of concomitant antihypertensive medications, and adverse effects reported by patients were also recorded.

- Study population /Sample size

Mean patient age was 74 ± 55 months (6.2 ± 4.6 years), with a range of 1 week to 16.8 years. Of the 72 patients, 70 (97.2%) had secondary hypertension. Underlying diagnoses for the 72 treatment courses in children with secondary hypertension included glomerulonephritis (18 patients), renal transplant (16 patients), liver transplant (16 patients), reflux nephropathy (5 patients), steroid-induced (5 patients), renovascular (3 patients), and other (9 patients). Hypertension in the solid organ transplant recipients was typically related to volume overload, the effects of immunosuppressive medications (corticosteroids and calcineurin inhibitors), pre-transplant hypertension, or a combination of these factors.

- Treatments

Isradipine was started at a dose of 0.05-0.1 mg/kg per dose every 8 h and adjusted as necessary until the target reduction of BP was reached. Frequency of dosing was increased to every 6 h if the patient's BP frequently exceeded the target range more than 1 h before the next

scheduled isradipine dose, or if additional doses were frequently being administered as described above. If BP control was not achieved with isradipine alone, additional antihypertensive agents were added as necessary.

Isradipine was administered either as commercially available 2.5- or 5-mg immediate-release capsules or as a 1.0 mg/ml extemporaneous compounded preparation.

In 38 of the 74 treatment courses (51.4%), target BP was reached with isradipine alone. In 28 instances (37.8%) one additional medication was required, and in 8 (10.8%) two additional medications were needed. Supplemental medications utilized included diuretics (20 patients), beta-adrenergic antagonists (10 patients), direct vasodilators (minoxidil or hydralazine, 7 patients), angiotensin converting enzyme inhibitors (5 patients), and transdermal clonidine (2 patients).

Table 1- Isradipine dose received according to age, diagnosis, or dosing regimen

Group	<i>n</i>	Dose received (mg/kg per day)
All treatment courses combined	74	0.36±0.17
Age groups		
0-1 year	9	0.27±0.11
1-6 years	32	0.38±0.20
6-12 years	21	0.39±0.16
>12 years	12	0.28±0.16
Solid organ transplant		
Glomerulonephritis	18	0.38±0.16
Isradipine monotherapy	38	0.31±0.12*
Combination therapy	36	0.40±0.21*
t.i.d. dosing	45	0.33±0.16**
q.i.d. dosing	20	0.45±0.18**

P*=0.04 for comparison of monotherapy with combination therapy (two-tailed *t*-test), *P*=0.01 for comparison of t.i.d. dosing with q.i.d. dosing (two-tailed *t*-test)

Patients' BP and heart rate during the 24 h prior to the use of isradipine were recorded, followed by their BP, heart rate, and isradipine dose on the day of discharge from the hospital. For outpatients, clinic BP and heart rates were recorded for the clinic visit immediately preceding the initial use of isradipine, followed by the patients' BP, heart rates, and isradipine dose on the first follow-up visit.

- Statistical Methods

Database software used included the Medlog clinical data management system and Excel 97. Further data analysis was performed utilizing SPSS for Windows 10.0.5.

Except where otherwise noted, data included in this report are expressed as mean±standard deviation, or as percentages. Statistical tests utilized included two-tailed, paired and unpaired *t*-tests to examine differences in group means for normally distributed variables and the Mann-Whitney and Wilcoxon signed ranks tests for non-normally distributed variables. The Chi-square test or Fisher's exact test was used to examine the differences in proportions between groups.

Linear regression analysis was performed to examine the relationship between variables. Statistical significance for all analyses was set at $P < 0.05$.

➤ Results

- Recruitment/ Number analysed

A total of 80 children were identified as having been treated with isradipine at the University of Michigan between July 1995 and May 2000. However, BP data were missing for 4 patients, and were incomplete for another 4 patients. Two additional patients received isradipine on two separate occasions (before and after renal transplantation in both instances), leaving 72 patients and 74 treatment courses that are analyzed in this report. BP and other data from the 4 treatment courses in the 2 children who received isradipine twice were treated as coming from 4 separate patients for purposes of analysis.

- Efficacy results

In 38 of the 74 treatment courses (51.4%), target BP was reached with isradipine alone. In 28 instances (37.8%) one additional medication was required, and in 8 (10.8%) two additional medications were needed.

Assessor's comment: for assessing the efficacy of isradipine, only the results of the monotherapy should be considered, as the results in this patient group only, are indicative of isradipine efficacy.

Table 2- BP reduction with isradipine monotherapy

Table 4 BP reduction with isradipine monotherapy^a

Group	n	BP prior to isradipine treatment	BP during isradipine treatment	Mean change in BP	P*
Age 0–1 years	6	117±13 77±13	97±17 58±15	21±11 19±12	0.006 0.01
Age 1–6 years	14	132±10 79±13	117±8 70±10	16±13 9±18	0.001 0.08
Age 7–12 years	10	127±11 79±8	120±10 71±8	7±11 8±11	0.07 0.04
Age >12 years	8	134±13 84±8	124±10 75±8	10±11 9±6	0.03 0.003
All treatment courses combined	38	129±12 80±11	116±14 69±11	13±12 10±13	<0.0001 <0.0001

* Two-tailed, paired *t*-test
^a For each row, the upper value is systolic BP (mean±SD) and the lower value is diastolic BP (all in mmHg)

For almost every age group, there was a significant reduction in BP following isradipine treatment. There was no significant change in heart rate with isradipine treatment, except in infants <1 year old, in whom heart rate decreased from 148 to 132 beats per min ($P=0.04$, two-tailed paired *t*-test).

To determine whether there was a dose-response relationship between isradipine dose and the change in BP, linear regression analysis was performed. In order to eliminate the effects of other antihypertensive medications, this analysis was restricted to the 38 treatment courses when isradipine was used as monotherapy.

No significant relationship was demonstrated between isradipine dose (in mg/kg per day) and change in systolic or diastolic BP, expressed either as absolute change in mmHg (baseline BP minus treatment BP), or as percentage change [(baseline BP minus treatment BP)/baseline BP].

Assessor's comment: dose-response analysis was correctly restricted to the 38 patients that received isradipine as monotherapy, and no significant relationship was established. In infants <1 year old, isradipine caused a significant reduction in heart rate from 148 to 132 beats per min ($P=0.04$). However it is noted that all infants under 1 year of age were on combination therapy.

- Safety results

Adverse effects attributed to isradipine treatment occurred in 7 of 74 treatment courses (9.5%) during the period of follow-up in this study, for a rate of 0.35 adverse events per patient-month of treatment. Adverse effects reported included headache (2 patients), flushing (2 patients), dizziness (1 patient), tachycardia (1 patient), and unspecified (1 patient). No patient reported more than one adverse effect.

- Discussion

Of note in the Flynn et al study, some measurements and comparisons have been carried out in monotherapy Versus combination therapy; however as they are not directly relevant to this assessment of the isradipine efficacy, they have not been included in this assessment report. In these children, nearly all of whom had secondary hypertension and were being treated as hospital inpatients, isradipine significantly lowered both systolic and diastolic BP. There was no significant effect of isradipine on heart rate, except in infants <1 year of age who received isradipine in combination with other agents. The lack of an effect on heart rate in patients of all other ages receiving isradipine monotherapy suggests that this change in children less than 1 years may have been related to the additional antihypertensives they received.

The doses of isradipine administered to the children in this study were significantly greater than doses typically used in adults. Although this has also been reported for several other calcium antagonists, most notably amlodipine, because of the retrospective, uncontrolled design of this study it is difficult to know whether children truly require greater doses than adults or whether this finding simply represents the prescribing practices at the centre. It may also be related to the fact that most of the children received isradipine in suspension form. Although the suspension remains stable after compounding, there may be differences in bioavailability of the suspension compared with the commercially available formulations that could reduce the magnitude of the antihypertensive effect of the suspension.

Another important finding was that most of the children in this study seemed to require administration of isradipine three or four times daily to maintain stable BP. While this is greater than the recommended frequency for adults of two times per day, it is consistent with the relatively short elimination half-life of isradipine (as little as 6 hr). It may also be related to the extensive first-pass hepatic metabolism of isradipine and the possibility that children may clear this drug more rapidly than adults due to their proportionately greater hepatic mass. Clearly, a formal pharmacokinetic study would be necessary to settle this issue.

Assessor's comment: This uncontrolled retrospective study showed that in 38 children receiving monotherapy, isradipine significantly lowered both systolic and diastolic BP from

baseline values. No significant relationship between dose and response was established in this patient group.

The doses of isradipine administered to the children were significantly greater than doses typically used in adults and most of the children required administration of isradipine three or four times daily to maintain stable BP. The authors suggested that, while this is greater than the recommended frequency for adults of two times per day, it may be consistent with the relatively short elimination half-life of isradipine. It may also be related to the extensive first-pass hepatic metabolism of isradipine and the possibility that children may clear this drug more rapidly than adults due to their proportionately greater hepatic mass. However as the authors have already recognised, a paediatric pharmacokinetic study is necessary to fully describe the PK parameters of isradipine in children.

There was no significant effect of isradipine on heart rate, except in infants <1 year of age who received isradipine in combination with other agents.

Adverse effects reported including headache, flushing, dizziness and tachycardia are amongst common or very common known side effects of isradipine, and are not of major concern.

In the absence of paediatric PK data, the inclusion of the results of this study in the 5.1 can be misleading. The MAH position of not changing the SmPC is acceptable.

IV.3.2 Isradipine therapy in hypertensive paediatric patients.

CE Johnson, PA Jacobson & MH Song. 1997.

The dosage and effectiveness of isradipine in controlling acute or chronic hypertension in 53 paediatric patients (22 girls, 31 boys), with a mean age of 5.8 +/- 4.0 years were evaluated. Retrospective medical records of hospitalized children aged 1 day to 16 years with hypertension treated with isradipine between January 1994 and March 1996 were reviewed. Patient age, gender, weight, disease states, current medications, isradipine dosage and formulation, pre- and post dose systolic and diastolic blood pressure measurements with each dose of isradipine, were collected.

21 patients (40%) received isradipine as monotherapy; the rest had combination therapy with other add-on antihypertensives. The mean dosage of isradipine in 46 patients who received regularly scheduled doses was 0.38 +/- 0.22 mg/kg/d. Patients who demonstrated a response received a mean dosage of 0.40 +/- 0.20 mg/kg/d. The total daily dosage was administered in one dose for 1 patient, two doses for 15 patients, three doses for 27 patients, and four doses for 3 patients.

Extrapolating dosage for paediatric patients from the usual adult isradipine dosage of 2.5-5 mg administered twice daily (based on average adult weight of 70kg) would result in an appreciably lower dosage of 0.07-0.14 mg/kg/d.

The overall change in blood pressure was evaluated by comparing a single blood pressure measurement prior to therapy with a single measurement at the end of therapy or at discharge. This did not assess the effect of the individual doses. The comparison of a mean of several blood pressures before and after treatment gives more accurate measurements.

An extemporaneously prepared oral suspension of isradipine 1 mg/mL in simple syrup has been formulated and determined to be stable for 35 days. 49 patients received the liquid formulation, 3 patients received both liquid and capsules and 1 patient received only capsules.

Table 3- Isradipine dosage and blood pressure changes in each disease group

PARAMETERS	ALL PATIENTS	RESP ^a	NR ^b	ALL TRANSPLANTS	PATIENTS BY DISEASE GROUPS			
					BMT	KIDNEY TRANSPLANTS	RENAL DISEASE ^c	IDIOPATHIC ^d
Isradipine dosage ^e (mg/kg/d)	0.38 ± 0.22 ^f	0.40 ± 0.20	0.24 ± 0.23	0.31 ± 0.18	0.22 ± 0.15	0.33 ± 0.20	0.43 ± 0.22	0.46 ± 0.28
Isradipine dosage range (mg/kg/d)	0.04 – 0.88	0.06 – 0.88	0.04 – 0.75	0.04 – 0.74	0.06 – 0.35	0.1 – 0.74	0.07 – 0.87	0.16 – 0.88
Systolic change (%) ^e	-11.8 ± 12.5	-14.8 ± 11.8	0.61 ± 6.89	-13.0 ± 10.1	- 9.9 ± 8.7	-12.8 ± 10.2	-13.9 ± 11.5	- 3.2 ± 18.7
Systolic change range (%)	-38.5 – 12.7	-38.5 – 12.7	-8.3 – 12.1	-32.9 – 11.9	-18.0 – 1.6	-31.0 – 11.9	-38.5 – 3.7	-34.8 – 12.7
Diastolic change (%) ^e	-17.3 ± 19.6	-22.0 ± 18.4	2.7 ± 9.2	-15.9 ± 14.7	-11.0 ± 8.8	-16.6 ± 16.2	-24.7 ± 16.9	-16.8 ± 24.2
Diastolic change range (%)	-60.8 – 21.4	-60.8 – 1.1	-8.4 – 21.4	-47.0 – 16.0	-19.8 – 1.1	-47.0 – 16.0	-54.5 – 1.5	-60.8 – 21.4
Group size	53	43	10	24 ^g	4	17	21	8

BMT = bone marrow transplant; NR = nonresponding patients; RESP = responding patients.

^aResponding patients: all patients responding with at least 10% reduction in either systolic or diastolic blood pressure following isradipine therapy.

^bNonresponding patients: all patients responding with less than a 10% reduction of both systolic and diastolic blood pressure following isradipine therapy.

^cHypertension secondary to renal disease without transplant.

^dHypertension secondary to nonrenal causes.

^eReported as mean ± SD.

^fSeven patients were not included in the mean for isradipine dosage for all patients because each received doses only as needed (n = 46).

^gIncludes three liver transplant patients.

In all 53 patients a mean change of $-11.8\% \pm 12.5\%$ and $-17.3\% \pm 19.6\%$, respectively was observed in systolic and diastolic blood pressure. Isradipine was an effective antihypertensive agent to reduce the systolic and/or diastolic blood pressure 10% or more compared with pre-treatment measurements in 43 (81%) of 53 paediatric patients.

Simple linear regression was used to determine statistical relationships between percent change in systolic and diastolic blood pressure and isradipine dose. No significant correlation was found.

Assessor's comment: This uncontrolled retrospective study showed that in 53 children receiving mono or combination therapy, isradipine has lowered both systolic and diastolic BP from baseline values. However no statistical analysis was performed, thus the significance of this finding is questionable. No significant relationship between dose and response was established in this patient group either.

Furthermore the results given in table 3 consists of both mono and combination therapy, making it impossible to evaluate effect of isradipine on its own.

The author's state that extrapolating a dosage for paediatric patients from the usual adult isradipine dosage of 2.5-5 mg administered twice daily (based on average adult weight of 70kg) would result in an appreciably lower dosage of 0.07-0.14 mg/kg/d. However the mean dosage used in this study was 0.38 +/- 0.22 mg/kg/d, in two or three equally divided doses, which is considerably higher than the recommended dosage for adults, but consistent with the observation of previous study (Flynn *et al.*, 2002). In the absence of paediatric PK data, it is not possible to comment on the dosing regimen.

The authors have acknowledged the limitations of the study and suggested a prospective controlled study. Adverse effects associated with isradipine were not recorded nor evaluated.

In the absence of statistical analysis and paediatric PK data, the inclusion of the results of this

study in the 5.1 could be misleading. The MAH position of not changing the SmPC is acceptable.

IV.3.3 Initial experience with isradipine for the treatment of hypertension in children.

LM. Strauser, T Groshong, & JD Tobias.

Pharmacy records were reviewed to identify paediatric patients who had received isradipine. The following demographic data were obtained: age, weight, sex, underlying medical problems, and initial blood pressure values. Information concerning isradipine included the initial dose and its interval, subsequent dose escalations, blood pressure response to the medication, and duration of therapy, some of which are presented in the table 4 below:

Table 4: Patients demographics and isradipine dosing regime

<i>Patient</i>	<i>Age/Sex</i>	<i>Weight, (kg)</i>	<i>Underlying Condition</i>	<i>Initial BP (mm Hg)</i>	<i>Effective Isradipine Dose</i>	<i>Monotherapy</i>
1	1.6 yr/F	7.6	CHF, CRF	140/86	1.5 mg q 8 hr (0.6 mg/kg/day)	No
2	5 yr/M	19.5	Kidney transplant rejection	134/84	3.0 mg q 8 hr (0.46 mg/kg/day)	No
3	8 yr/F	20.0	Hemolytic-uremic syndrome	145/105	2.5 mg q 8 hr (0.37 mg/kg/day)	No
4	10 d/F	4.2	Polycystic kidneys	130/72	0.4 mg q 8 hr (0.3 mg/kg/day)	Yes
5	4 yr/M	19.0	Nephrotic syndrome	140/95	2.5 mg q 8 hr (0.4 mg/kg/day)	Yes
6	2 yr/M	10.0	Nephrotic syndrome	148/95	3.0 mg q 8 hr (0.9 mg/kg/day)	No
7	3 yr/F	13.7	Hemolytic-uremic syndrome	133/84	1.4 mg q 8 hr (0.3 mg/kg/day)	Yes
8	9 yr/M	36.0	Poststreptococcal GN	210/110	7.2 mg q 6 hr (0.8 mg/kg/day)	Yes
9	6 yr/F	22.0	Henoch-Schönlein purpura	174/104	6.6 mg q 6 hr (1.2 mg/kg/day)	Yes
10	2 yr/F	11.7	Medulloblastoma	170/114	3.5 mg q 6 hr (1.2 mg/kg/day)	No
11	11 yr/M	39.0	Closed head injury	164/110	3.9 mg q 6 hr (0.4 mg/kg/day)	Yes
12	6.2 yr/M	26.0	Closed head injury	180/110	3.9 mg q 6 hr (0.6 mg/kg/day)	Yes

BP = Blood pressure; CHF = congestive heart failure; CRF = chronic renal failure; q = every; GN = glomerulonephritis.

Twelve patients who had received isradipine for control of mean arterial pressure over a 3-year period from 1996 to 1999 were identified. There were 6 boys and 6 girls with a mean age of 4.8 ± 3.3 years (range 10 days - 11 years) and a mean weight of 19.1 ± 10.7 kg (range 4.15 – 39 kg). In 9 of the 12 patients, hypertension had a renal aetiology and 3 patients had neurosurgical problems. Isradipine was used as monotherapy in 7 patients and in combination therapy in 5 patients. Isradipine was used as initial therapy for urgent hypertension as well as after nicardipine infusions for patients with emergent hypertension.

The mean isradipine dose required for effective blood pressure control was 0.6mg/kg/day. Hypertension of non-renal aetiology resulted in a slightly greater dose requirement of 0.7mg/kg/day versus 0.6mg/kg/day in patients with hypertension caused by renal disease.

There was a reduction of 32.8 ± 18.3 mm Hg (20%) of the initial systolic blood pressure and 22 ± 16.6 mm Hg (28%) of the initial diastolic blood pressure. Isradipine failed to provide adequate blood pressure reduction in 2 of 12 patients in doses of 3.5mg every 6 hours (1.2mg/kg/day). The authors consider isradipine an effective, orally administered agent for control of hypertension in children.

Documentation of the exact incidence of adverse effects is difficult in retrospective reviews; however, isradipine therapy was not discontinued in any of our 12 cases and no adverse effects were documented in the patients' medical records.

Assessor's comment: This uncontrolled retrospective study showed that in 12 children receiving mono/combo combination therapy, isradipine has lowered both systolic and diastolic BP from baseline values. There was a reduction of 32.8 ± 18.3 mm Hg (20%) of the initial systolic blood pressure and 22 ± 16.6 mm Hg (28%) of the initial diastolic blood pressure. Although there is a large reduction in both systolic and diastolic pressure, no statistical analysis was performed, thus the significance of this finding is questionable. Furthermore some children received combination therapy, thus is not possible to differentiate the effect of isradipine.

The mean isradipine dose required for effective blood pressure control in hypertension of non-renal aetiology was 0.7mg/kg/day versus 0.6mg/kg/day in patients with hypertension caused by renal disease. This dose is approximately 10 folds higher than the 0.07-0.14 mg/kg/d dose extrapolated from adults (based on average adult weight of 70kg) but consistent with the observation of previous studies (Flynn *et al.*, 2002 and Johnson *et al.*, 1997). In the absence of paediatric PK data, it is not possible to comment on the dosing regimen.

No adverse effects were documented in this study.

In the absence of statistical analysis and paediatric PK data, the inclusion of the results of this study in the 5.1 can be misleading. The MAH position of not changing the SmPC is acceptable.

Safety

PSUR covering the period 01 Feb 2007-- 31 Jan 2010

During this period 3 adverse event reports related to children were received by the MAH:

- A 3-year-old boy with medical history of multiple malformations syndrome with chronic renal failure and vesicoureteral reflux. He was treated with nadolol and with Lomir (isradipine), both for arterial hypertension. The patient was hospitalized for colocolostomy in a surgery unit. During postoperative recovery, blood pressure aggravated with hypertensive peak at 130/66 mmHg and intravenous nicardipine hydrochloride was administered. Lomir was stopped. The child experienced cough and oedemas and he was diagnosed with acute pulmonary and left cardiac failure on the following day. Intravenous cardiotoxic drugs were administered, and assisted ventilation and urethral catheterization were implemented. The patient recovered within 6 days. Hypertension was controlled with intravenous nicardipine hydrochloride. The next day, nicardipine hydrochloride and nadolol were discontinued.
- An 8 year old boy with overdose,(sparse report with no further information).
- A 17 year old girl with renal transplant reported oedema of lower limbs, erythema and pain in limbs. This is likely to be confounded by the underlying condition.

Assessor's comment: these 3 cases do not present new or unknown safety concerns for the paediatric population.

V. MEMBER STATES overall conclusion AND RECOMMENDATION

➤ Overall conclusion

The applicant has submitted three retrospective studies based on reviews of paediatric patient records. The Flynn *et al.*, study demonstrated that in 38 children receiving isradipine only, blood pressure was statistically significantly reduced. However this was a non randomized, uncontrolled, low powered retrospective study and thus the weight of the evidence is undermined. Furthermore no retrospective comparison was made with other antihypertensive agents used in the same population, and all data collection was performed by a single individual which could lead to bias. From regulatory point of view the evidence is not robust enough to support either a paediatric indication or a posology.

The other two studies by Johnson *et al.*, and Strauser *et al.*, were also uncontrolled, retrospective pharmacy record reviews in 53 and 12 children respectively receiving mono or combination therapy. The authors reported that isradipine lowered both systolic and diastolic BP from baseline values. However no statistical analysis was performed, thus the significance of this finding is not known.

Furthermore the doses administered in children in all 3 studies ranged from 0.5-1.0 mg/kg three or four times daily. Dosage extrapolated from the usual adult isradipine dosage of 2.5-5 mg administered twice daily (based on average adult weight of 70kg) would result in an almost 10 fold lower dosage of 0.07-0.14 mg/kg/d. There is a common consensus that extrapolation from adult dose does not necessarily produce correct dosing for children, however in the absence of paediatric PK parameters, it is not possible to suggest a dose based on the submitted studies.

In conclusion, although some effect was shown in these studies, data from these studies should not be added to section 5.1 of the SmPC. In the absence of paediatric PK information, inclusion of such summaries will create false conclusions and mislead the prescriber.

The submitted PSUR covering the time period from 01 Feb 2007 to 31 Jan 2010 and the subsequent analysis of safety information did not reveal any new relevant safety findings with isradipine.

The Rapporteur is of the opinion that the applicant's position is acceptable and no fundamental changes to the SmPC are required as a result of this submission. This opinion is endorsed by all concerned members of states after circulation of PPdAR. There is no List of Questions and the Rapporteur and all concerned members of state agree that no further action is required.

➤ Recommendation

No further action required. A type IB variation should be submitted by the MAH only if the current SmPC and PIL are lacking paediatric information.

Proposed SmPC/PIL changes

If the current SmPC and PIL are lacking paediatric information; the following proposed text should be implemented nationally.

SmPC- Section 4.2

Paediatric population

The safety and efficacy of isradipine in children have not been established. No data are available.

PIL- Chapter 3

Use in children

<Product name> tablets/capsules are not recommended for children.

**VI. LIST OF MEDICINAL PRODUCTS AND MARKETING
AUTHORISATION HOLDERS INVOLVED**

ICAZ 2.5 mg capsules; Daiichi Sankyo France SAS

ICAZ 5 mg capsules; Daiichi Sankyo France SAS

Lomir 2.5 mg tablets; Daiichi Sankyo Portugal Lda. Lomir SRO 5 mg capsules; Daiichi Sankyo Portugal Lda.

Lomir 2.5 mg tablets; Daiichi Sankyo Belgium N.V.-S.A.

Lomir retard 5 mg capsules; Daiichi Sankyo Belgium N.V.-S.A.

LomirSRO 2.5 mg capsules; Daiichi Sankyo Italia SpA

Lomir SRO 5.0 mg capsules, Daiichi Sankyo Italia SpA