SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nife-Par 5 mg / ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral solution contains 5 mg nifedipine.

Excipients:	
Ethanol 96º	0.47g
Sunset Yellow colouring (E-110)	0.2mg
Ethyl parahydroxybenzoate (E-214)	1.75mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For delaying imminent preterm birth in pregnant women:
- having regular uterine contractions lasting at least 30 seconds and with a frequency of 4 or more contractions every 30 minutes.
- having cervical dilation of 1 -3 cm (or 0 - 3 cm for nulliparous women) and cervical effacement of more than 50%.
- being at least 18 years old
- with a gestational age of 24 - 33 full weeks
- normal foetal heart rate.

4.2. Posology and method of administration

Treatment with Nife-Par should be initiated and maintained by a physician experienced in the treatment of pre-term labour.

It is administered orally. Dose will be adjusted individually according to the seriousness of threatened preterm birth and patient response.

The general posology regime is as follows:

Initial dose (first hour):

- 2.0 ml (10.0 mg nifedipine).
- If contractions are not suppressed, administer a second dose of 1.5 ml (7.5 mg nifedipine) after 15 minutes. This new dose of 1.5 mg (7.5 mg nifedipine) every 15 minutes until contractions are suppressed. Maximum dose during the first hour is 8 ml (40 mg).

Once contractions have been suppressed and 6 hours have elapsed since the last dose, the regime will be:

Maintenance dose (for the following 6 - 48 hours):
3 ml (15 mg nifedipine every 6 – 8 hours, according to response.

Maximum daily dose is 32 ml/day (160 mg nifedipine).

Treatment duration will be 48 hours and may be extended depending on progression of risk of preterm birth, but in principle should not be continued for more than 72 hours.

Paediatric population
The safety and efficacy of nifedipine have not been established in children and adolescents younger than 18 years old.

4.3. Contraindications

Hypersensitivity to nifedipine or to any of the excipients listed in section 6.1.

It must not be used in the event of cardiovascular shock, eclampsia, or in patients with chronic heart conditions.
Nife-Par is contraindicated in cases of marked hypotension (severe hypotension with systolic pressure of <90 mmHg), hypertension, clear heart failure and severe aortic stenosis.

Treatment with Nife-Par is contraindicated in the presence of high activity situations, such as hyperthyroidism.

Do not use in the following situations:

- Gestational age below 24 weeks or above 33 full weeks
- Premature breakage of membranes after 30 weeks of gestation
- Delayed intrauterine growth and abnormal foetal heart rate
- Prepartum uterine haemorrhage which requires immediate delivery
- Intrauterine foetal death
- Suspected intrauterine infection
- Abruptio placenta (premature detachment of the placenta)
- Any other condition in the mother or foetus which makes continuation of pregnancy dangerous.

Treatment with Nife-Par is contraindicated in the presence of unstable angina and in the event of recent myocardial infarction.

It must not be administered concomitantly with ritodrine. It must not be administered concomitantly with rifampicin given that the enzyme-inducing effect of this drug reduces plasma concentrations of nifedipine (see section 4.5).

4.4. Special warnings and precautions for use

Nife-Par should only be administered concomitantly with other vasoactive drugs such as magnesium sulphate and atosiban when justified by gestational age, must be carefully monitored and special precautions taken.

During administration, maternal heart rate and arterial pressure must be monitored, and a cardiotocography recording made one hour after the first dose of nifedipine, maintained or repeated according to progression of uterine contractions and in any case after 24 hours.

Treatment with Nife-Par can cause an exaggerated drop in blood pressure accompanied by reflex tachycardia, which may give rise to complications.

Nifedipine in metabolised by the cytochrome P450 3A4 system. For this reason, drugs that have an effect on this enzyme system may alter the metabolism or clearance of nifedipine (see section **4.5 Interaction with other drugs and other forms of interaction**).

Arterial pressure and uterine function shall be monitored closely when Nife-Par is administered concomitantly with these drugs, and dose shall be adjusted if necessary.

Patients with impaired liver function must be closely monitored and dosage reduced if necessary.

Medicinal products with tocolytic activity, such as calcium channel blockers, are associated with increased risk of pulmonary oedema, and therefore nifedipine must be used with caution in cases of multiple pregnancies and diabetes.

There is limited clinical experience of Nife-Par use in multiple pregnancies and at gestational ages of between 24 and 27 weeks. The benefit for these groups is therefore uncertain and greater precautions must be taken.

When nifedipine is used in patients for whom the risk of premature breakage of membranes cannot be ruled out, the benefits of delaying birth must be evaluated against the potential risk of chorioamnionitis.

Warning about excipients:

This medicinal product contains 44% ethanol, equivalent to 0.88 g per dose of 2.0 ml. This medicinal product is harmful for patients with alcoholism.
The alcohol content must be taken into account for pregnant or breastfeeding women, children and high-risk populations such as patients with liver conditions or epilepsy.

This medicinal product may cause allergic reactions because it contains Sunset Yellow colouring (E-110). It may cause asthma, particularly in patients allergic to acetylsalicylic acid.

It may cause allergic reactions because it contains ethyl parahydroxybenzoate (E-214).

4.5. Interaction with other drugs and other forms of interaction

The hypotensive effect of nifedipine may be exacerbated by the action of other antihypertensive medication.

Nifedipine is metabolised by the cytochrome P450 3A4 system, located in both intestinal mucous membrane and the liver. For this reason, drugs that have an effect on this enzyme system may alter the metabolism or clearance of nifedipine (see section **4.4 Special warnings and precautions for use**).

Nifedipine must not be administered with other vasoactive drugs, particularly ritodrine.

Drugs which have a weak or moderate inhibitor effect on the cytochrome P450 3A4 system, and which may therefore increase plasma concentrations of nifedipine, are:

- antibiotics
- anti-HIV protease inhibitors
- azol antifungals
- anti-depressants
- cimetidine
- anti-epileptics
- immunosuppressant drugs
- anti-arrhythmia drugs and cardiotonic drugs

Rifampicin is a powerful cytochrome P450 3A4 system inducer, so nifedipine bioavailability is considerably reduced. For this reason, use of nifedipine in combination with rifampicin is contraindicated (see section **4.3 Contraindications**).

Studies have shown that concomitant administration of drugs which induce or inhibit the cytochrome P450 3A4 system change –reducing or increasing- the bioavailability of nifedipine. Clinical response must therefore be monitored and dose adjusted accordingly.

Potential interactions

Substances which inhibit the cytochrome P450 3A4 system
No specific studies have been carried out on the interaction between nifedipine and these drugs, but due to their inhibitor effect on the cytochrome P450 3A4 system, cimetidine, erythromycin, fluoxetine, indinavir, ritonavir, saquinavir, amprenavir, nelfinavir, delarvidine, diltiazem, quinupristin, dalfopristin, tacrolimus, ketoconazole, itraconazole, fluconazole, nefadozone and valproic acid can increase plasma concentrations of nifedipine.

Substances which induce the cytochrome P450 3A4 system
Barbiturates such as phenobarbital, carbamazepine and phenytoin induce cytochrome P450 3A4, therefore if administered simultaneously a reduction of nifedipine plasma concentrations can be expected.

Interactions with food
Grapefruit juice is an inhibitor of the cytochrome P450 3A4 system. As with other dihydropyridines, grapefruit juice can cause lasting inhibition of nifedipine metabolism, leading to increased plasma concentrations and strengthened pharmacological effects. Patients being treated with Nife-Par must not drink grapefruit juice.

4.6. Fertility, pregnancy and breast-feeding

Pregnancy:

Nife-Par is contraindicated during the first 24 weeks of pregnancy.

Cases of acute pulmonary oedema have been reported when nicardipine has been used as tocolytic during pregnancy (see section 4.8), particularly in cases of multiple pregnancy (twins or more), administered intravenously and/or with concomitant use of beta-2 agonists. Nifedipine belongs to the same family of compounds (calcium antagonists) and therefore a similar risk cannot be ruled out.

Breast-feeding:

Nifedipine is excreted in maternal milk. Since there is no experience regarding the possible effects on breast-feeding children, as a precaution breast feeding should not be commenced until 36 hours have elapsed after the last administration.

4.7. Effects on ability to drive and use machines

Not applicable.

4.8. Adverse reactions

The table below lists adverse effects categorised by order of frequency of occurrence, collated on the basis of clinical trial data for nifedipine capsules or tablets with placebo control (clinical trials database: nifedipine n = 2661; placebo n = 1486; status: 22 Feb 2006, and the ACTION study (nifedipine = 3825; placebo n = 3840).

System organ class	Common > 1/100, < 1/10	Uncommon > 1/1000, < 1/100	Rare > 1/10,000, < 1/1000	Very rare < 1/10,000	Unknown
Immune system disorders		Allergic reaction. Allergic oedema / angioedema (including laryngeal oedema). Pruritus. Exanthema. Erythema.			
Psychiatric disorders		Anxiety reactions. Sleep disturbance. Agitation. Nervousness.			
Nervous system disorders	Headache. Dizziness.	Vertigo. Migraine. Tremor.	Paraesthesia. Dysesthesia.		
Ocular disorders		Changes to vision.			
Cardiac disorders		Tachycardia. Palpitations. Chest angina.			
Vascular disorders	Oedema, including peripheral oedema. Vasodilation.	Hypotension, including orthostatic hypotension. Syncope.		Hypotension that may lead to QT interval prolongation and ventricular fibrillation.	
Blood and lymphatic system disorders				Agranulocytosis. Purpura.	
Respiratory, thoracic and mediastinal disorders		Epistaxis. Nasal congestion. Chest pain. Dyspnoea.			Acute pulmonary oedema*.
Gastrointestinal disorders	Constipation. Nausea.	Abdominal and gastrointestinal pain. Dyspepsia. Flatulence. Dry mouth. Diarrhoea.	Gingival hyperplasia. Swollen abdomen. Anorexia. Vomiting.		
Hepatobiliary disorders		Temporary increase in hepatic enzyme levels.			
Metabolism and nutrition disorders				Hyperglycaemia.	
Skin and subcutaneous tissue disorders		Erythema. Sweating.		Exfoliative dermatitis and caused by light sensitivity. Hives.	

Musculoskeletal and connective tissue disorders		Muscle cramps. Swollen joints.	Myalgia.		
Renal and urinary disorders		Polyuria. Dysuria.			
General disorders and administration site conditions	Feeling unwell.	Non-specific pain. Shivering. Asthenia.			

* Cases have been reported when calcium antagonists have been used as tocolytic during pregnancy (see section 4.6).

The meta-analysis carried out with the quality clinical trials available showed that 16% of patients treated with nifedipine showed maternal adverse reaction to the drug, the most frequent being headache, flushing, palpitations and nausea.

As regards neonatal effects, an open, multi-centre, controlled and randomized clinical trial in which 95 women received oral nifedipine tocolysis showed a 49% admission rate to the neonatal intensive care unit, with 21% incidence of neonatal respiratory distress syndrome, 18% intracranial haemorrhage, and 52% neonatal jaundice.

A meta-analysis of clinical trials with nifedipine as tocolytic showed that the incidence of adverse reactions was significantly higher at total daily doses of above 60 mg.

Cases of acute pulmonary oedema have been reported when nicardipine has been used as tocolytic during pregnancy (see section 4.8), particularly in cases of multiple pregnancy (twins or more), administered intravenously and/or with concomitant use of beta-2 agonists. Nifedipine belongs to the same family of compounds (calcium antagonists) and therefore a similar risk cannot be ruled out.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Spanish Pharmacovigilance System for Medicines for Human Use: www.notificaRAM.es

4.9. Overdose

Symptoms

The following symptoms in cases of intoxication through overdosage with nifedipine have been observed: altered states of consciousness including coma, sudden hypotension, bradycardia or tachycardia and cardiac arrhythmia, hyperglycaemia, metabolic acidosis, hypoxia, cardiac collapse with pulmonary oedema.

Treatment of overdose

Elimination of active substance and restoration of stable cardiovascular conditions are priority. Gastric lavage with irrigation of small intestine is recommended to prevent subsequent absorption of active ingredient. Haemodialysis is not effective since Nife-Par is not dialyzable, although plasmapheresis is advisable (high binding to plasma proteins, relatively low distribution volume).

Alterations of heart rate (bradycardia) must be treated symptomatically with beta-sympathomimetic drugs, and in cases of very severe heart rate alterations, a temporary pacemaker may be fitted.

Hypotension resulting from cardiogenic shock and arterial vasodilation can be treated with calcium (10-20 ml of a 10% calcium gluconate solution administered via slow intravenous injection, which may be repeated if necessary). This may result in serum calcium levels reaching values equal to or slightly higher than the normal maximum limit. If arterial pressure is not raised sufficiently with calcium and isoprenaline, additional vasoconstrictor sympathomimetic drugs such as dopamine or noradrenaline shall be administered. The dose of these drugs is determined solely by the effect obtained.

Additional fluids shall be administered to restore volume, but exercising caution due to risk of cardiac overload.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC code: G02CX.

Nifedipine is a dihydropyridine type 2 calcium antagonist which blocks the flow of calcium ions in the slow channels of the uterine wall smooth muscle tissue.

This pharmacological activity gives it a pronounced relaxing effect on the myometrium, thus behaving as tocolytic.

Nifedipine efficacy and safety for the treatment of Threatened Preterm Labour has been demonstrated in 12 controlled clinical trials carried out with solid oral forms (capsules or tablets) on a total of 1029 women.

5.2. Pharmacokinetic properties

Nife-Par is absorbed rapidly and almost completely (approx. 100%). However, its bioavailability is 45-68% due to a first-pass effect. Administration at the same time as food delays, but does not reduce, its absorption.

It is rapidly distributed throughout the organism and metabolized almost entirely in the liver, mainly by oxidation processes. The resulting metabolites have no pharmacokinetic activity. It is excreted principally as metabolites via the renal pathway, and around 5-15% via the biliary pathway in stools. Non-metabolised active ingredient is only recovered in trace amounts (less than 1%) in urine.

In patients with impaired renal function, no relevant changes compared with healthy volunteers have been detected.

In patients with impaired liver function, a marked increase in elimination half-life and reduced clearance were observed. In severe cases, reduced dosage of Nife-Par should be considered.

Pharmacokinetic parameters

For a 30 mg dose of Nife-Par administered orally, maximum mean plasma concentrations were 419 mcg/l and were reached 20 minutes post-administration.

Cmax (mcg/l): **419**
Tmax (h) fasting: **0.3**
T1/2 (h): **1.7 – 3.4**

Nife-Par binds approximately 95% to plasma proteins (albumin).

Total clearance (systemic): IV: 6-10 $ml.min^{-1}.kg^{-1}$ p.c. Accumulated elimination of metabolites in urine after IV administration: 0-48 h: 60 - 80% of dose. Nife-Par has been detected in umbilical cord blood and amniotic fluid.

5.3. Preclinical safety data

Preclinical data obtained from conventional studies on single and repeat dose toxicity, genotoxicity and carcinogenic potential, do not indicate particular danger for humans.

Experimental data from three different species (rats, mice and rabbits) have revealed teratogenic effects including digital abnormalities, deformed extremities, cleft palate, cleft sternum and deformed ribcage. Nifedipine administration has been linked to diverse embryotoxic, placentotoxic and fetotoxic effects, including foetal atrophy (rats, mice, rabbits), small placenta and undeveloped chorionic villi (monkeys), embryo and foetus death (rats, mice, rabbits) and gestation prolongation/reduced neonatal survival (rats, not evaluated in other species).

These effects have only been observed at toxic doses for the mother (above 10 times higher than the maximum recommended dose for humans).

Clinical experiments with nifedipine in women more than 24 weeks pregnant have not shown increased risk of foetal malformations. Furthermore, short treatment duration and the fact that when treatment is initiated, embryogenesis is complete, minimizes the already remote risk of foetal malformation.

6 . PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Ethanol 96°, glycerol, sodium cyclamate (E-952), sodium saccharin (E-954), ethyl parahydroxybenzoate (E-214), sunset yellow colouring (E-110), lemon essence and purified water.

6.2. Incompatibilities

None described

6.3. Shelf life

2 years.
After opening, the solution remains stable for 96 hours.

6.4. Special precautions for storage

Keep the bottle in its box to protect it from light.

6.5. Nature and contents of container

Amber glass bottle with polyethylene screw lid and obturator, plus 5 ml syringe for oral use.

6.6. Special precautions for disposal and other handling

Insert the syringe, included in the package, into the orifice in the perforated stopper. Invert the bottle and extract the dose required.

Disposal of unused medicinal product and all materials that have come into contact with it shall be done in accordance with local regulations.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

78.233

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

1 December 2013

10. DATE OF REVISION OF TEXT

January 2018

Detailed and updated information on this medicinal product is available on the Spanish Agency of Medicines and Healthcare Devices website (AEMPS) http://www.aemps.es/