

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

**Minoxidil**

**Loniten, Lonoten, Lonnoten, Lonolox**

**MT/W/0003/pdWS/001**

**Finalisation procedure (day 120):** 11/10/2011

**Date of finalisation of PAR** 09/12/2011

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## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VI Loniten Lonoten Lonnoten Lonolox
INN (or common name) of the active substance(s):	Minoxidil
MAH (s):	See section VI Pfizer Corporation Austria GesmbH Pfizer Pharma GmbH Pfizer Holding France Pfizer SA Pfizer bv Pharmacia Ireland Limited Pharmacia Italia SrL Pharmacia Limited
Pharmaco-therapeutic group (ATC Code):	CO2DC01
Pharmaceutical form(s) and strength(s):	2.5 mg, 5 mg and 10mg Tablets

## ABBREVIATIONS

BP	Blood pressure
DBP	Diastolic blood pressure
MAH	Marketing Authorisation Holder
PdWS	Paediatric work sharing
PL	Patient leaflet
PSUR	Periodic safety update report
SBP	Systolic blood pressure
SmPC	Summary of product characteristics

## I. EXECUTIVE SUMMARY

SmPC and PL changes are proposed in sections 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3.

### Summary of outcome

- No change
- Change
- New study data: sections 5.1, 5.2 and 5.3
- New safety information: sections 4.4 and 4.8
- Paediatric information clarified: section 4.2

Since its introduction in the 1970s minoxidil has been used effectively in conjunction with diuretics and a beta-blocker in the treatment of severe refractory systemic hypertension. As a result of its efficacy in lowering severe blood pressure which was resistant to other agents, there was a large demand for minoxidil in severe refractory hypertension and hypertensive emergencies including those which occurred in children.

Because of success in refractory hypertension it was added to existing treatment. No controlled clinical trials were ethically possible. However, information from partially controlled trials was obtained. As it was not possible to use patients as controls, the pre-trial findings were used for this purpose. These studies have confirmed the efficacy of minoxidil. There are still concerns regarding the safety of minoxidil in young children, especially in infants, because of insufficient data. Available data involved only a small number of children.

Data packages were submitted by the marketing authorisation holder (MAH) for paediatric work sharing (PdWS) in conformity with Article 45 of the Paediatric regulation (EC) 1901/2006 as amended.

Minoxidil has been shown to be effective and well tolerated but has the disadvantage of adverse effects including the development of hypertrichosis. This is an important consideration when it is used in children. There is also concern about serious safety issues associated with its use, mainly fluid retention (requiring the use of a concomitant diuretic) and reflex tachycardia (requiring concomitant use of a beta blocker or methyldopa). The use of minoxidil is restricted in children. It is indicated for use in children with severe hypertension with target organ involvement which has not responded to treatment with other anti-hypertensive agents. The number of studies carried out in children with severe refractory hypertension is small because of the rarity of the condition in children.

SmPC and PL changes are proposed in Section II.

## II. RECOMMENDATION

In connection with the Paediatric Work Sharing (PdWS) Procedure according to Article 45 of the Paediatric Regulation (EC) No 1901/2006 as amended, with Procedure Number

MT/W/0003/pdWS/001, basing on a review of the paediatric data submitted by the Marketing Authorisation Holder (MAH) regarding the treatment with minoxidil of severe refractory hypertension in children, basing on comments made by other Member States following the Day 70 Preliminary Paediatric Assessment Report (PPdAR), and after consideration of the MAH's response to the amended PdAR sent on the 13<sup>th</sup> of April, 2011, it is recommended that the following changes be made to the SmPC

### **Summary of Product Characteristics**

#### **Section 4.2 Posology and method of administration**

##### *Patients younger than 12 years of age*

The use of minoxidil in children is restricted to children with severe hypertension associated with target organ damage where other treatment has failed. The data regarding the use of minoxidil in children is very limited, especially in infants. The dosage recommendations can only be considered as a rough guide to treatment at present as this is based on the publication of a few case reports and studies involving a small number of children. The starting dose used basing on these reports is 0.2mg/kg of minoxidil as a single or divided dose. Careful titration increasing in steps of 0.1 to 0.2 mg/kg/day at intervals of at least 3 days is essential. The effective dose range is 0.25 to 1.0 mg/kg/day. The maximum dose is 50mg/day.

Treatment of children with minoxidil should only be initiated under the close supervision of a specialist in hospital.

##### *Patients over 12 years and adults*

The recommended starting dose is 5mg per day. If required, this dosage can later be increased up to 20 mg, and then to 40 mg daily (given as a single dose or in two divided doses). Dose increases should be made at increments of 5 mg to 10 mg minoxidil per day at intervals of three or more days. If a dose of 50 mg of minoxidil has been reached, the dose may be increased by 25 mg minoxidil per day to a maximum dose of 100 mg per day.

If the desired decrease of diastolic blood pressure exceeds 30 mmHg, dosage should be divided to two daily doses to keep daily blood pressure fluctuations as low as possible.

#### **Section 4.4 Special warnings and precautions for use**

The following should be added to this section:

##### ***Paediatric population***

Children strictly require appropriate and individualised dosing of minoxidil, beta-blockers and diuretics. They should be under close specialist supervision in hospital. Caution is required when there is significant renal impairment. The development of peripheral oedema or any signs suggestive of congestive heart failure or of pericardial or pleural effusion should be carefully watched for. Renal function should be monitored. Body weight and urine output should be monitored.

Regular follow up must be ensured during treatment with minoxidil.

Before starting treatment parents and carers should be warned of the likely occurrence of hypertrichosis.

## **Section 4.8 Undesirable effects**

Post authorisation experience has shown that, in a particular study, out of 50 patients on oral minoxidil, one case involved a two year old female with a history of chronic renal failure and peritoneal dialysis who developed pericardial effusion from which she recovered after treatment.

In addition, the estimated total exposure (based on only nine months of data) was about 17,000 patient-years with however no appreciable use in children.

## **Section 5.1 Pharmacodynamic properties**

As severe hypertension requiring multi-drug therapy is uncommon in children, paediatric use of minoxidil was limited in the development programme and has remained so in published literature. Data available in children younger than 10 years of age is very limited; it involves approximately 40 patients, eight of whom were under one year of age.

## **Section 5.2 Pharmacokinetic properties**

No pharmacokinetic data regarding minoxidil in the paediatric population is currently available.

## **Section 5.3 Preclinical safety data**

No data regarding juvenile animal toxicity studies is currently available.

## **Package Leaflet**

A section regarding safety information for children should be **added or included** in the PL.

### **Children**

During treatment with minoxidil the child should be under specialist supervision. The daily dose of minoxidil will be determined by the specialist and it may be adjusted according to the child's needs. During treatment the child will be additionally treated with other medicines as decided by the specialist to prevent rapid heart beat and accumulation of fluid in the body. You should contact the doctor if the child has any of the following: a very rapid heart beat, rapid breathing, swelling of the legs, rapid weight gain, and reduced urine. While on treatment with minoxidil the child will need to be regularly seen by the doctor.

A Type IB variation is requested from the MAH within 90 days of publication of the Public AR.

## **III. INTRODUCTION**

In connection with this PdWS procedure the MAH submitted the following documentation required in accordance Article 45 of the Regulation no 1901/2006:

- Critical Expert Overview Minoxidil Article 45.
- Reports of efficacy and safety studies:
  - Study – 2703 - study report: “Minoxidil, an anti-hypertensive in patients refractory to marketed anti-hypertensives”
  - Study - 2703 - summary

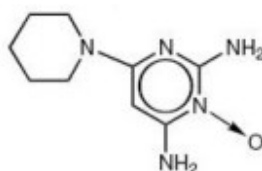
Study - 2703 – synopsis

- Study - 2709 - protocol  
Study - 2709 - partially controlled clinical studies  
Summary of clinical trials of minoxidil in the USA  
Study - 2709 – synopsis
- Publications from the medical literature concerning minoxidil and its use in children.
- A Justification was also submitted by the applicant proposing that no changes are necessary to: both the SmPC and PL A Justification was also submitted by the applicant proposing that no changes are necessary to: both the SmPC and PL
- Following a request for information (RFI) by the Rapporteur, the MAH also submitted a Country SmPC Comparative Table together with SmPCs of countries where minoxidil tablets are currently on the market in the EU.

## IV. SCIENTIFIC DISCUSSION

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

Minoxidil is an antihypertensive peripheral vasodilator. Minoxidil occurs as a white to off-white, odourless crystalline powder that is soluble in alcohol and propylene glycol; sparingly soluble in methanol; slightly soluble in water; practically insoluble in chloroform, acetone and ethyl acetate. The chemical name for minoxidil is 2,4-pyrimidinediamine, 6-(1-piperidinyl)-,3-oxide. The structural formula is represented below:



$C_9H_{15}N_5O$

M.W. 209.25

Minoxidil tablets for oral administration contain 2.5 mg, 5mg or 10 mg of minoxidil. The inactive ingredients are: colloidal silicon dioxide, anhydrous lactose, magnesium stearate, microcrystalline cellulose, sodium starch glycollate. It should be protected from light

### Uses and Administration (1)

Minoxidil is an antihypertensive that acts mainly by causing direct peripheral vasodilatation of the arterioles. It produces effects on the cardiovascular system similar to those of hydralazine. Minoxidil is given orally for the treatment of severe hypertension unresponsive to standard

therapy. When applied topically to the scalp minoxidil may stimulate hair growth to a limited extent and is used in the treatment of alopecia.

In the treatment of hypertension minoxidil is given with a beta blocker, or with methyldopa, to diminish the cardiac-accelerating effects, and with a diuretic, usually a loop diuretic, to control oedema. After a single oral dose, the maximum hypotensive effect usually occurs after two to three hours, although the full effects may not occur until after three to seven days of continuous treatment. An initial dose of 5 mg of minoxidil daily (or 2.5 mg daily in the elderly) is gradually increased at intervals of not less than three days to 40 or 50 mg daily according to response; in exceptional circumstances up to 100 mg daily has been given. If more rapid control of blood pressure is required, dosage increments of 5 mg may be made every six hours with careful monitoring. The daily dose may be given as a single dose or in two divided doses.

Reduced doses may be required in patients with renal impairment **(1)**

### **Administration in children**

Minoxidil has been used in children aged 12 years and under to treat severe hypertension unresponsive to standard therapy. The initial oral dose used is 200 micrograms/kg daily in one or two divided doses, increased according to response by 100 to 200 micrograms/kg increments at intervals of not less than three days to a maximum daily dose of 1 mg/kg or 50 mg.

### **Administration in renal impairment (1)**

A study of the pharmacokinetics of minoxidil in patients with varying degrees of renal impairment found that the non-renal clearance was also impaired as renal function worsened. Substantial accumulation of minoxidil might occur in these patients during multiple-dose therapy. It was advised that minoxidil be started with smaller doses or at longer dosage intervals in patients with renal impairment. **(1)**

### **Alopecia**

Minoxidil is used topically to stimulate hair growth in alopecia although its mechanism of action is poorly understood. Increases in pigmented non-vellus hair may be due to thickening and pigmentation of existing vellus rather than new growth

## **IV.2 Clinical aspects**

### **Introduction**

Systemic hypertension occurs commonly in adults, and if untreated, is a major risk factor for myocardial infarction, stroke and renal failure. The prevalence of hypertension increases with age ranging from 15% in young adults to 60% in individuals older than 65 years. In infants and younger children, systemic hypertension is uncommon, with a prevalence of <1% but when present it is usually indicative of an underlying disease process (secondary hypertension). In contrast, adolescents may develop primary or essential hypertension (without underlying cause). Essential hypertension during childhood may track into adulthood, as demonstrated by several large clinical studies. Children with blood pressure >90<sup>th</sup> percentile have a 2.4-fold greater risk of having hypertension as adults **(2)**

In the past physicians were mainly concerned with the occurrence of secondary hypertension in children resulting from parenchymal renal disease and renal artery stenosis. During the past three decades considerable progress has been made regarding information about systemic hypertension in children and adolescents. The routine measurement of blood pressure (BP) in children and adolescents as well as the publication of norms for BP in these subjects not only enabled more frequent detection of significant asymptomatic hypertension secondary to previously undetected disorders but also brought about greater awareness that mild elevations of blood pressure during childhood were more common than previously recognized and that this may represent the onset of early essential hypertension.

In general the younger the child, the greater is the probability that the hypertension is secondary to a cause which can be identified. After puberty essential hypertension is more likely.

A review of the literature revealed that 78% of 563 young patients with secondary hypertension had a renal parenchymal abnormality. In the remaining 22%, the cause of hypertension, in order of frequency was renal artery stenosis, coarctation of the aorta, phaeochromocytoma and a variety of other conditions.

The common causes of hypertension in children by age are as follows:

<b>Infants</b>	<b>1 to 6 years</b>	<b>7 to 12 years</b>	<b>12 to 18 years</b>
Thrombosis of renal artery or vein	Renal artery stenosis	Renal parenchymal disease	Essential hypertension
Congenital renal anomalies	Renal parenchymal disease	Renovascular abnormalities	Renal parenchymal disease
Coarctation of the aorta	Wilms tumor	Endocrine causes	Endocrine causes
Bronchopulmonary dysplasia	Neuroblastoma	Essential hypertension	
	Coarctation of the aorta		

Children and adolescents with hypertension can be asymptomatic. Infants are unable to complain even if they have symptoms. Children with secondary hypertension can have mild to severe elevations of blood pressure. If it is rising rapidly there may be symptoms of headache apart from the clinical manifestations of the underlying disease. With substantial hypertension headache, dizziness, epistaxis, anorexia, visual changes and seizures may occur. Hypertensive encephalopathy is suggested by the presence of vomiting, ataxia, pyrexia, stupor, and seizures. Regardless of the cause, end-organ (cardiac and renal) dysfunction occurs with marked hypertension.

Young children and infants with unexplained heart failure or seizures should have their blood pressure measured. Such patients often cannot communicate symptoms such as headache, and their behaviour may not be considered abnormal. After BP has been lowered, parents of hypertensive infants often comment in retrospect that their child had been increasingly irritable before the hypertension was recognised (2).

**Clinical study(ies)**

The following is based on the protocol reports and references submitted by the Marketing Authorisation Holder

Protocol report 2703 regarding the effective oral vasodilator minoxidil in hypertensive emergencies had to be a partially controlled study because of ethical reasons. No controls could be used so that information is historical and further information regarding its use was obtained from the medical literature. The findings were related to the patients' blood pressure pre-trial. In the study a total of 1,071 patients were administered 1,160 courses of minoxidil therapy.

Two thirds of the patients were male, slightly more than half were black and the average age was 39 years. Ninety-eight patients were under 20 years. Hypertension was essential in 63%, due to renal parenchymal disease in 11%, to renal artery stenosis in 9% and to miscellaneous causes in 17%. Pre-trial average supine BP was 190/120mmHg and most patients had evidence of target organ damage. Ninety-five percent had been refractory to other hypertensive therapy.

Minoxidil was used in conjunction with propranolol and diuretics.

Evidence of efficacy: The supine systolic and diastolic blood pressure declined approximately 15% initially and 20% after one year of therapy. Standing pressures were reduced less because drugs producing orthostatic effects were discontinued. Supine and standing pressures during treatment were essentially the same. Standing BP was reduced either to  $\leq 90$ mmHg or by 20mmHg in approximately 75% of the population throughout the study.

An average increase in heart rate of one to four beats/min was confined to the first eight weeks of administration. Significant improvement in target-organ damage following minoxidil therapy in at least one category of the 371 patients with target-organ damage was reported. This was consistent with reports quoted from the literature.

Evidence of safety: Significant side effects noted during minoxidil therapy were oedema and hypertrichosis. The incidence of oedema rose from a pre-trial level of 30% to a maximum of 38% after two weeks, but then declined to below the pre-trial level during the 24 to the 52 week interval. The onset of hypertrichosis was delayed by approximately two weeks but developed rapidly thereafter to affect 60% of the treated population at one year. Minoxidil therapy was noted to be accompanied by a decline in incidence of adverse reactions attributed to discontinuation of prior anti-hypertensive medications.

### Studies in Children

The use of minoxidil in children with severe refractory hypertension was reported in two company sponsored case series viz. protocol 2703 and protocol 2709.

*Effect of minoxidil on arterial blood pressure, cardiac index, and plasma renin activity in 6 severely hypertensive children. Investigators Pennisi et al. (Protocol 2703).<sup>a</sup>*

#### Reference:

Pennisi A J et al.; Minoxidil therapy in children with severe hypertension; Journal of Pediatrics.1977;90:813-9 **(3)**

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<sup>a</sup> This study was based on the data available in the company-sponsored case study protocol 2703  
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#### Study Design:

Six children (two male, four female) with the hemolytic uremic syndrome, (two patients) systemic arteritis (two patients), and the remainder with renal transplant rejection, four, whose hypertension was uncontrollable with standard agents, were switched from a baseline regimen of hydralazine, furosemide and either propranolol, methyldopa, or clonidine to minoxidil, furosemide and either propranolol, methyldopa or clonidine. Blood pressure, cardiac index (measured by echocardiography) and plasma rennin activity in the upright position were recorded on the baseline regimen and at the maximum minoxidil dosage (0, 1 to 1.4 mg/kg/day).

Minoxidil lowered arterial blood pressure substantially more than the previous regimen and, surprisingly, cardiac output and peripheral plasma renin activity in the upright position fell when minoxidil was substituted for hydralazine. In four of the six patients, minoxidil facilitated discharge from the hospital, ending prolonged periods of hospitalization for uncontrollable hypertension.

The major side effect was fluid retention; congestive heart failure occurred twice in one patient, ultimately necessitating discontinuation of minoxidil. In another patient hemodialysis was needed to control excessive fluid retention. In three patients it was possible to either discontinue or decrease the dosage of minoxidil after three to eight months of therapy, without return of severe hypertension. All three patients experienced improved renal function, as measured by serial serum creatinine determinations, while blood pressure was being controlled by minoxidil. Several other significant adverse effects were seen during the study. In three patients on prolonged minoxidil therapy, persistent right ventricular dilation was detected by echocardiographic

#### *Minoxidil versus methyldopa (Protocol 2709).*

#### Reference:

Sinaiko et al.; Clinical response of hypertensive children to long-term minoxidil therapy; Journal of Cardiovascular Pharmacology.1980;2; Suppl 2:S181-8 **(4)**

#### Objective of Study:

The purpose of Protocol 2709 was to compare the effect of methyldopa, propranolol, and propranolol plus minoxidil in the management of hypertension associated with renal disease in children. .

#### Experimental Design:

Nine subjects age three to 17 years were selected from a paediatric renal hypertensive clinic population of the University of Minnesota Medical School; they had either received no prior medication or were considered therapeutic failures on their current regimens. Any untreated subject who could be controlled by diuretic treatment alone was to be so treated and excluded from further study. All patients had documented renal pathology, diastolic blood pressure of 85 to 95 mmHg, depending upon age, and had neither liver pathology nor evidence of hypertension due to causes other than renal.

#### Procedure:

Following a baseline period treatment with hydrochlorothiazide or furosemide (four weeks) patients were randomly assigned to one of three regimens:

Regimen A - Diuretic plus methyldopa.

Regimen B - Diuretic plus propranolol.

Regimen C - Diuretic plus propranolol plus minoxidil.

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Assignment was made in such a way that each investigational treatment was preceded and followed by equal numbers of other treatments. Each drug was titrated for each patient according to clinical response. In most cases the doses were hydrochlorothiazide 200 mg per day, furosemide 100 mg per day, minoxidil 30 mg per day, propranolol 100 mg per day and methyldopa 2 g per day.

After a six week treatment period, patients had a two week washout period on diuretic alone and went on to the second six week treatment; the third leg of the crossover was carried out similarly. The three way cross-over design was carried out in double-blinded fashion in nine patients.

#### Results:

The individual and mean blood pressures were measured during the central and three treatment periods. The combination of minoxidil, propranolol, and hydrochlorothiazide was statistically significantly superior to the other regimens in reducing diastolic pressure and significantly superior to all regimens except methyldopa in its effect on systolic pressure.

#### Adverse and Side Effects:

No adverse electrocardiographic, radiographic, hepatic or renal effects were observed which could be attributed to minoxidil. One patient who entered the study with progressively deteriorating renal function continued to have a steady decrease in creatinine clearance over the entire 28 week period despite a significant improvement in blood pressure control. The only side effect directly associated with minoxidil administration was increased hair growth. The hair growth, was particularly apparent across the forehead, on all extremities, and over the lower back. It uniformly appeared during the first two weeks of minoxidil therapy, increased in intensity throughout the six week course of therapy, and was not related to the dose administered. The increase in hair growth was not permanent and returned to the pre-treatment pattern of hair distribution within two to three months after minoxidil therapy was withdrawn. Minoxidil therapy appeared to be well-tolerated in children in this small study.

Apart from the results of the above mentioned clinical studies on the use of minoxidil in children with refractory hypertension further information regarding its efficacy and safety in children was published in the medical literature. Strife and others (5) reported about the efficacy of minoxidil in rapidly lowering acutely raised blood pressure in 13 children aged two to 18 years. Puri and others (6) reported their experience with long term treatment of hypertension over a period of 6.5 years in 16 children aged 1 to 16 years.

## **V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION**

### **Overall conclusion**

Minoxidil is effective in children with severe hypertension not responding to treatment with other medications. Experience of the use of minoxidil in young children and infants is limited. Initial treatment should be started in hospital under direct specialist supervision starting with a small dose which is gradually increased until effect is safely achieved. During the course treatment with minoxidil beta-blockers are used to prevent rapid heart rate and diuretics are used to prevent sodium and water retention. Too rapid a lowering of the blood pressure should be

avoided. Pericardial effusion and water retention may develop. Parents should be informed of the eventual development of hypertrichosis which recedes after the cessation of treatment. During treatment with minoxidil regular follow up is essential.

Minoxidil is a useful anti-hypertensive agent in children. It is effective and safe when used according to the authorised indication under close medical supervision.

### **Recommendation**

Type IB variation to be requested from the MAH within 90 days of the publication of this Public Assessment Report.

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

Loniten - Pfizer Corporation Austria GesmbH (Austria)  
Lonoten - Pfizer Holding France (France)  
Lonolox - Pfizer Pharma GmbH (Germany)  
Loniten - Pharmacia Ireland Limited (Ireland)  
Loniten - Pharmacia Italia SrL (Italy)  
Lonnoten - Pfizer bv (Netherlands)  
Loniten - Pfizer SA (Spain)  
Loniten - Pharmacia Limited (United Kingdom)

### **References**

1. Martindale: The Complete Drug Reference. (Latest modification: 24-Aug-2010)
2. Nelson Textbook of Paediatrics 18<sup>th</sup> Edition. Saunders 2007
3. Pennisi A J et al.; Minoxidil therapy in children with severe hypertension; Journal of Pediatrics.1977;90:813-9
4. Sinaiko et al.; Clinical response of hypertensive children to long-term minoxidil therapy; Journal of Cardiovascular Pharmacology.1980;2; Suppl 2:S181-8
5. Strife C F et al.; Paediatrics. Minoxidil for control of acute blood pressure elevation in chronically hypertensive children; 1986;78: 861-5
6. Puri H C et al. ; Severe hypertension in children with renal disease: treatment with minoxidil; American Journal of Kidney Diseases; 1983;3:71-5