UKPAR

ADANIF XL 30MG AND 60 MG TABLETS
PL 20046/0059-60

TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lay Summary</td>
<td>2</td>
</tr>
<tr>
<td>Scientific discussion</td>
<td>3</td>
</tr>
<tr>
<td>Steps taken for assessment</td>
<td>14</td>
</tr>
<tr>
<td>Steps taken after authorisation – summary</td>
<td>15</td>
</tr>
<tr>
<td>Summary of Product Characteristics</td>
<td></td>
</tr>
<tr>
<td>Product Information Leaflet</td>
<td></td>
</tr>
<tr>
<td>Labelling</td>
<td></td>
</tr>
</tbody>
</table>
ADANIF XL 30MG AND 60 MG TABLETS
PL 20046/0059/60

LAY SUMMARY

On 19th May 2010, the MHRA granted Focus Pharmaceuticals Limited Marketing Authorisations (licences) for the medicinal products Adanif XL 30mg and 60mg Tablets. These medicines are only available on prescription from your doctor.

Adanif XL Tablets contain nifedipine, a medicine known as a calcium channel blocker.

Adanif XL Tablets are prescribed for:
- High blood pressure (Hypertension): nifedipine works by widening blood vessels, allowing blood to flow more freely, thus reducing the strain on your heart
- Angina (Lack of oxygen to the muscles of the heart leading to pain in the centre of the chest radiating over the left side of the body, up the neck and down the left arm). Nifedipine reduces the frequency of angina attacks by opening the blood vessels (arteries) of the heart allowing more oxygen and blood to reach the muscles of the heart.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Adanif XL 30mg and 60mg Tablets outweigh the risks. Hence Marketing Authorisations have been granted.
ADANIF XL 30MG AND 60MG TABLETS  
PL 20046/0059/60

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction  
Page 4

Pharmaceutical assessment  
Page 5

Preclinical assessment  
Page 8

Clinical assessment (including statistical assessment)  
Page 9

Overall conclusions and risk benefit assessment  
Page 13
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Adanif XL 30mg and 60mg Tablets (PL 20046/0059-60) on the 19th May 2010. These products are prescription-only medicines (POM).

These are national abridged applications for Adanif XL 30mg and 60mg Tablets submitted under article 10 (1) of Directive 2001/83/EC, as amended. The application claims the products to be generic medicinal products of Adalat® LA 30 and 60mg Tablets (Bayer PLC, UK) which have been licensed in the UK since 16th March 1992 (PL 00010/0174-5). The products used in the bioequivalence studies are Adalat® LA 60mg Tablets (Bayer PLC, UK) and Chronadalate® LP 30mg Retard Tablets (Bayer, France).

In the bioequivalence study the test product was referred as Nifedipine LA 30mg and 60mg Tablets and these are considered to be the same as Adanif XL 30mg and 60mg Tablets.

Nifedipine is a calcium antagonist of the 1,4-dihydropyridine type. Calcium antagonists reduce the transmembranal influx of calcium ions through the slow calcium channel into the cell. As a specific and potent calcium antagonist, nifedipine acts particularly on the cells of the myocardium and the smooth muscle cells of the coronary arteries and the peripheral resistance vessels. The main action of nifedipine is to relax arterial smooth muscle, both in the coronary and peripheral circulation. The Adanif XL Tablet is formulated to achieve controlled delivery of nifedipine in a release profile sufficient to enable once-daily administration to be effective in clinical use.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Nomenclature
rINN: Nifedipine
Chemical names: Dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1, 4-dihydropyridine3,5-dicarboxylate
Structure

Molecular formula: C_{17}H_{18} N_{2} O_{6}
Molecular weight: 346.3

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines (EDQM) certificate of suitability.

DRUG PRODUCT
Other ingredients
Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, povidone K30, talc, hypromellose, carbomer 974P, anhydrous colloidal silica, magnesium stearate, ferric oxide (red) (E172), titanium dioxide(E171), macrogol 4000 and Eudragit “E”.

All excipients used comply with their respective European Pharmacopoeia monograph with the exception of Ferric oxide (red), which is USP and Eudragit “E” which comply with in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate and magnesium stearate, none of the excipients are sourced from animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals, under the same conditions as milk for human consumption. The magnesium stearate is from vegetable origin and a declaration from the manufacturer is provided.

Pharmaceutical development
Suitable pharmaceutical development data have been provided for these applications. Comparable dissolution and impurity profile are provided for these products versus the originator product.
Manufacture
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results appear satisfactory.

Finished product specification
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System
Product is packaged in aluminium/PVC/PVDC blisters in pack sizes of 28 tablets. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years with storage conditions of ‘Do not store above 25 degree C’ and ‘Store in the original package to protect from light’ are set and these are acceptable.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labelling
The SPC, PIL and labelling are pharmaceutically satisfactory.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Pharmacovigilance System and Risk Management Plan
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for these products.

Marketing Authorisation Application Form
The MAA form is pharmaceutically satisfactory.

Expert Report
The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.
Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
PRECLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of nifedipine are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A preclinical expert report has been provided, written by an appropriately qualified person. This is satisfactory.

A suitable justification has been provided for non-submission of an environmental risk assessment.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

BIOEQUIVALENCE
Five bioequivalence studies were performed comparing Nifedipine LA 30mg and 60mg Tablets (generic name for Adanif® LA 30mg and 60mg) against the reference branded products, Chronadalahte® LP 30 (Bayer Pharma, France) and Adalat® LA 60(Bayer PLC, UK). Chronadalahte LP 30 (France) is accepted as equivalent to Adalat LA 30mg, marketed in the UK.

Single Dose Bioequivalence Study (30mg)
This study was a single dose, fasting, two-way, crossover, open, randomised, bioequivalence study comparing Nifedipine LA 30mg Tablets (Euderma, Italy) and Chronadalahte® LP 30mg Retard Tablets (Bayer Pharma, France) in healthy volunteers.

Results

Table 1: Summary of Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of Nifedipine LA 30mg Tablets versus Chronadalahte® LP 30mg Retard Tablets under fasting conditions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geometric Mean</th>
<th>Test/Reference</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{max} (ng/ml)</td>
<td>14.76</td>
<td>15.31</td>
<td>0.964</td>
</tr>
<tr>
<td>AUC_{0-1} (ng/ml)</td>
<td>290.97</td>
<td>277.52</td>
<td>1.048</td>
</tr>
</tbody>
</table>

The test formulation, Nifedipine LA 30mg Tablets, was found to be bioequivalent to the reference product, Chronadalahte® LP 30mg Tablets in this study.

Multiple Dose Bioequivalence Study (30mg)
This study was a multiple dose, two-way, crossover, open, randomised, bioequivalence study comparing Nifedipine LA 30mg Tablets (Euderma, Italy) and Chronadalahte® LP 30mg Retard Tablets (Bayer Pharma, France) in healthy volunteers over multiple consecutive days.

Table 2: Summary of Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) Nifedipine LA 30mg Tablets versus Chronadalahte® LP 30mg Retard Tablets under steady state

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geometric Mean</th>
<th>Test/Reference</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{max} (ng/ml)</td>
<td>26.27</td>
<td>24.67</td>
<td>1.065</td>
</tr>
<tr>
<td>C_{min} (ng/ml)</td>
<td>13.23</td>
<td>14.58</td>
<td>0.907</td>
</tr>
<tr>
<td>AUC_{0-1} (ng/ml)</td>
<td>529.76</td>
<td>488.99</td>
<td>1.083</td>
</tr>
</tbody>
</table>

Data obtained in this trial confirm the test formulation is bioequivalent to the originator both containing 30mg of nifedipine in prolonged release formulations, when administered in repeated dose regimen to steady state in healthy volunteers.
Multiple Dose Bioequivalence Study (60mg)
This study was a multiple dose, two-way crossover, open, randomised, bioequivalence study comparing Nifedipine LA 60mg Tablets (Euderma, Italy) and Adalat® LA 60mg Tablets (Bayer, UK) to healthy volunteers over multiple consecutive days.

Table 3: Summary of Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) Nifedipine LA 60mg Tablets versus Adalat® LA 60mg Tablets under steady state

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geometric Mean</th>
<th>Test/ Reference</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>54.43</td>
<td>51.56</td>
<td>1.056</td>
</tr>
<tr>
<td>Cmin (ng/ml)</td>
<td>14.45</td>
<td>14.35</td>
<td>1.007</td>
</tr>
<tr>
<td>AUC0-τ (ng/ml)</td>
<td>1059.24</td>
<td>1054.13</td>
<td>1.005</td>
</tr>
</tbody>
</table>

Cmax and AUC0-τ produced 90% confidence intervals within the 0.80-1.25 range. PTF and tmax did not show any statistically significant differences between test and reference. Cmin showed 90% confidence intervals on the borderline of the predefined range accepted in assessing bioequivalence, namely 0.743-1.364 vs 0.75-1.34. This was attributed to the relative high variability of Cmin. However, considering that PTF was similar between test and reference, the test formulation the Cmin confidence intervals are accepted.

Single Dose 3-Way Food Interaction Study (30mg)
This study was a single dose, three-way, six-sequence, crossover, open, randomised, fasting and non-fasting, bioequivalence study comparing Nifedipine LA 30mg Tablets and Chronadalate® LP 30mg Retard Tablets in healthy volunteers.

Table 4: Bioequivalence analysis results of Nifedipine LA 30mg Tablets versus Chronadalate® LP 30mg Retard Tablets under fasting/non-fasting conditions

<table>
<thead>
<tr>
<th>Tnf versus Rnf</th>
<th>90% Confidence Intervals</th>
<th>Kruskal-Wallis’ Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng.ml⁻¹)</td>
<td>0.897-1.175</td>
<td>-</td>
</tr>
<tr>
<td>AUC0-τ (ng.ml⁻¹.h)</td>
<td>0.843-1.146</td>
<td>-</td>
</tr>
<tr>
<td>tmax</td>
<td>-</td>
<td>NS</td>
</tr>
</tbody>
</table>

Tnf: Test non Fasting   Rnf: Reference non fasting

The results are in line with the same food effect for test and reference.

Conclusion
- The effect of food and fasting on the rate of absorption was to marginally increase its extent of absorption, as described in literature with prolonged release formulations of nifedipine, thus this was as expected.
- The plasma concentration-time profiles and pharmacokinetic parameters of test and reference products administered after the high-fat content breakfast were comparable and produced results of specific tests in line with the EU criteria to assess bioequivalence.
- The test formulation is thus bioequivalent to Chronadalate LP 30® when administered after a high-fat content breakfast.

**Single Dose Food Interaction Study (60mg)**

This study was a single dose, three-way, six-sequence, crossover, open, randomised, fasting/non-fasting bioequivalence study comparing Nifedipine LA 60mg Tablets and Adalat® LA 60mg Tablets in healthy volunteers.

**Table 5: Bioequivalence analysis results of Nifedipine LA 60mg Tablets vs. Adalat® LA 60mg Tablets under fasting/non-fasting conditions**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Test (fasting)</th>
<th>Mean Test (non-fasting)</th>
<th>Mean Reference (non-fasting)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>30.19</td>
<td>39.30</td>
<td>40.51</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-4&lt;/sub&gt; (ng/ml x h)</td>
<td>595.94</td>
<td>725.65</td>
<td>760.73</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>14.71</td>
<td>8.75</td>
<td>8.83</td>
</tr>
<tr>
<td>t&lt;sub&gt;lag&lt;/sub&gt; (h)</td>
<td>2.35</td>
<td>2.31</td>
<td>2.31</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>19.38</td>
<td>17.35</td>
<td>17.15</td>
</tr>
</tbody>
</table>

**Table 5.1: Summary of Parametric ratios (Test non-fasting versus reference non-fasting ratios of geometric means) and the 90% confidence interval**

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GEOM. MEAN T&lt;sub&gt;ref&lt;/sub&gt;</th>
<th>GEOM. MEAN R&lt;sub&gt;ref&lt;/sub&gt;</th>
<th>T&lt;sub&gt;ref&lt;/sub&gt;/R&lt;sub&gt;ref&lt;/sub&gt;</th>
<th>90% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>35.69</td>
<td>37.81</td>
<td>0.949</td>
<td>0.843 – 1.069</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-4&lt;/sub&gt;</td>
<td>652.50</td>
<td>697.70</td>
<td>0.950</td>
<td>0.844 – 1.069</td>
</tr>
</tbody>
</table>

T<sub>ref</sub>: Test non-Fasting  R<sub>ref</sub>: Reference non-fasting

The 90% confidence intervals for C<sub>max</sub> and AUC<sub>0-4</sub> for comparison of the test and reference 60mg formulations after a high-fat breakfast were within the 0.80-1.25 range.

**Overall conclusions**

The five clinical studies presented above confirm that the test product, Adanif XL 30mg and 60mg Tablets are bioequivalent to Adalat LA / Chronadalate LP 30mg and 60mg Retard Tablets.

**Efficacy**

No new efficacy data have been submitted and none are required for these applications.

**Safety**

No new safety data have been submitted and none are required for these applications.

**Expert Report**

A clinical expert report has been written by clinical consultant to the pharmaceutical industry. The report is satisfactory.
SUMMARY OF PRODUCT CHARACTERISTICS
Clinically satisfactory

PATIENT INFORMATION LEAFLET
This is satisfactory

LABELLING
These are satisfactory.

MARKETING AUTHORISATION FORMS
These are satisfactory.

CONCLUSIONS
The Applicant appears to have demonstrated that the product and the reference compound are bioequivalent.

The grant of Marketing Authorisations is recommended.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Adanif XL 30mg and 60mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
No new data have been submitted and none are required for an application of this type.

Adanif XL 30mg and 60mg Tablets are bioequivalent to the reference product Adalat® LA 30 and 60 mg Tablets (Bayer PLC, UK). Adalat® LA is an established therapeutic agent in the UK and is a suitable reference product on which to base this application. The same reference product is also marketed under the name, Chronadalate® LP 30 & 60mg in France (Bayer, France).

The product proposed for marketing contains the same quantitative and qualitative composition of the active ingredients, nifedipine and is the same pharmaceutical form as the nominated reference product. Bioequivalence between test and reference products has been demonstrated.

In accordance with UK requirements for modified release preparations, a suitable brand name has been proposed and accepted.

No new safety data are supplied or required for these applications. Nifedipine has a well-established side-effect profiles and is generally well-tolerated.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT
The risk benefit is considered to be satisfactory.
**ADANIF XL 30MG AND 60MG TABLETS**  
**PL 20046/0059-60**

**STEPS TAKEN FOR ASSESSMENT**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 11\textsuperscript{th} November 2008</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 27\textsuperscript{th} November 2008</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information on 4\textsuperscript{th} March 2009</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 13\textsuperscript{th} March 2009</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 19\textsuperscript{th} May 2010</td>
</tr>
</tbody>
</table>
ADANIF XL 30MG AND 60MG TABLETS
PL 20046/0059-60

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Adanif XL 30mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One tablet contains 30mg nifedipine.
For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Prolonged release film-coated tablet.
Pale red, round biconvex tablets.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
For the treatment of all grades of hypertension.
For the prophylaxis of chronic stable angina pectoris either as monotherapy or in combination with a beta-blocker.

4.2 Posology and method of administration
For oral administration, the tablets should be swallowed whole with a glass of water, either with or without food. The tablets should be taken at approximately 24-hour intervals, i.e. at the same time each day, preferably during the morning. Adanif XL Tablets must be swallowed whole; under no circumstances should they be bitten, chewed or broken up.

In mild to moderate hypertension, the recommended initial dose is one 20mg tablet once-daily. In severe hypertension, the recommended initial dose is one 30mg tablet once-daily. If necessary, the dosage can be increased according to individual requirements up to a maximum of 90mg once-daily.

For the prophylaxis of angina pectoris, the recommended initial dose is one 30mg tablet once-daily. The dosage can be increased according to individual requirements up to a maximum of 90mg once-daily.

Patients in whom hypertension or anginal symptoms are controlled on other nifedipine containing preparations may be safely switched to Adanif XL. Prophylactic anti-anginal efficacy is maintained when patients are switched from other calcium antagonists such as diltiazem or verapamil to Adanif XL. Patients switched from other calcium antagonists should initiate therapy at the recommended initial dose of 30mg Adanif XL once-daily. Subsequent titration to a higher dose may be initiated as warranted clinically.

The pharmacokinetics of nifedipine are altered in the elderly so that lower maintenance doses of nifedipine may be required compared to younger patients.

Co-administration with CYP 3A4 inhibitors or CYP 3A4 inducers may result in the recommendation to adapt the nifedipine dose or not to use nifedipine at all (see Section 4.5).

Patients with renal impairment should not require adjustment of dosage.

Treatment may be continued indefinitely.

Nifedipine is not recommended for use in children.

Adanif XL should not be taken with grapefruit juice (see Section 4.5)

4.3 Contraindications
- Adanif XL should not be administered to patients with known hypersensitivity to nifedipine, or to other dihydropyridines because of the theoretical risk of cross-reactivity, or to any of the excipients.
• Adanif XL is contraindicated in pregnancy before week 20 and during breastfeeding (see also Sections 4.4, 4.6 and 5.3).
• Adanif XL should not be used in cases of cardiogenic shock, clinically significant aortic stenosis, unstable angina, or during or within one month of a myocardial infarction.
• Adanif XL should not be used for the treatment of acute attacks of angina.
• The safety of Adanif XL in malignant hypertension has not been established.
• Adanif XL should not be used for secondary prevention of myocardial infarction.
• Owing to the duration of action of the formulation, Adanif XL should not be administered to patients with hepatic impairment.
• Adanif XL should not be administered to patients with a history of gastro-intestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastro-intestinal tract.
• Adanif XL is contra-indicated in patients with inflammatory bowel disease or Crohn's disease.
• Adanif XL should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction (see Section 4.5).

4.4 Special warnings and precautions for use
Adanif XL Tablets must be swallowed whole; under no circumstances should they be bitten, chewed or broken up.

Caution should be exercised in patients with hypotension as there is a risk of further reduction in blood pressure and care must be exercised in patients with very low blood pressure (severe hypotension with systolic blood pressure less than 90mm Hg).

Careful monitoring of blood pressure must be exercised when administering nifedipine with I.V. magnesium sulphate, owing to the possibility of an excessive fall in blood pressure, which could harm both mother and foetus. For further information regarding use in pregnancy, refer to Section 4.6.

Adanif XL may be used in combination with beta-blocking drugs and other antihypertensive agents but the possibility of an additive effect resulting in postural hypotension should be borne in mind. Adanif XL will not prevent possible rebound effects after cessation of other antihypertensive therapy.

Adanif XL should be used with caution in patients whose cardiac reserve is poor. Deterioration of heart failure has occasionally been observed with nifedipine.

Diabetic patients taking Adanif XL may require adjustment of their control. In dialysis patients with malignant hypertension and hypovolaemia, a marked decrease in blood pressure can occur.

Nifedipine is metabolised via the cytochrome P450 3A4 system. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass or the clearance of nifedipine (see Section 4.5).

Drugs, which are known inhibitors of the cytochrome P450 3A4 system, and which may therefore lead to increased plasma concentrations of nifedipine include, for example:
- macrolide antibiotics (e.g., erythromycin)
- anti-HIV protease inhibitors (e.g., ritonavir)
- azole antifungals (e.g., ketoconazole)
- the antidepressants, nefazodone and fluoxetine
- quinupristin/dalfopristin
- valproic acid
Upon co-administration with these drugs, the blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose should be considered.

As the outer membrane of the Adanif XL Tablet is not digested, what appears to be the complete tablet may be seen in the toilet or associated with the patient's stools. Also, as a result of this, care should be exercised when administering Adanif XL to patients, as obstructive symptoms may occur. Bezoars can occur in very rare cases and may require surgical intervention. In single cases, obstructive symptoms have been described without known history of gastrointestinal disorders.

Adanif XL must not be administered to patients with Kock pouch (ileostomy after proctocolectomy).

A false positive effect may be experienced when performing a barium contrast x-ray.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs that affect nifedipine

Nifedipine is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in the liver. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass (after oral administration) or the clearance of nifedipine.

The extent as well as the duration of interactions should be taken into account when administering nifedipine together with the following drugs:

- Rifampicin: Rifampicin strongly induces the cytochrome P450 3A4 system.

Upon co-administration with rifampicin, the bioavailability of nifedipine is distinctly reduced and thus its efficacy weakened. The use of nifedipine in combination with rifampicin is therefore contraindicated (see Section 4.3).

Upon co-administration of known inhibitors of the cytochrome P450 3A4 system, the blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered (see Sections 4.2 and 4.4). In the majority of these cases, no formal studies to assess the potential for a drug interaction between nifedipine and the drug(s) listed have been undertaken, thus far.

Drugs increasing nifedipine exposure:

- macrolide antibiotics (e.g., erythromycin)
- anti-HIV protease inhibitors (e.g., ritonavir)
- azole anti-mycotics (e.g., ketoconazole)
- fluoxetine
- nefazodone
- quinupristin/dalfopristin
- cisapride
- valproic acid
- diltiazem

Upon co-administration of inducers of the cytochrome P450 3A4 system, the clinical response to nifedipine should be monitored and, if necessary, an increase in the nifedipine dose considered. If the dose of nifedipine is increased during co-administration of both drugs, a reduction of the nifedipine dose should be considered when the treatment is discontinued.

Drugs decreasing nifedipine exposure:
- rifampicin (see above)
- phenytoin
- carbamazepine
- phenobarbital

Effects of nifedipine on other drugs
Nifedipine may increase the blood pressure lowering effect of concomitant applied antihypertensives. When nifedipine is administered simultaneously with β-receptor blockers the patient should be carefully monitored, since deterioration of heart failure is also known to develop in isolated cases.

*Digoxin:* The simultaneous administration of nifedipine and digoxin may lead to reduced digoxin clearance and, hence, an increase in the plasma digoxin level. The patient should therefore be subjected to precautionary checks for symptoms of digoxin overdosage and, if necessary, the glycoside dose should be reduced.

*Quinidine:* Co-administration of nifedipine with quinidine may lower plasma quinidine levels, and after discontinuation of nifedipine, a distinct increase in plasma quinidine levels may be observed in individual cases. Consequently, when nifedipine is either additionally administered or discontinued, monitoring of the quinidine plasma concentration, and if necessary, adjustment of the quinidine dose are recommended. Blood pressure should be carefully monitored and, if necessary, the dose of nifedipine should be decreased.

*Tacrolimus:* Tacrolimus is metabolised via the cytochrome P450 3A4 system. Published data indicate that the dose of tacrolimus administered simultaneously with nifedipine may be reduced in individual cases. Upon co-administration of both drugs, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose is considered.

**Drug food interactions**
Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of nifedipine together with grapefruit juice thus results in elevated plasma concentrations and prolonged action of nifedipine due to a decreased first pass metabolism or reduced clearance. As a consequence, the blood pressure lowering effect of nifedipine may be increased. After regular intake of grapefruit juice, this effect may last for at least three days after the last ingestion of grapefruit juice. Ingestion of grapefruit/grapefruit juice is therefore to be avoided while taking nifedipine (see Section 4.2).

**Other forms of interaction**
Nifedipine may increase the spectrophotometric values of urinary vanillylmandelic acid, falsely. However, HPLC measurements are unaffected.

### 4.6 Pregnancy and lactation
Nifedipine is contraindicated in pregnancy before week 20.

In animal studies, nifedipine has been shown to produce embryotoxicity, foetotoxicity and teratogenicity (see Section 5.3 Preclinical safety data). There are no adequate well controlled studies in pregnant women.

From the clinical evidence available a specific prenatal risk has not been identified, although an increase in perinatal asphyxia, caesarean delivery, as well as prematurity and intrauterine growth retardation have been reported. It is unclear whether these reports are due to the underlying hypertension, its treatment, or to a specific drug effect.

The available information is inadequate to rule out adverse drug effects on the unborn and newborn child. Therefore any use in pregnancy after week 20 requires a very careful individual risk benefit assessment and should only be considered if all other treatment options are either not indicated or have failed to be efficacious.
In single cases of \textit{in vitro} fertilisation calcium antagonists like nifedipine have been associated with reversible biochemical changes in the spermatozoa's head section that may result in impaired sperm function. In those men who are repeatedly unsuccessful in fathering a child by \textit{in vitro} fertilisation, and where no other explanation can be found, calcium antagonists like nifedipine should be considered as possible causes.

Nifedipine passes into the breast milk. As there is no experience of possible effects on infants, breastfeeding should first be stopped if nifedipine treatment becomes necessary during the breastfeeding period.

4.7 **Effects on ability to drive and use machines**
Reactions to the drug, which vary in intensity from individual to individual, may impair the ability to drive or to operate machinery. This applies particularly at the start of treatment, on changing the medication and in combination with alcohol.

4.8 **Undesirable effects**
Adverse drug reactions (ADRs) based on placebo-controlled studies with nifedipine sorted by CIOMS III categories of frequency (clinical trial data base: nifedipine n = 2,661; placebo n = 1,486; and the ACTION study: nifedipine n = 3,825; placebo n = 3,840) are listed below:

ADRs listed under "common" were observed with a frequency below 3% with the exception of oedema (9.9%) and headache (3.9%).

ADRs derived from post marketing reports are listed in the Frequency Not Known column.

<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Frequency Not Known</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1% to &lt;10%</td>
<td>&gt;0.1% to &lt;1%</td>
<td>&gt;0.01% to &lt;0.1%</td>
<td></td>
</tr>
</tbody>
</table>

**Immune System Disorders**
- Allergic reaction
- Allergic oedema/angioedema
- Pruritus
- Urticaria
- Rash
- Anaphylactic/anaphylactoid reaction

**Psychiatric Disorders**
- Anxiety reactions
- Sleep disorders

**Nervous System Disorders**
- Headache
- Vertigo
- Migraine
- Dizziness
- Tremor
- Par-/Dysaesthesia

**Eye Disorders**
- Visual disturbances

**Cardiac Disorders**
- Tachycardia
- Palpitations

**Vascular Disorders**
- Oedema
- Hypotension
In dialysis patients with malignant hypertension and hypovolaemia a distinct fall in blood pressure can occur as a result of vasodilation.

### 4.9 Overdose

#### Symptoms

The following symptoms are observed in cases of severe nifedipine intoxication:

Disturbances of consciousness to the point of coma, a drop in blood pressure, tachycardia, bradycardia, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema.

#### Treatment

As far as treatment is concerned, elimination of nifedipine and the restoration of stable cardiovascular conditions have priority. Elimination must be as complete as possible,
including the small intestine, to prevent the otherwise inevitable subsequent absorption of the active substance. The benefit of gastric decontamination is uncertain.

1. Consider activated charcoal (50g for adults, 1g/kg for children) if the patient presents within 1 hour of ingestion of a potentially toxic amount.

Although it may seem reasonable to assume that late administration of activated charcoal may be beneficial for sustained release (SR, MR) preparations there is no evidence to support this.

2. Alternatively consider gastric lavage in adults within 1 hour of a potentially life-threatening overdose.

3. Consider further doses of activated charcoal every 4 hours if a clinically significant amount of a sustained release preparation has been ingested with a single dose of an osmotic laxative (e.g. sorbitol, lactulose or magnesium sulphate).

4. Asymptomatic patients should be observed for at least 4 hours after ingestion and for 12 hours if a sustained release preparation has been taken.

Haemodialysis serves no purpose as nifedipine is not dialysable. Hypotension as a result of cardiogenic shock and arterial vasodilatation can be treated with calcium (10-20ml of a 10% calcium gluconate solution administered intravenously over 5-10 minutes). If the effects are inadequate, the treatment can be continued, with ECG monitoring. If an insufficient increase in blood pressure is achieved with calcium, vasoconstricting sympathomimetics such as dopamine or noradrenaline should be administered. The dosage of these drugs should be determined by the patient's response.

Symptomatic bradycardia may be treated with atropine, beta-sympathomimetics or a temporary cardiac pacemaker, as required. Additional fluids should be administered with caution to avoid cardiac overload.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: C08 CA05

Nifedipine is a calcium antagonist of the 1,4-dihydropyridine type. Calcium antagonists reduce the transmembranal influx of calcium ions through the slow calcium channel into the cell. As a specific and potent calcium antagonist, nifedipine acts particularly on the cells of the myocardium and the smooth muscle cells of the coronary arteries and the peripheral resistance vessels. The main action of nifedipine is to relax arterial smooth muscle, both in the coronary and peripheral circulation. The Adanif XL Tablet is formulated to achieve controlled delivery of nifedipine in a release profile sufficient to enable once-daily administration to be effective in clinical use.

In hypertension, the main action of nifedipine is to cause peripheral vasodilatation and thus reduce peripheral resistance. Nifedipine administered once-daily provides 24-hour control of raised blood pressure. Nifedipine causes reduction in blood pressure such that the percentage lowering is proportional to its initial level. In normotensive individuals, nifedipine has little or no effect on blood pressure.

In angina, Adanif XL reduces peripheral and coronary vascular resistance, leading to an increase in coronary blood flow, cardiac output and stroke volume, whilst decreasing afterload. Additionally, nifedipine dilates submaximally both clear and atherosclerotic coronary arteries, thus protecting the heart against coronary artery spasm and improving perfusion to the ischaemic myocardium. Nifedipine reduces the frequency of painful attacks and the ischaemic ECG changes irrespective of the relative contribution from coronary artery spasm or atherosclerosis.

In a multi-national, randomised, double-blind, prospective study involving 6321 hypertensive patients with at least one additional risk factor followed over 3 to 4.8 years, Adanif XL 30 and 60 (nifedipine GITS) were shown to reduce blood pressure to a comparable degree as a standard diuretic combination.
5.2 Pharmacokinetic properties

*General characteristics:*

Adanif XL Tablets are formulated to provide nifedipine at an approximately constant rate over 24 hours. Nifedipine is released from the tablet at a zero-order rate by a membrane-controlled, osmotic push-pull process. The pharmacokinetic profile of this formulation is characterized by low peak-trough fluctuation. 0-24 hour plasma concentration versus time profiles at steady state are plateau-like, rendering the Adanif XL Tablet appropriate for once-a-day administration.

The delivery rate is independent of gastrointestinal pH or motility. Upon swallowing, the biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the faeces as an insoluble shell. Orally administered nifedipine is almost completely absorbed in the gastro-intestinal tract. The systemic availability of orally administered nifedipine immediate release formulations (nifedipine capsules) is 45–56% owing to a first pass effect. At steady-state, the bioavailability of Adanif XL Tablets ranges from 68-86% relative to Nifedipine capsules. Administration in the presence of food slightly alters the early rate of absorption but does not influence the extent of drug availability.

Nifedipine is about 95% bound to plasma protein (albumin). The distribution half-life after intravenous administration has been determined to be 5 to 6 minutes.

After oral administration, nifedipine is metabolised in the gut wall and in the liver, primarily by oxidative processes. These metabolites show no pharmacodynamic activity. Nifedipine is eliminated in the form of its metabolites, predominantly via the kidneys, with approximately 5-15% being excreted via the bile in the faeces. Non-metabolised nifedipine can be detected only in traces (below 1.0%) in the urine.

The terminal elimination half-life is 1.7 to 3.4 hours in conventional formulations (nifedipine capsules). The terminal half-life following Adanif XL administration does not represent a meaningful parameter as a plateau-like plasma concentration is maintained during release from the tablets and absorption. After release and absorption of the last dose the plasma concentration finally declines with an elimination half-life as seen in conventional formulations.

*Characteristics in patients:*

There are no significant differences in the pharmacokinetics of nifedipine between healthy subjects and subjects with renal impairment. Therefore, dosage adjustment is not needed in these patients.

In patients with hepatic impairment, the elimination half-life is distinctly prolonged and the total clearance is reduced. Owing to the duration of action of the formulation, Adanif XL should not be administered in these patients.

5.3 Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of single and repeated dose toxicity, genotoxicity and carcinogenic potential.

Following acute oral and intravenous administration of nifedipine in various animal species, the following LD50 (mg/kg) values were obtained:

<table>
<thead>
<tr>
<th>Animal</th>
<th>Oral</th>
<th>i.v.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>494 (421-572)*</td>
<td>4.2 (3.8-4.6)*</td>
</tr>
<tr>
<td>Rat</td>
<td>1022 (950-1087)*</td>
<td>15.5 (13.7-17.5)*</td>
</tr>
<tr>
<td>Rabbit</td>
<td>250-500;</td>
<td>2-3.</td>
</tr>
<tr>
<td>Cat</td>
<td>~ 100;</td>
<td>0.5-8.</td>
</tr>
<tr>
<td>Dog</td>
<td>&gt; 250;</td>
<td>2-3.</td>
</tr>
</tbody>
</table>

* 95% confidence interval.
In subacute and subchronic toxicity studies in rats and dogs, nifedipine was tolerated without damage at doses of up to 50mg/kg (rats) and 100mg/kg (dogs) p.o. over periods of thirteen and four weeks, respectively. Following intravenous administration, dogs tolerated up to 0.1mg/kg nifedipine for six days without damage. Rats tolerated daily intravenous administration of 2.5mg/kg nifedipine over a period of three weeks without damage.

In chronic toxicity studies in dogs with treatment lasting up to one year, nifedipine was tolerated without damage at doses up to and including 100mg/kg p.o. In rats, toxic effects occurred at concentrations above 100ppm in the feed (approximately 5-7mg/kg bodyweight).

In a carcinogenicity study in rats (two years), there was no evidence of a carcinogenic effect of nifedipine.

Nifedipine has been shown to produce teratogenic findings in rats, mice and rabbits, including digital anomalies, malformation of the extremities, cleft palates, cleft sternum and malformation of the ribs.

Digital anomalies and malformation of the extremities are possibly a result of compromised uterine blood flow, but have also been observed in animals treated with nifedipine solely after the end of the organogenesis period. Nifedipine administration was associated with a variety of embryotoxic, placental toxic and foetal toxic effects, including stunted foetuses (rats, mice, rabbits), small placentas and underdeveloped chorionic villi (monkeys), embryonic and foetal deaths (rats, mice, rabbits) and prolonged pregnancy/decreased neonatal survival (rats; not evaluated in other species).

The risk to humans cannot be ruled out if a sufficiently high systemic exposure is achieved, however, all of the doses associated with the teratogenic, embryotoxic or foetal toxic effects in animals were maternally toxic and were several times the recommended maximum dose for humans.

In in vitro and in vivo tests, nifedipine has not been associated with mutagenic properties.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

**Tablet Core**

Povidone K30

Talc

Hypermellose

Carbomer 974P

Anhydrous colloidal silica

Magnesium stearate

Lactose monohydrate

**Coating**

Ferric oxide (red) (E172)

Titanium dioxide (E171)

Macrogol 4000

Eudragit “E”

Hypermellose

Magnesium stearate

Talc

**6.2 Incompatibilities**

Not applicable.
6.3 Shelf life
36 months

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package to protect from light.

6.5 Nature and contents of container
28 tablets in PVC/PVdC – Aluminium blisters.

6.6 Special precautions for disposal
No additional information.

7 MARKETING AUTHORISATION HOLDER
Focus Pharmaceuticals Ltd
Unit 5 Faraday Court
First Avenue
Centrum 100
Burton upon Trent
Staffordshire
DE14 2WX

8 MARKETING AUTHORISATION NUMBER(S)
PL 20046/0059

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/05/2010

10 DATE OF REVISION OF THE TEXT
19/05/2010
1 NAME OF THE MEDICINAL PRODUCT
Adanif XL 60mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One tablet contains 60mg nifedipine.
For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Prolonged release film-coated tablet.
Pale red, round biconvex tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
For the treatment of all grades of hypertension.
For the prophylaxis of chronic stable angina pectoris either as monotherapy or in combination with a beta-blocker.

4.2 Posology and method of administration
For oral administration, the tablets should be swallowed whole with a glass of water, either with or without food. The tablets should be taken at approximately 24-hour intervals, i.e. at the same time each day, preferably during the morning. Adanif XL Tablets must be swallowed whole; under no circumstances should they be bitten, chewed or broken up.

In mild to moderate hypertension, the recommended initial dose is one 20mg tablet once-daily. In severe hypertension, the recommended initial dose is one 30mg tablet once-daily. If necessary, the dosage can be increased according to individual requirements up to a maximum of 90mg once-daily.

For the prophylaxis of angina pectoris, the recommended initial dose is one 30mg tablet once-daily. The dosage can be increased according to individual requirements up to a maximum of 90mg once-daily.

Patients in whom hypertension or anginal symptoms are controlled on other nifedipine containing preparations may be safely switched to Adanif XL. Prophylactic anti-anginal efficacy is maintained when patients are switched from other calcium antagonists such as diltiazem or verapamil to Adanif XL. Patients switched from other calcium antagonists should initiate therapy at the recommended initial dose of 30mg Adanif XL once-daily. Subsequent titration to a higher dose may be initiated as warranted clinically.

The pharmacokinetics of nifedipine are altered in the elderly so that lower maintenance doses of nifedipine may be required compared to younger patients.

Co-administration with CYP 3A4 inhibitors or CYP 3A4 inducers may result in the recommendation to adapt the nifedipine dose or not to use nifedipine at all (see Section 4.5). Patients with renal impairment should not require adjustment of dosage.

Treatment may be continued indefinitely.

Nifedipine is not recommended for use in children.
Adanif XL should not be taken with grapefruit juice (see Section 4.5).

4.3 Contraindications
• Adanif XL should not be administered to patients with known hypersensitivity to nifedipine, or to other dihydropyridines because of the theoretical risk of cross-reactivity, or to any of the excipients.
• Adanif XL is contraindicated in pregnancy before week 20 and during breastfeeding (see also Sections 4.4, 4.6 and 5.3).
• Adanif XL should not be used in cases of cardiogenic shock, clinically significant aortic stenosis, unstable angina, or during or within one month of a myocardial infarction.
• Adanif XL should not be used for the treatment of acute attacks of angina.
• The safety of Adanif XL in malignant hypertension has not been established.
• Adanif XL should not be used for secondary prevention of myocardial infarction.
• Owing to the duration of action of the formulation, Adanif XL should not be administered to patients with hepatic impairment.
• Adanif XL should not be administered to patients with a history of gastro-intestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastro-intestinal tract.
• Adanif XL is contra-indicated in patients with inflammatory bowel disease or Crohn's disease.
• Adanif XL should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction (see Section 4.5).

4.4 Special warnings and precautions for use
Adanif XL Tablets must be swallowed whole; under no circumstances should they be bitten, chewed or broken up.

Caution should be exercised in patients with hypotension as there is a risk of further reduction in blood pressure and care must be exercised in patients with very low blood pressure (severe hypotension with systolic blood pressure less than 90mm Hg).

Careful monitoring of blood pressure must be exercised when administering nifedipine with I.V. magnesium sulphate, owing to the possibility of an excessive fall in blood pressure, which could harm both mother and foetus. For further information regarding use in pregnancy, refer to Section 4.6.

Adanif XL may be used in combination with beta-blocking drugs and other antihypertensive agents but the possibility of an additive effect resulting in postural hypotension should be borne in mind. Adanif XL will not prevent possible rebound effects after cessation of other antihypertensive therapy.

Adanif XL should be used with caution in patients whose cardiac reserve is poor. Deterioration of heart failure has occasionally been observed with nifedipine.

Diabetic patients taking Adanif XL may require adjustment of their control. In dialysis patients with malignant hypertension and hypovolaemia, a marked decrease in blood pressure can occur.

Nifedipine is metabolised via the cytochrome P450 3A4 system. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass or the clearance of nifedipine (see Section 4.5).

Drugs, which are known inhibitors of the cytochrome P450 3A4 system, and which may therefore lead to increased plasma concentrations of nifedipine include, for example:
- macrolide antibiotics (e.g., erythromycin)
- anti-HIV protease inhibitors (e.g., ritonavir)
- azole antimycotics (e.g., ketoconazole)
- the antidepressants, nefazodone and fluoxetine
- quinupristin/dalfopristin
- valproic acid
- cimetidine
Upon co-administration with these drugs, the blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose should be considered.

As the outer membrane of the Adanif XL Tablet is not digested, what appears to be the complete tablet may be seen in the toilet or associated with the patient's stools. Also, as a result of this, care should be exercised when administering Adanif XL to patients, as obstructive symptoms may occur. Bezoars can occur in very rare cases and may require surgical intervention. In single cases, obstructive symptoms have been described without known history of gastrointestinal disorders.

Adanif XL must not be administered to patients with Kock pouch (ileostomy after proctocolectomy).

A false positive effect may be experienced when performing a barium contrast x-ray.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs that affect nifedipine

Nifedipine is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in the liver. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass (after oral administration) or the clearance of nifedipine.

The extent as well as the duration of interactions should be taken into account when administering nifedipine together with the following drugs:

**Rifampicin**: Rifampicin strongly induces the cytochrome P450 3A4 system. Upon co-administration with rifampicin, the bioavailability of nifedipine is distinctly reduced and thus its efficacy weakened. The use of nifedipine in combination with rifampicin is therefore contraindicated (see Section 4.3).

Upon co-administration of known inhibitors of the cytochrome P450 3A4 system, the blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered (see Sections 4.2 and 4.4). In the majority of these cases, no formal studies to assess the potential for a drug interaction between nifedipine and the drug(s) listed have been undertaken, thus far.

**Drugs increasing nifedipine exposure:**
- macrolide antibiotics (e.g., erythromycin)
- anti-HIV protease inhibitors (e.g., ritonavir)
- azole anti-mycotics (e.g., ketoconazole)
- fluoxetine
- nefazodone
- quinupristin/dalfopristin
- cisapride
- valproic acid
- cimetidine
- diltiazem

Upon co-administration of inducers of the cytochrome P450 3A4 system, the clinical response to nifedipine should be monitored and, if necessary, an increase in the nifedipine dose considered. If the dose of nifedipine is increased during co-administration of both drugs, a reduction of the nifedipine dose should be considered when the treatment is discontinued.

**Drugs decreasing nifedipine exposure:**
- rifampicin (see above)
- phenytoin
- carbamazepine
- phenobarbital

Effects of nifedipine on other drugs

Nifedipine may increase the blood pressure lowering effect of concomitant applied antihypertensives. When nifedipine is administered simultaneously with β-receptor blockers the patient should be carefully monitored, since deterioration of heart failure is also known to develop in isolated cases.

**Digoxin:** The simultaneous administration of nifedipine and digoxin may lead to reduced digoxin clearance and, hence, an increase in the plasma digoxin level. The patient should therefore be subjected to precautionary checks for symptoms of digoxin overdosage and, if necessary, the glycoside dose should be reduced.

**Quinidine:** Co-administration of nifedipine with quinidine may lower plasma quinidine levels, and after discontinuation of nifedipine, a distinct increase in plasma quinidine levels may be observed in individual cases. Consequently, when nifedipine is either additionally administered or discontinued, monitoring of the quinidine plasma concentration, and if necessary, adjustment of the quinidine dose are recommended. Blood pressure should be carefully monitored and, if necessary, the dose of nifedipine should be decreased.

**Tacrolimus:** Tacrolimus is metabolised via the cytochrome P450 3A4 system. Published data indicate that the dose of tacrolimus administered simultaneously with nifedipine may be reduced in individual cases. Upon co-administration of both drugs, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose considered.

**Drug food interactions**

Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of nifedipine together with grapefruit juice thus results in elevated plasma concentrations and prolonged action of nifedipine due to a decreased first pass metabolism or reduced clearance. As a consequence, the blood pressure lowering effect of nifedipine may be increased. After regular intake of grapefruit juice, this effect may last for at least three days after the last ingestion of grapefruit juice. Ingestion of grapefruit/grapefruit juice is therefore to be avoided while taking nifedipine (see Section 4.2).

**Other forms of interaction**

Nifedipine may increase the spectrophotometric values of urinary vanillylmandelic acid, falsely. However, HPLC measurements are unaffected.

4.6 **Pregnancy and lactation**

Nifedipine is contraindicated in pregnancy before week 20.

In animal studies, nifedipine has been shown to produce embryotoxicity, foetotoxicity and teratogenicity (see Section 5.3 Preclinical safety data). There are no adequate well controlled studies in pregnant women.

From the clinical evidence available a specific prenatal risk has not been identified, although an increase in perinatal asphyxia, caesarean delivery, as well as prematurity and intrauterine growth retardation have been reported. It is unclear whether these reports are due to the underlying hypertension, its treatment, or to a specific drug effect.

The available information is inadequate to rule out adverse drug effects on the unborn and newborn child. Therefore any use in pregnancy after week 20 requires a very careful individual risk benefit assessment and should only be considered if all other treatment options are either not indicated or have failed to be efficacious.

In single cases of *in vitro* fertilisation calcium antagonists like nifedipine have been associated with reversible biochemical changes in the spermatozoa's head section that may result in impaired sperm function. In those men who are repeatedly unsuccessful in fathering a child by
in vitro fertilisation, and where no other explanation can be found, calcium antagonists like nifedipine should be considered as possible causes.

Nifedipine passes into the breast milk. As there is no experience of possible effects on infants, breastfeeding should first be stopped if nifedipine treatment becomes necessary during the breastfeeding period.

### 4.7 Effects on ability to drive and use machines
Reactions to the drug, which vary in intensity from individual to individual, may impair the ability to drive or to operate machinery. This applies particularly at the start of treatment, on changing the medication and in combination with alcohol.

### 4.8 Undesirable effects
Adverse drug reactions (ADRs) based on placebo-controlled studies with nifedipine sorted by CIOMS III categories of frequency (clinical trial data base: nifedipine n = 2,661; placebo n = 1,486; and the ACTION study: nifedipine n = 3,825; placebo n = 3,840) are listed below:

ADRs listed under "common" were observed with a frequency below 3% with the exception of oedema (9.9%) and headache (3.9%).

ADRs derived from post marketing reports are listed in the Frequency Not Known column.

<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Frequency Not Known</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1% to &lt;10%</td>
<td>&gt;0.1% to &lt;1%</td>
<td>&gt;0.01% to &lt;0.1%</td>
<td></td>
</tr>
</tbody>
</table>

#### Immune System Disorders
- Allergic reaction
- Allergic oedema/angioedema
- Pruritus
- Urticaria
- Rash
- Anaphylactic/anaphylactic reaction

#### Psychiatric Disorders
- Anxiety reactions
- Sleep disorders

#### Nervous System Disorders
- Headache
  - Vertigo
  - Migraine
- Dizziness
  - Tremor
- Par-/Dysaesthesia

#### Eye Disorders
- Visual disturbances

#### Cardiac Disorders
- Tachycardia
- Palpitations

#### Vascular Disorders
- Oedema
- Hypotension
- Vasodilatation
- Syncope

#### Respiratory Disorders
Nosebleed
Nasal congestion
Dyspnœa

**Gastrointestinal Disorders**

<table>
<thead>
<tr>
<th>Constipation</th>
<th>Gastrointestinal and abdominal pain</th>
<th>Gingival hyperplasia</th>
<th>Bezoar</th>
<th>Dysphagia</th>
<th>Intestinal obstruction</th>
<th>Intestinal ulcer</th>
<th>Vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Constipation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flatulence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hepatobiliary Disorders**

<table>
<thead>
<tr>
<th>Transient increase in liver enzymes</th>
</tr>
</thead>
</table>

**Skin and Subcutaneous Tissue Disorders**

<table>
<thead>
<tr>
<th>Erythema</th>
</tr>
</thead>
</table>

**Musculoskeletal and Connective Tissue Disorders**

<table>
<thead>
<tr>
<th>Muscle cramps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint swelling</td>
</tr>
</tbody>
</table>

**Renal and Urinary Disorders**

<table>
<thead>
<tr>
<th>Polyuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysuria</td>
</tr>
</tbody>
</table>

**Reproductive System Disorders**

| Erectile dysfunction |

**General Disorders and Administration Site Conditions**

<table>
<thead>
<tr>
<th>Feeling unwell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unspecific pain</td>
</tr>
<tr>
<td>Chills</td>
</tr>
</tbody>
</table>

In dialysis patients with malignant hypertension and hypovolaemia a distinct fall in blood pressure can occur as a result of vasodilation.

### 4.9 Overdose

**Symptoms**

The following symptoms are observed in cases of severe nifedipine intoxication:

- Disturbances of consciousness to the point of coma, a drop in blood pressure, tachycardia, bradycardia, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema.

**Treatment**

As far as treatment is concerned, elimination of nifedipine and the restoration of stable cardiovascular conditions have priority. Elimination must be as complete as possible, including the small intestine, to prevent the otherwise inevitable subsequent absorption of the active substance. The benefit of gastric decontamination is uncertain.
1. Consider activated charcoal (50g for adults, 1g/kg for children) if the patient presents within 1 hour of ingestion of a potentially toxic amount.

Although it may seem reasonable to assume that late administration of activated charcoal may be beneficial for sustained release (SR, MR) preparations there is no evidence to support this.

2. Alternatively consider gastric lavage in adults within 1 hour of a potentially life-threatening overdose.

3. Consider further doses of activated charcoal every 4 hours if a clinically significant amount of a sustained release preparation has been ingested with a single dose of an osmotic laxative (e.g. sorbitol, lactulose or magnesium sulphate).

4. Asymptomatic patients should be observed for at least 4 hours after ingestion and for 12 hours if a sustained release preparation has been taken.

Haemodialysis serves no purpose as nifedipine is not dialysable. Hypotension as a result of cardiogenic shock and arterial vasodilatation can be treated with calcium (10-20ml of a 10% calcium gluconate solution administered intravenously over 5-10 minutes). If the effects are inadequate, the treatment can be continued, with ECG monitoring. If an insufficient increase in blood pressure is achieved with calcium, vasoconstricting sympathomimetics such as dopamine or noradrenaline should be administered. The dosage of these drugs should be determined by the patient's response.

Symptomatic bradycardia may be treated with atropine, beta-sympathomimetics or a temporary cardiac pacemaker, as required. Additional fluids should be administered with caution to avoid cardiac overload.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: C08 CA05

Nifedipine is a calcium antagonist of the 1,4-dihydropyridine type. Calcium antagonists reduce the transmembranal influx of calcium ions through the slow calcium channel into the cell. As a specific and potent calcium antagonist, nifedipine acts particularly on the cells of the myocardium and the smooth muscle cells of the coronary arteries and the peripheral resistance vessels. The main action of nifedipine is to relax arterial smooth muscle, both in the coronary and peripheral circulation. The Adanif XL Tablet is formulated to achieve controlled delivery of nifedipine in a release profile sufficient to enable once-daily administration to be effective in clinical use.

In hypertension, the main action of nifedipine is to cause peripheral vasodilatation and thus reduce peripheral resistance. Nifedipine administered once-daily provides 24-hour control of raised blood pressure. Nifedipine causes reduction in blood pressure such that the percentage lowering is proportional to its initial level. In normotensive individuals, nifedipine has little or no effect on blood pressure.

In angina, Adanif XL reduces peripheral and coronary vascular resistance, leading to an increase in coronary blood flow, cardiac output and stroke volume, whilst decreasing afterload. Additionally, nifedipine dilates submaximally both clear and atherosclerotic coronary arteries, thus protecting the heart against coronary artery spasm and improving perfusion to the ischaemic myocardium. Nifedipine reduces the frequency of painful attacks and the ischaemic ECG changes irrespective of the relative contribution from coronary artery spasm or atherosclerosis.

In a multi-national, randomised, double-blind, prospective study involving 6321 hypertensive patients with at least one additional risk factor followed over 3 to 4.8 years, Adanif XL 30 and 60 (nifedipine GITS) were shown to reduce blood pressure to a comparable degree as a standard diuretic combination.
5.2 Pharmacokinetic properties

General characteristics:

Adanif XL Tablets are formulated to provide nifedipine at an approximately constant rate over 24 hours. Nifedipine is released from the tablet at a zero-order rate by a membrane-controlled, osmotic push-pull process. The pharmacokinetic profile of this formulation is characterized by low peak-trough fluctuation. 0-24 hour plasma concentration versus time profiles at steady state are plateau-like, rendering the Adanif XL Tablet appropriate for once-a-day administration.

The delivery rate is independent of gastrointestinal pH or motility. Upon swallowing, the biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the faeces as an insoluble shell. Orally administered nifedipine is almost completely absorbed in the gastro-intestinal tract. The systemic availability of orally administered nifedipine immediate release formulations (nifedipine capsules) is 45–56% owing to a first pass effect. At steady-state, the bioavailability of Adanif XL Tablets ranges from 68-86% relative to Nifedipine capsules. Administration in the presence of food slightly alters the early rate of absorption but does not influence the extent of drug availability.

Nifedipine is about 95% bound to plasma protein (albumin). The distribution half-life after intravenous administration has been determined to be 5 to 6 minutes.

After oral administration, nifedipine is metabolised in the gut wall and in the liver, primarily by oxidative processes. These metabolites show no pharmacodynamic activity. Nifedipine is eliminated in the form of its metabolites, predominantly via the kidneys, with approximately 5-15% being excreted via the bile in the faeces. Non-metabolised nifedipine can be detected only in traces (below 1.0%) in the urine.

The terminal elimination half-life is 1.7 to 3.4 hours in conventional formulations (nifedipine capsules). The terminal half-life following Adanif XL administration does not represent a meaningful parameter as a plateau-like plasma concentration is maintained during release from the tablets and absorption. After release and absorption of the last dose the plasma concentration finally declines with an elimination half-life as seen in conventional formulations.

Characteristics in patients:

There are no significant differences in the pharmacokinetics of nifedipine between healthy subjects and subjects with renal impairment. Therefore, dosage adjustment is not needed in these patients.

In patients with hepatic impairment, the elimination half-life is distinctly prolonged and the total clearance is reduced. Owing to the duration of action of the formulation, Adanif XL should not be administered in these patients.

5.3 Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of single and repeated dose toxicity, genotoxicity and carcinogenic potential.

Following acute oral and intravenous administration of nifedipine in various animal species, the following LD50 (mg/kg) values were obtained:

<table>
<thead>
<tr>
<th>Species</th>
<th>Oral (mg/kg)</th>
<th>i.v. (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>494 (421-572)*</td>
<td>4.2 (3.8-4.6)*</td>
</tr>
<tr>
<td>Rat</td>
<td>1022 (950-1087)*</td>
<td>15.5 (13.7-17.5)*</td>
</tr>
<tr>
<td>Rabbit</td>
<td>250-500</td>
<td>2-3</td>
</tr>
<tr>
<td>Cat</td>
<td>~ 100</td>
<td>0.5-8</td>
</tr>
<tr>
<td>Dog</td>
<td>&gt; 250</td>
<td>2-3</td>
</tr>
</tbody>
</table>

* 95% confidence interval.
In subacute and subchronic toxicity studies in rats and dogs, nifedipine was tolerated without damage at doses of up to 50mg/kg (rats) and 100mg/kg (dogs) p.o. over periods of thirteen and four weeks, respectively. Following intravenous administration, dogs tolerated up to 0.1mg/kg nifedipine for six days without damage. Rats tolerated daily intravenous administration of 2.5mg/kg nifedipine over a period of three weeks without damage.

In chronic toxicity studies in dogs with treatment lasting up to one year, nifedipine was tolerated without damage at doses up to and including 100mg/kg p.o. In rats, toxic effects occurred at concentrations above 100ppm in the feed (approximately 5-7mg/kg bodyweight).

In a carcinogenicity study in rats (two years), there was no evidence of a carcinogenic effect of nifedipine.

Nifedipine has been shown to produce teratogenic findings in rats, mice and rabbits, including digital anomalies, malformation of the extremities, cleft palates, cleft sternum and malformation of the ribs.

Digital anomalies and malformation of the extremities are possibly a result of compromised uterine blood flow, but have also been observed in animals treated with nifedipine solely after the end of the organogenesis period. Nifedipine administration was associated with a variety of embryotoxic, placental toxic and foetotoxic effects, including stunted foetuses (rats, mice, rabbits), small placentas and underdeveloped chorionic villi (monkeys), embryonic and foetal deaths (rats, mice, rabbits) and prolonged pregnancy/decreased neonatal survival (rats; not evaluated in other species).

The risk to humans cannot be ruled out if a sufficiently high systemic exposure is achieved, however, all of the doses associated with the teratogenic, embryotoxic or foetotoxic effects in animals were maternally toxic and were several times the recommended maximum dose for humans.

In in vitro and in vivo tests, nifedipine has not been associated with mutagenic properties.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

**Tablet Core**
- Povidone K30
- Talc
- Hypermellose
- Carbomer 974P
- Anhydrous colloidal silica
- Magnesium stearate
- Lactose monohydrate

**Coating**
- Ferric oxide (red) (E172)
- Titanium dioxide (E171)
- Macrogol 4000
- Eudragit “E”
- Hypermellose
- Magnesium stearate
- Talc

#### 6.2 Incompatibilities

Not applicable.
6.3  **Shelf life**
36 months

6.4  **Special precautions for storage**
Do not store above 25°C. Store in the original package to protected from light.

6.5  **Nature and contents of container**
28 tablets in PVC/PVdC – Aluminium blisters.

6.6  **Special precautions for disposal**
No additional information.

7  **MARKETING AUTHORISATION HOLDER**
Focus Pharmaceuticals Ltd
Unit 5 Faraday Court
First Avenue
Centrum 100
Burton upon Trent
Staffordshire
DE14 2WX

8  **MARKETING AUTHORISATION NUMBER(S)**
PL 20046/0060

9  **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
19/05/2010

10  **DATE OF REVISION OF THE TEXT**
19/05/2010
PATIENT INFORMATION LEAFLET

Adanif® XL 30mg Tablets
Adanif® XL 60mg Tablets
Nifedipine

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Adanif XL Tablets are and what are they used for
2. Before you take Adanif XL Tablets
3. How to take Adanif XL Tablets
4. Possible side effects
5. How to store Adanif XL Tablets
6. Further information

1. What Adanif XL Tablets are and what are they used for
Your medicine is called Adanif XL 30mg or 60mg Tablets: they contain nifedipine as the active ingredient. (They will be called Adanif XL Tablets throughout this leaflet.)

What this medicine does
Your doctor has prescribed Adanif XL Tablets for:
- High blood pressure (hypertension): nifedipine works by widening blood vessels, allowing blood to flow more freely, thus reducing the strain on your heart.
- Angina (lack of oxygen to the muscles of the heart leading to pain in the centre of the chest radiating over the left side of the body, up the neck and down the left arm). Nifedipine reduces the frequency of angina attacks by opening the blood vessels (arteries) of the heart, allowing more oxygen and blood to reach the muscles of the heart.

Adanif XL Tablets contain nifedipine, a medicine known as a selective calcium channel blocker.

Tell your doctor or pharmacist if you have any of the above.

Using other medicines
Make sure your doctor knows if you are taking a medicine listed here:
Medicines that may decrease the levels and effects of nifedipine are:
- Rifampicin an antibiotic used for legionnaire’s disease and leprosy.
- Phenytoin used to treat epilepsy and pain around the face.
- Carbamazepine used to treat epilepsy.
- Phenobarbital used to help you sleep and to treat some types of epilepsy.
Medicines that may increase the levels and effects of nifedipine are:
- Macrolide antibiotics such as erythromycin, clarithromycin and azithromycin used for many types of infections, such as tonsillitis, bronchitis and skin infections.
- Anti-HIV Protease Inhibitors such as ritonavir, indinavir and nefilnavir used to treat HIV.
- Azole anti-fungals (anti-mycotics) such as ketoconazole, itraconazole and fluconazole used for many types of fungal infections.
- Fluoxetine and Nefazodone used to treat depression and obsessive-compulsive disorders.
- Quinupristin and Dalfopristin antibiotics used for various skin and blood infections.
- Cisapride used for night-time heartburn.
- Valproic acid used to treat epilepsy.
- Cimetidine used to treat stomach ulcers and for reducing the amount of stomach acid.
- Diltiazem used for angina and high blood pressure.

Other medicines that are affected by nifedipine are:
- Beta-blocking medicines such as propranolol or atenolol used to help prevent heart attacks and an irregular heartbeat or to treat high blood pressure and angina. These medicines may decrease blood pressure too much and can lead to dizziness especially when you go from a sitting to standing position or from lying to sitting position.
- Digoxin used for heart failure and abnormal heartbeats. Nifedipine...
2. Before you take Adanif XL Tablets

Do not take Adanif XL Tablets

- if you are allergic (hypersensitive) to nifedipine or other similar medicines such as amiodipine and felodipine or any of the other ingredients of Adanif XL Tablets (see Section 6);
- before week 20 of pregnancy or planning on becoming pregnant;
- if you are breast-feeding;
- if you have any other heart conditions such as:
  - your heart is not pumping blood properly, a condition known a cardiogenic shock;
  - you have a narrowing of the main artery (the aorta) from the heart to the rest of the body. This condition is known as an aortic stenosis;
  - unstable angina;
  - if you have had a heart attack within the past month;
- if you are having an acute angina attack – DO NOT TAKE Adanif XL Tablets when an angina attack occurs;
- if your blood pressure continues rising despite treatment;
- to prevent a heart attack;
- if you have liver problems;
- if you suffer with any narrowing or obstruction of your intestines (guts) or oesophagus (gullet);
- if you suffer from Crohn’s disease or any disease that causes swelling or inflammation of the intestines (gut);
- if you are taking rifampicin, an antibiotic. See "Using other medicines" section.

Talk to your doctor, pharmacist or nurse if any of the following apply to you:

- if you already have low or very low blood pressure (a systolic pressure of less than 90mmHg). Symptoms of this may include feeling dizzy or passing out when you stand up;
- if you have a heart condition or you have been told your heart is failing;
- if you are diabetic (high levels of sugar in the blood);
- if you are having kidney dialysis;
- if you have an ileostomy bag (a special bag, also called a Kock pouch, attached to the intestines to collect waste from the body);
- if you are having a x-ray procedure that uses a barium meal or contrast (a special solution used for diagnosing patients having certain x-ray procedures);
- if you have any urine tests. Nifedipine may increase the amounts of vanillylmandelic acid (a waste product excreted in your water) if measured using certain methods.

reduces clearance of digoxin so your doctor may reduce the dose of digoxin to prevent overdosing.

- Quinidine used to treat increased and abnormal heartbeats. The levels of quinidine are reduced by nifedipine, regardless of dose of quinidine taken. Blood pressure and levels of quinidine should be monitored.
- Tacrolimus used to suppress the immune system and prevent organ rejection in transplant patients. Nifedipine increases levels of tacrolimus so a reduction in dose maybe necessary.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Using Adanif XL Tablets with food and drink

Do not take Adanif XL Tablets within 3 days of having anything containing grapefruit.

- Do not take Adanif XL Tablets with grapefruit or grapefruit juice because it may increase the levels of nifedipine leading to an increased effect or ever overdose.
- Swallow the tablets whole with a glass of water, with or without food.

Pregnancy and breast-feeding

- Do not take Adanif XL Tablets before week 20 of pregnancy. If you are thinking of getting pregnant or breast-feeding,
- Speak to your doctor or pharmacist for advice before taking Adanif XL Tablets, especially if you are having magnesium sulphate injections (used for magnesium deficiency).
- Nifedipine may affect male fertility, your fertility will return once you stop taking the drug. If you are trying to father a child without success tell your doctor that you are taking nifedipine.

Driving and using machines

- Adanif XL Tablets may decrease your ability to drive or operate machinery safely;
- Do not drive or operate machines if you are affected.

Important information about some of the ingredients in Adanif XL Tablets

- Adanif XL Tablets contain lactose monohydrate - if you have been told by your doctor that you have or intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Adanif XL Tablets

Always take Adanif XL Tablets exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

ALWAYS: swallow the tablet whole, with a glass of water, at about the same time each day.
DO NOT bite, chew or break-up the tablet. Do not take within 3 days of having grapefruit or grapefruit juice.

Adults
- The usual starting dose is one 30mg tablet taken once a day.
- The dose may be increased to a maximum of 90mg once daily depending on your response to the drug.
- Take at about the same time each day, preferably in the morning.
- If you are already taking other nifedipine containing medicines your doctor may have switched you to a long-acting formulation, such as Adanif XL Tablets. If this is the case the starting dose above should be used.

Elderly
- You may need a lower dose and your doctor will discuss this with you.

Children
- Adanif XL tablets should not be given to children.

Tell your doctor:
- If your chest pain (angina) gets worse (comes on more often or more severely) over a matter of hours or days. You may be advised not to take Adanif XL Tablets.
- If you have chest pains after taking your first dose of Adanif XL Tablets. Your doctor may wish to change your treatment.
- If you notice increased breathlessness.
- If you notice swelling of the ankles.

Tell your doctor before you take the next dose if any of these apply to you.

If you take more Adanif XL Tablets than you should
- If you take more Adanif XL Tablets than your doctor has prescribed, or you think a child has accidentally swallowed any, call your doctor or go to the nearest hospital emergency department immediately. Take the medicine or this leaflet with you to show the doctor.

If you forget to take Adanif XL Tablets
- Do not take a double amount to make up for a forgotten dose.
- Take the next dose immediately.
- Continue taking your tablets at your usual time of day; but wait at least 12 hours before taking your next dose.

If you stop using Adanif XL Tablets
- Do not stop taking Adanif XL Tablets suddenly.
- Speak to your doctor before you stop taking Adanif XL Tablets.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

Other side effects (where the frequency is not known)
- Breathlessness or difficulty breathing;
- Being sick (vomiting);
- Formation of a mass of foreign material in the stomach or intestines (gut);
- Blockage or obstruction of the intestines (gut);
- Ulceration of the intestines (gut);
- Difficulty swallowing.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Adanif XL Tablets

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the carton. The expiry date refers to the last day of that month.

Do not store above 25°C. Store the original package to protect from light.

Do not use if you notice any damage or discolouration of the tablets. Return them to your pharmacist.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further Information

What Adanif XL Tablets contain:
- The active substance is nifedipine.
- The other ingredients are: tablet core: lactose monohydrate (E534), colloidal anhydrous and magnesium stearate; coating - Eudragit RL, titanium dioxide (E171), ferric oxide (E172), talc (E533b), magnesium stearate, hypromellose and macrogol 4000.

What Adanif XL Tablets look like and contents of the pack
Adanif XL 30mg and 60mg Tablets: round tablets with a pale red colour.
Each carton of Adanif XL Tablets contains 28 tablets.

Marketing Authorisation Holder
Focus Pharmaceuticals Limited, Unit 5, Faraday Court, First Avenue, Centrum 100, Burton upon Trent, Staffordshire DE14 2WX
Tel: 01283 495 280 Fax: 01283 495 290
Email: medinfo@focuspharma.co.uk
Manufacturer
4. Possible Side Effects

Like all medicines, Adanif XL Tablets can cause side effects, although not everybody gets them.

Take immediate action if you have any of the following side effects:
severe allergic reaction which may include a red and lumpy skin rash, difficulty breathing, swelling of face, mouth, lips or eyelids, unexplained high temperature (fever) and feeling faint. If the swelling affects your throat and makes breathing and swallowing difficult, go to hospital straight away.

Common (up to 1 in 10 people)
- headache;
- flushing due to widening of the blood vessels (vasodilation);
- constipation;
- swelling (oedema), sometimes of the hands, feet and/or ankles;
- generally feeling unwell.

Uncommon (up to 1 in 100 people)
- feeling anxious;
- problems sleeping;
- migraine;
- trembling or involuntary movements;
- changes in your vision;
- pain of the abdomen, stomach, intestines (gut) or generally all over;
- dizziness;
- low blood pressure (leading to fainting or feeling dizzy), especially when you stand up if sitting or sit up after lying down;
- fainting or loss of consciousness;
- increased heart rate;
- an irregular and/or forceful heart beat (palpitations);
- nosebleeds;
- blocked nose or congestion;
- chills;
- dry mouth;
- indigestion;
- wind (flatulence);
- feeling sick (nausea);
- changes to the levels of some liver enzymes;
- muscle cramps;
- swelling of the joints;
- dizziness or feeling unbalanced (vertigo);
- redness or flushing of the skin;
- difficulty achieving or maintaining an erection (Impotence);
- passing an increased amount of water or pain when urinating.

Rare (up to 1 in 1000 people)
- change in sensitivity to touch (either increased, decreased or loss), tingling, pins and needles and very sensitive skin;
- itching, rash, swelling or blisters (hives);
- swelling or enlargement of the gums.