Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mobilflex Vials 20 mg Powder and Solvent for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 Vial contains 20 mg tenoxicam.
1 Ampoule contains 2 ml water for injections.
The reconstituted solution gives a tenoxicam concentration of 10 mg/ml.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection
Powder: A green-yellow coloured powder.
Solvent: Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Mobiflex is indicated for the relief of pain and inflammation in osteoarthritis and rheumatoid arthritis. It is also indicated for the short term management of acute musculoskeletal disorders including strains, sprains and other soft-tissue injuries. IV, IM tenoxicam is available for these indications in those patients considered unable to take oral tenoxicam.

4.2 Posology and method of administration

Adults
Mobiflex Vials should be given IV or IM. A single daily dose of 20mg for one to two days initially to be continued with the oral form, with administration at the same time each day. For patients needing long-term treatment a reduction to a daily oral dose of 10mg may be tried for maintenance.

The lyophilisate should be dissolved in 2ml of the solvent provided (2ml sterile water for injections). This reconstituted solution should be used immediately.

Higher doses should be avoided as they do not usually achieve significantly greater therapeutic effect but may be associated with a higher risk of adverse events.

In acute musculoskeletal disorders treatment should not normally be required for more than 7 days, but in severe cases it may be continued up to a maximum of 14 days.

Elderly
As with other non-steroidal anti-inflammatory drugs, Mobiflex should be used with special caution in elderly patients since they may be less able to tolerate side-effects than younger patients. They are also more likely to be receiving concomitant medication or to have impaired hepatic, renal or cardiovascular function. The lowest dose should be used in elderly patients and the patient should be monitored for symptoms of GI bleeding (e.g. melaena) for 4 weeks following initiation of non-steroidal anti-inflammatory drugs (NSAID) therapy.

Children
There are insufficient data to make a recommendation for administration of Mobiflex to children and adolescents.

Use in renal and hepatic insufficiency

Creatinine clearance	**Dosage regimen**
Greater than 25ml/min	Usual dosage but monitor patients carefully (see *Special warnings and special precautions for use*)
Less than 25ml/min	Insufficient data to make dosage recommendations

There is insufficient information to make dosage recommendations for Mobiflex in patients with pre-existing hepatic impairment.

4.3 Contraindications

1. Active peptic ulceration and a past history of peptic ulceration, gastro-intestinal bleeding (melaena, haematemesis) or severe gastritis.

2. Known hypersensitivity to Mobiflex, to any component of the product or to other NSAIDs. Mobiflex should also be avoided in cases where the patient has suffered a hypersensitivity reaction (symptoms of asthma, rhinitis, angioedema or urticaria) to other non-steroidal anti-inflammatory drugs, or salicylates including aspirin, as the potential exists for cross-sensitivity to Mobiflex.

4.4 Special warnings and precautions for use

NSAIDs should only be given with care to patients with a history of gastrointestinal disease.

Any patient being treated with Mobiflex who presents with symptoms of gastro-intestinal disease should be closely monitored. If peptic ulceration or gastro-intestinal bleeding occurs, Mobiflex should be withdrawn immediately.

In rare cases, non-steroidal anti-inflammatory drugs may cause interstitial nephritis, glomerulonephritis, papillary necrosis and the nephrotic syndrome. Such agents inhibit the synthesis of renal prostaglandin which plays a supportive role in the maintenance of renal perfusion in patients whose renal blood flow and blood volume are decreased. In these patients, administration of a non-steroidal anti-inflammatory drug may precipitate overt renal decompensation, which returns to the pre-treatment state upon withdrawal of the drug. Patients at greatest risk of such a reaction are those with pre-existing renal disease (including diabetics with impaired renal function), nephrotic syndrome, volume depletion, hepatic disease, congestive cardiac failure and those patients receiving concomitant therapy with diuretics or potentially nephrotoxic drugs. Such patients should have their renal, hepatic and cardiac functions carefully monitored due to the possibility of serious blood loss. Patients therefore require close monitoring during and after surgery. The dose should be kept as low as possible.

NSAIDs should be given with care to patients with a history of heart failure or hypertension since oedema has been reported in association with NSAID administration.

Caution is required if administration to patients suffering from or with a previous history of bronchial asthma since NSAIDs have been reported to cause bronchospasm in such patients.

Occasional elevations of serum transaminases or other indicators of liver function have been reported. In most cases these have been small and transient increases above the normal range. If the abnormality is significant or persistent, Mobiflex should be stopped and follow-up tests carried out. Particular care is required in patients with pre-existing hepatic disease.

Mobiflex reduces platelet aggregation and may prolong bleeding time. This should be borne in mind for patients who undergo major surgery (e.g. joint replacement) and when bleeding time needs to be determined.

Patients having coagulation disorders or receiving drug therapy that interferes with hemostasis should be carefully observed when Mobiflex is administered.

Particular care should be taken to regularly monitor elderly patients to detect possible interactions with concomitant therapy and to review renal, hepatic and cardiovascular function which may be potentially influenced by non-steroidal anti-inflammatory drugs.

Adverse eye findings have been reported with non-steroidal anti-inflammatory drugs, therefore it is recommended that patients who develop visual disturbances during treatment with Mobiflex have ophthalmic evaluation.

If severe skin reactions (e.g. Lyell's or Stevens-Johnson Syndrome) occur, Mobiflex treatment should be discontinued immediately.

Because of the high plasma protein-binding of tenoxicam, caution is required when plasma albumin concentrations are markedly reduced (e.g. in nephrotic syndrome) or when bilirubin concentrations are high.

As known for other anti-inflammatory drugs, Mobiflex may mask the usual signs of infection.

The use of tenoxicam, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulty conceiving or are undergoing investigation of infertility, withdrawal of tenoxicam should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids may reduce the rate, but not the extent, of absorption of Mobiflex. The differences are not likely to be of clinical significance. No interaction has been found with concomitantly administered cimetidine. In healthy subjects no clinically relevant interaction between Mobiflex and low molecular weight heparin has been observed.

It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.

The clinical effect of oral antidiabetic drugs glibornuride, glibenclamide, tolbutamide, was not modified by Mobiflex. However as for other NSAIDs, careful monitoring is recommended when patients concomitantly receive oral antidiabetic drugs.

Mobiflex and other NSAIDs can reduce the effects of anti-hypertensive drugs. NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels when co-administered with cardiac glycosides.

As with all NSAIDs Mobiflex should not be administered concurrently with potassium sparing diuretics. There is a known interaction which may cause hyperkalaemia and renal failure.

As with all NSAIDs caution is advised when ciclosporin is co-administered because of the increased risk of nephrotoxicity.

Concomitant use of two or more NSAIDs should be avoided.

Patients taking quinolones may have an increased risk of developing convulsions.

Salicylates can displace tenoxicam from protein-binding sites and so increase the clearance and volume of distribution of Mobiflex. Concurrent treatment with salicylates or other non-steroidal anti-inflammatory drugs should therefore be avoided because of the increased risk of adverse reactions (particularly gastro-intestinal).

Non-steroidal anti-inflammatory drugs have been reported to decrease elimination of lithium. If tenoxicam is

prescribed for a patient receiving lithium therapy, the frequency of lithium monitoring should be increased, the patient warned to maintain fluid intake and to be aware of symptoms of lithium intoxication.

Non-steroidal anti-inflammatory drugs may cause sodium, potassium and fluid retention and may interfere with the natriuretic action of diuretic agents, which can increase the risk of nephrotoxicity of NSAIDs. These properties should be kept in mind when treating patients with compromised cardiac function or hypertension since they may be responsible for a worsening of those conditions.

No clinically relevant interaction was found in small numbers of patients receiving treatment with penicillamine or parenteral gold.

The co-administration of some NSAIDs and methotrexate has been associated with reduced renal tubular secretion of methotrexate, higher plasma concentrations of methotrexate and severe methotrexate toxicity. Therefore caution should be exercised when Mobiflex is administered concurrently with methotrexate.

NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.

As with all NSAIDs, caution should be taken when co-administering cortico-steroids because of the increased risk of GI bleeding.

Aminoglycosides: reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.

Probenecid: reduction in metabolism and elimination of NSAID and metabolites.

4.6 Pregnancy and lactation

The safety of Mobiflex during pregnancy and lactation has not been established and the drug should therefore not be given in these conditions. Congenital abnormalities have been reported in association with NSAID administration in man; however these are low in frequency and do not appear to follow any discernible pattern.

Although no teratogenic effects were seen in animal studies, Mobiflex, like other non-steroidal anti-inflammatory drugs, is associated with prolonged and delayed parturition and an adverse influence on neonatal viability when administered to animals in late pregnancy. Non-steroidal anti-inflammatory agents are also known to induce closure of the ductus arteriosus in infants, therefore use in late pregnancy should be particularly avoided.

In the limited studies available so far, NSAIDs appear in the breast milk in very low concentrations and is unlikely to adversely affect the breast fed infant. Nevertheless, infants should be weaned or Mobliflex discontinued.

4.7 Effects on ability to drive and use machines

Patients experiencing adverse events that may affect driving or using machines, such as vertigo, dizziness or visual disturbances should refrain from driving or using machines.

4.8 Undesirable effects

For most patients, any side-effects are transient and resolve without discontinuation of treatment.

The most common side-effects relate to the gastro-intestinal tract. They include dyspepsia, nausea, vomiting, abdominal pain and discomfort, constipation, diarrhoea, flatulence, indigestion, gastritis, epigastric distress, stomatitis and anorexia. As with other non-steroidal anti-inflammatory drugs, there is a risk of peptic ulceration, gastro-intestinal bleeding and GI perforation, all of which have been reported with Mobiflex. Should this occur, Mobiflex is to be discontinued immediately and appropriate treatment instituted.

As with other non-steroidal anti-inflammatory drugs, peripheral oedema of mild or moderate degree and without

clinical sequelae occurred in a small proportion of patients and the possibility of precipitating congestive cardiac failure in elderly patients or those with compromised cardiac function should therefore be borne in mind.

Central nervous system reactions of headache and dizziness have been reported in a small number of patients. Somnolence, insomnia, depression, nervousness, dream abnormalities, mental confusion, paraesthesias, appetite loss, dry mouth and vertigo have been reported rarely.

Hypersensitivity reactions have been reported following treatment with NSAIDs these include:

a. Non specific allergic reactions and anaphylaxis,
b. Respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea or,
c. Skin reactions of rash, angioedema and pruritus have been reported. Nail disorders, alopecia, erythema, exanthema, urticaria and photosensitivity reactions have been reported rarely. As with other non-steroidal anti-inflammatory drugs, Lyell's syndrome and Stevens-Johnson syndrome may develop in rare instances. Vesiculobullous reactions and vasculitis have been reported rarely.

Reversible elevations of blood urea nitrogen and creatinine have been reported (see Special Warnings and Special Precautions for Use).

Decreases in haemoglobin, unrelated to gastro-intestinal bleeding, have occurred. Anaemia, aplastic anaemia, haemolytic anaemia, thrombocytopenia and non-thrombocytopenic purpura, leucopenia and eosinophilia have been reported. Epistaxis has been reported infrequently. Rare cases of agranulocytosis have been reported.

As with most other non-steroidal anti-inflammatory drugs, changes in various liver function parameters have been observed. Some patients may develop raised serum transaminase levels during treatment. Although such reactions are rare, if abnormal liver function tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop or if systemic manifestations occur (e.g. eosinophilia, rash), Mobiflex should be discontinued. Hepatitis and jaundice have also been reported in isolated cases.

Palpitations, elevated blood pressure and dyspnoea have also been reported rarely. Metabolic abnormalities, such as weight decrease or increase and hyperglycaemia, have occurred rarely.

Swollen eyes, blurred vision and eye irritation have been reported. Ophthalmoscopy and slit-lamp examination have revealed no evidence of ocular changes. Malaise and tinnitus may occur.

Nephrotoxicity has been reported in various forms, including interstitial nephritis, nephritic syndrome and renal failure.

Isolated cases of female infertility have been reported with drugs known to inhibit cyclooxygenase/prostaglandin synthesis including tenoxicam.

4.9 Overdose

There is no reported experience of serious overdosage with Mobiflex. No specific measures are available; administration of H2-antagonist drugs may be of benefit. Gastric lavage should be carried out as soon as possible after drug ingestion and the patient should be closely observed and general supportive measures taken as necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mobiflex is a non-steroidal anti-inflammatory drug which has marked anti-inflammatory and analgesic activity and some antipyretic activity. As with other non-steroidal anti-inflammatory drugs, the precise mode of action is unknown, though it is probably multifactorial, involving inhibition of prostaglandin biosynthesis and reduction of leucocyte accumulation at the inflammatory site.

5.2 Pharmacokinetic properties

Mobiflex is long-acting; a single daily dose is effective.

After oral administration, Mobiflex is rapidly and completely absorbed as unchanged drug. Concomitant food reduces the rate, but not the extent, of absorption of Mobiflex. Tenoxicam penetrates well into synovial fluid to give concentrations approximately half those in plasma. The mean plasma elimination half-life is approximately 72 hours.

Following intravenous administration of 20mg tenoxicam, plasma levels of the drug decline rapidly during the first two hours mainly due to distribution processes.

After this short period, no difference in plasma concentrations between intravenous and oral dosing is seen. Following intramuscular injection levels at or above 90% of the maximally achieved concentrations are reached as early as 15 minutes after a dose, i.e. earlier than after oral dosing. However, again the difference in blood levels between the two routes of administration is restricted to the first two hours after a dose. The bioavailability after an intramuscular dose is complete and indistinguishable from that determined after oral dosing.

With the recommended dosage regimen of 20mg once daily, steady-state plasma concentrations are reached within 10 - 15 days, with no unexpected accumulation.

Mobiflex is strongly bound to plasma proteins.

Mobiflex is cleared from the body almost exclusively by metabolism. Approximately two-thirds of an orally administered dose is excreted in the urine, mainly as the pharmacologically inactive 5-hydroxypyridyl metabolite, and the remainder in the bile, much of it as glucuronide conjugates of hydroxy-metabolites.

No age-specific changes in the pharmacokinetics of Mobiflex have been found although inter-individual variation tends to be higher in elderly persons.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Ascorbic Acid
Disodium edentate
Sodium hydroxide
Tromethamine
Hydrochloric acid
Water for injections

6.2 Incompatibilities

None known.

6.3 Shelf Life

3 years.

Reconstituted solution – use immediately.

6.4 Special precautions for storage

Store below 30ºC. Do not freeze as the water ampoule may burst.

6.5 Nature and contents of container

Packs of 5 vials, Type 1, Ph. Eur. with 5 glass ampoules, Type 1, Ph. Eur., containing 2 ml of sterile water for injections Ph. Eur. as diluent.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only. Discard any unused contents.

The reconstituted preparation results in a clear, green-yellow coloured solution. Visual inspection of the solution is necessary after reconstitution. Only clear solutions practically free from particles should be used.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 50/67/5

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