Public Assessment Report

Decentralised Procedure

Nefopam Hydrochloride 30mg Film-coated Tablets

(Nefopam hydrochloride)

Procedure No: UK/H/6245/001/DC

UK Licence Number: PL 30306/0774

Actavis Group PTC ehf.
LAY SUMMARY

Nefopam Hydrochloride 30mg Film-coated Tablets
(Nefopam hydrochloride, film-coated tablet, 30mg)

This is a summary of the Public Assessment Report (PAR) for Nefopam Hydrochloride 30mg Film-coated Tablets (PL 30306/0774; UK/H/6245/001/DC). It explains how Nefopam Hydrochloride 30mg Film-coated Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Nefopam Hydrochloride 30mg Film-coated Tablets.

The product will be referred to as Nefopam Tablets throughout the remainder of this public assessment report (PAR).

For practical information about using Nefopam Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Nefopam Tablets and what are they used for?
Nefopam Tablets are a 'generic medicine'. This means that Nefopam Tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Acupan 30 mg Tablets (Meda Pharmaceuticals Ltd, UK).

Nefopam Tablets are used to relieve acute and chronic pain (for example pain after an operation, dental pain, joint or muscle pain, after an injury, or pain caused by cancer). Nefopam Tablets should not be used to treat the pain from a heart attack.

How do Nefopam Tablets work?
Nefopam Tablets belong to a group of medicines called analgesics, commonly known as pain killers or pain relievers. The active substance, nefopam hydrochloride, interrupts the pain messages being sent to the brain, and it also acts in the patient’s brain to stop pain messages being felt. This means that Nefopam Tablets do not stop the pain from happening, but the patient will not be able to feel the pain as much.

How are Nefopam Tablets used?
The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

Adults
The recommended initial dose is two tablets taken three times a day. The patient’s doctor may increase this dose up to a maximum of three tablets taken three times a day according to their needs.

The patient should ask their doctor or pharmacist if:
- they are not sure how many tablets to take or when to take them
- they think the effect is too strong or too weak.

Swallow the tablets with water.
Use in children and adolescents
Over 12 years - as per adults (see above).

Under 12 years - **Nefopam Tablets should not be taken by children under 12.**

**Elderly**
In older patients the doctor may reduce the number of tablets that are taken.

**Patients with kidney and/or liver problems**
The patient’s doctor may adjust the dose of Nefopam Tablets depending upon their condition.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Nefopam Tablets are used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

**What benefits of Nefopam Tablets have been shown in studies?**
Because Nefopam Tablets are a generic medicine, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicine Acupan 30 mg Tablets (Meda Pharmaceuticals Ltd, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Nefopam Tablets?**
Because Nefopam Tablets is a generic medicine and is bioequivalent to the reference medicine Acupan 30 mg Tablets (Meda Pharmaceuticals Ltd, UK), its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Nefopam Tablets, see section 4 of the package leaflet available on the MHRA website.

**Why were Nefopam Tablets approved?**
It was concluded that, in accordance with EU requirements, Nefopam Tablets has been shown to have comparable quality and to be bioequivalent to Acupan 30 mg Tablets (Meda Pharmaceuticals Ltd, UK). Therefore, the MHRA decided that, as for Acupan 30 mg Tablets (Meda Pharmaceuticals Ltd, UK); the benefits are greater than the risks and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Nefopam Tablets?**
A risk management plan (RMP) has been developed to ensure that Nefopam Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Nefopam Tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.
Other information about Nefopam Tablets
A Marketing Authorisation was granted in the UK on 30 August 2016.

The full PAR for Nefopam Tablets follows this summary.

For more information about treatment with Nefopam Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in October 2016.
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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Actavis Group PTC ehf, a marketing authorisation for the medicinal product Nefopam Tablets (PL 30306/0774; UK/H/6245/001/DC). The product is a prescription only medicine (POM) indicated for the relief of acute and chronic pain, including post-operative pain, dental pain, musculoskeletal pain, acute traumatic pain and cancer pain.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Iceland as Concerned Member State (CMS). The applicant subsequently withdrew the application in Iceland during the procedure, leaving no CMS. The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Acupan 30 mg Tablets which were first authorised in the UK to 3M Health Care Limited (PL 00068/0061) on 02 March 1978 and subsequently underwent several changes of ownership procedures the most recent of which was to the current marketing authorisation holder (MAH), Meda Pharmaceuticals Ltd, UK (PL 15142/0109) on 02 February 2010.

Nefopam hydrochloride is a potent and rapidly-acting analgesic. It is totally distinct from other centrally-acting analgesics such as morphine, codeine, pentazocine and propoxyphene.

Unlike the narcotic agents, nefopam has been shown not to cause respiratory depression. There is no evidence from pre-clinical research of habituation occurring with nefopam.

One bioequivalence study (conducted under fasting conditions) was submitted to support this application. The applicant has stated that the bioequivalence study was conducted in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that this is a generic medicinal product of an originator product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Nefopam Tablets outweigh the risks and a Marketing Authorisation was granted on 30 August 2016.
II QUALITY ASPECTS

II.1 Introduction
Each film-coated tablet contains 30 mg nefopam hydrochloride, as the active ingredient. Other ingredients consist of the pharmaceutical excipients:

**Tablet core:**
Anhydrous lactose, colloidal anhydrous silica, microcrystalline cellulose, sodium starch glycolate (type A) and magnesium stearate

**Film-coating (Opadry II white 85F184221):**
Polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol/PEG 3350 (E1521) and talc (E553b).

The finished product is packed in to polyvinyl chloride (PVC)/polyethylene (PE)/polyvinylidene chloride (PVdC)/aluminium (Alu) blisters in a pack size of 90 film-coated tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance
INN: Nefopam hydrochloride
Chemical name: 3,4,5,6-tetrahydro-5-methyl-1-phenyl-1H-2,5-benzoxazocine hydrochloride

Structure:

![Molecular structure of nefopam hydrochloride](image)

Molecular formula: $\text{C}_{17}\text{H}_{20}\text{ClNO}$
Molecular weight: 289.80 g/mol
Description: White crystalline powder.
Solubility: Soluble in water and methanol. Slightly soluble in chloroform.

Nefopam hydrochloride is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.
An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious film-coated tablets containing 30 mg nefopam hydrochloride per tablet, that are a generic version of the reference product Acupan 30 mg Tablets (Meda Pharmaceuticals Ltd, UK). A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the Opadry II white 85F184221 film-coating colour which is controlled to a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose anhydrous none of the excipients used contain material of animal or human origin. The supplier of lactose anhydrous has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale batch size and has shown satisfactory results.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided which comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with no special storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.
II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of nefopam hydrochloride are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Nefopam Tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of nefopam hydrochloride is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of nefopam hydrochloride.

Based on the data provided, Nefopam Tablets can be considered bioequivalent to Acupan 30 mg Tablets (Meda Pharmaceuticals Ltd, UK).

IV.2 Pharmacokinetics
In support of this application, the applicant submitted the following bioequivalence study:

STUDY
An open label, randomised, two-treatment, two period, two-sequence, single oral dose, crossover, bioequivalence study of the applicant’s test product Nefopam Hydrochloride 30mg Film-coated Tablets (Actavis Group PTC ehf) versus the reference product Acupan 30 mg Tablets (Meda Pharmaceuticals Ltd, UK) in healthy, adult, subjects under fasting conditions.
Subjects were administered a single dose (1 x 30 mg film-coated tablet) of the test or the reference product.

Blood samples were collected for plasma levels before dosing and up to and including 24 hours after each administration. The washout period between the treatment phases was 5 days. The pharmacokinetic results are presented below:

Table: Summary of pharmacokinetic data for nefopam:

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>ACUPAN™ (Reference Product)</th>
<th>Nefopam (Test Product)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Geometric mean</td>
<td>Arithmetic mean</td>
</tr>
<tr>
<td>AUC₀⁻ᵗ (ng.h/mL)</td>
<td>314.92</td>
<td>339.39</td>
</tr>
<tr>
<td>Cₘₐₓ (ng/mL)</td>
<td>39.45</td>
<td>41.86</td>
</tr>
</tbody>
</table>

AUC₀⁻ᵗ: area under the plasma concentration-time curve from zero to t hours  
Cₘₐₓ: maximum plasma concentration

Table: ratio at 90% confidence interval of the test product versus the reference product:

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Ratio (%)</th>
<th>90% Confidence Intervals</th>
<th>Intra Subject Variability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower 90% CI (%)</td>
<td>Upper 90% CI (%)</td>
</tr>
<tr>
<td>AUC₀⁻ᵗ</td>
<td>98.90</td>
<td>93.80</td>
<td>104.29</td>
</tr>
<tr>
<td>Cₘₐₓ</td>
<td>98.31</td>
<td>90.77</td>
<td>106.49</td>
</tr>
</tbody>
</table>

Conclusion
The 90% confidence intervals of the test/reference ratio for AUC and Cₘₐₓ values for nefopam lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product, Nefopam Hydrochloride 30mg Film-coated Tablets (Actavis Group PTC ehf), is bioequivalent to the reference product, Acupan 30 mg Tablets (Meda Pharmaceuticals Ltd, UK).

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for applications of this type.

IV.5 Clinical safety
No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities
and interventions designed to identify, characterise, prevent or minimise risks relating to nefopam hydrochloride.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
Summary table of safety concerns:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
</tr>
</thead>
</table>
| **Important identified risks** | - Patients with a history of convulsive disorders  
- Hypersensitivity  
- Patients concurrently taking mono-amine-oxidase (MAO) inhibitors or within 2 weeks of discontinuing  
- Patients with hepatic insufficiency  
- Patients with renal insufficiency |
| **Important potential risks** | - Concurrent administration with tricyclic antidepressants  
- Additive effect with sympathomimetics, anticholinergics  
- Cardiac, cardiovascular effects  
- CNS effects (e.g. hallucinations, confusion)  
- Overdose  
- Urinary retention  
- Impaired ability to drive safely or operate machinery  
- False positive screening results when tested for benzodiazepines and opioids |
| **Missing information** | - Treatment of myocardial infarction or heart pain  
- Use during pregnancy and lactation  
- Use in children under 12 years |

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

**IV.7 Discussion on the clinical aspects**
The grant of a marketing authorisation is recommended for this application.

**V User consultation**
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Nefopam Hydrochloride 30mg Film-coated Tablets (NRIM Limited; PL 41830/0014 and 0034). The bridging report submitted by the applicant is acceptable.

**VI Overall conclusion, benefit/risk assessment and recommendation**
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with nefopam hydrochloride is considered to have demonstrated the therapeutic value of the compound. The product is bioequivalent to the marketed reference product and its benefit/risk balance is considered similar and positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below: