ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCT, ROUTES OF ADMINISTRATION, MARKETING AUTHORISATION HOLDER IN THE MEMBER STATES

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content**
Austria	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Artok	4 mg	Film-coated tablet	Oral	4 mg
	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Lornox	4 mg	Film-coated tablet	Oral	4 mg
	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Xefo	4 mg	Film-coated tablet	Oral	4 mg
	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Artok	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Xefo	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed Danmark ApS, Langebjerg 1, 4000 Roskilde, Denmark	Xefo Rapid	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Lornoxicam “Nycomed”	4 mg/ml	Powder and solvent for solution for injection	Intravenous use Intramuscular use	8 mg
	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Xefo	4 mg/ml	Powder and solvent for solution for injection	Intravenous use Intramuscular use	8 mg
Belgium	Nycomed Christians, Gentsesteenweg 615, 1080 Brussels, Belgium	Xefo	4 mg	Film-coated tablet	Oral	4 mg
	Nycomed Christians, Gentsesteenweg 615, 1080 Brussels, Belgium	Xefo	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed Christians, Gentsesteenweg 615, 1080 Brussels, Belgium	Xefo Acute	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed Christians, Gentsesteenweg 615, 1080 Brussels, Belgium	Xefo	4 mg/ml	Powder and solvent for solution for injection	Intravenous use Intramuscular use	8 mg
Bulgaria	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Xefo	4 mg	Film-coated tablet	Oral	4 mg
	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Xefo	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Xefo	4 mg/ml	Powder and solvent for solution for injection	Intravenous use Intramuscular use	8 mg
Czech Republic	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Xefo	4 mg	Film-coated tablet	Oral	4 mg

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content**
Czech Republic	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Xefo	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Xefo	4 mg/ml	Powder and solvent for solution for injection	Intravenous use Intramuscular use	8 mg
Denmark	Nycomed Danmark ApS, Langebjerg 1, 4000 Roskilde, Denmark	Lornoxicam "Nycomed"	4 mg	Film-coated tablet	Oral	4 mg
	Nycomed Danmark ApS, Langebjerg 1, 4000 Roskilde, Denmark	Xefo	4 mg	Film-coated tablet	Oral	4 mg
	Nycomed Danmark ApS, Langebjerg 1, 4000 Roskilde, Denmark	Lornoxicam "Nycomed"	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed Danmark ApS, Langebjerg 1, 4000 Roskilde, Denmark	Xefo	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed Danmark ApS, Langebjerg 1, 4000 Roskilde, Denmark	Xefo Rapid	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed Danmark ApS, Langebjerg 1, 4000 Roskilde, Denmark	Lornoxicam "Nycomed"	4 mg/ml	Powder and solvent for solution for injection	Intravenous use Intramuscular use	8 mg
	Nycomed Danmark ApS, Langebjerg 1, 4000 Roskilde, Denmark	Xefo	4 mg/ml	Powder and solvent for solution for injection	Intravenous use Intramuscular use	8 mg
Estonia	Nycomed SEFA, Jaama 55B, 63308 Pölva, Estonia	Xefo	4 mg	Film-coated tablet	Oral	4 mg
	Nycomed SEFA, Jaama 55B, 63308 Pölva, Estonia	Xefo	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed SEFA, Jaama 55B, 63308 Pölva, Estonia	Xefo Rapid	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed SEFA, Jaama 55B, 63308 Pölva, Estonia	Xefo	4 mg/ml	Powder and solvent for solution for injection	Intravenous use Intramuscular use	8 mg
Germany	Nycomed Danmark ApS, Langebjerg 1, 4000 Roskilde, Denmark	Lornoxicam "Nycomed"	4 mg	Film-coated tablet	Oral	4 mg
	Nycomed Pharma GmbH, Edisonstrasse 16, 85716 Unterschleissheim, Germany	Telos	4 mg	Film-coated tablet	Oral	4 mg
	Nycomed Danmark ApS, Langebjerg 1, 4000 Roskilde, Denmark	Lornoxicam "Nycomed"	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed Pharma GmbH, Edisonstrasse 16, 85716 Unterschleissheim, Germany	Telos	8 mg	Film-coated tablet	Oral	8 mg

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content**
Greece	Nycomed Hellas S.A., 196 Kifissias Avenue, 15231 Athens, Greece	Xefo	4 mg	Film-coated tablet	Oral	4 mg
	Nycomed Hellas S.A., 196 Kifissias Avenue, 15231 Athens, Greece	Xefo	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed Hellas S.A., 196 Kifissias Avenue, 15231 Athens, Greece	Xefo Rapid	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed Hellas S.A., 196 Kifissias Avenue, 15231 Athens, Greece	Xefo	4 mg/ml	Powder and solvent for solution for injection	Intravenous use Intramuscular use	8 mg
Hungary	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Xefo	4 mg	Film-coated tablet	Oral	4 mg
	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Xefo	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Xefo	4 mg/ml	Powder and solvent for solution for injection	Intravenous use Intramuscular use	8 mg
Italy	Nycomed Italy S.r.l., Via Carducci 125, Edificio A, 20099 Sesto San Giovanni, Italy	Taigalor	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed Italy S.r.l., Via Carducci 125, Edificio A, 20099 Sesto San Giovanni, Italy	Xefo	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed Italy S.r.l., Via Carducci 125, Edificio A, 20099 Sesto San Giovanni, Italy	Taigalor	4 mg/ml	Powder and solvent for solution for injection	Intravenous use Intramuscular use	8 mg
	Nycomed Italy S.r.l., Via Carducci 125, Edificio A, 20099 Sesto San Giovanni, Italy	Xefo	4 mg/ml	Powder and solvent for solution for injection	Intravenous use Intramuscular use	8 mg
Latvia	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Xefo	4 mg	Film-coated tablet	Oral	4 mg
	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Xefo	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed SEFA, Jaama 55B, 63308 Pölva, Estonia	Xefo Rapid	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Xefo	4 mg/ml	Powder and solvent for solution for injection	Intravenous use Intramuscular use	8 mg
Lithuania	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Xefo	4 mg	Film-coated tablet	Oral	4 mg
	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Xefo	8 mg	Film-coated tablet	Oral	8 mg

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content**
Lithuania	Nycomed SEFA, Jaama 55B, 63308 Pölva, Estonia	Xefo Rapid	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Xefo	4 mg/ml	Powder and solvent for solution for injection	Intravenous use Intramuscular use	8 mg
Luxembourg	Nycomed Christians, Gentsesteenweg 615, 1080 Brussels, Belgium	Xefo	4 mg	Film-coated tablet	Oral	4 mg
	Nycomed Christians, Gentsesteenweg 615, 1080 Brussels, Belgium	Xefo	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed Christians, Gentsesteenweg 615, 1080 Brussels, Belgium	Xefo Acute	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed Christians, Gentsesteenweg 615, 1080 Brussels, Belgium	Xefo	4 mg/ml	Powder and solvent for solution for injection	Intravenous use Intramuscular use	8 mg
Portugal	Euro-Labor SA, Rua Alfredo da Silva n^{o}16, 2610-016 Amadora, Portugal	Acabel	4 mg	Film-coated tablet	Oral	4 mg
	Euro-Labor SA, Rua Alfredo da Silva n^{o}16, 2610-016 Amadora, Portugal	Bosporon	4 mg	Film-coated tablet	Oral	4 mg
	Euro-Labor SA, Rua Alfredo da Silva n^{o}16, 2610-016 Amadora, Portugal	Acabel	8 mg	Film-coated tablet	Oral	8 mg
Portugal	Euro-Labor SA, Rua Alfredo da Silva n^{o}16, 2610-016 Amadora, Portugal	Bosporon	8 mg	Film-coated tablet	Oral	8 mg
	Euro-Labor SA, Rua Alfredo da Silva n^{o}16, 2610-016 Amadora, Portugal	Acabel Rapid	8 mg	Film-coated tablet	Oral	8 mg
	Euro-Labor SA, Rua Alfredo da Silva n^{o}16, 2610-016 Amadora, Portugal	Bosporon Rapid	8 mg	Film-coated tablet	Oral	8 mg
	Euro-Labor SA, Rua Alfredo da Silva n^{o}16, 2610-016 Amadora, Portugal	Acabel	4 mg/ml	Powder and solvent for solution for injection	Intravenous use Intramuscular use	8 mg
	Euro-Labor SA, Rua Alfredo da Silva n^{o}16, 2610-016 Amadora, Portugal	Bosporon	4 mg/ml	Powder and solvent for solution for injection	Intravenous use Intramuscular use	8 mg
Romania	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Xefo	4 mg	Film-coated tablet	Oral	4 mg
	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Xefo	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed Austria GmbH, St. Peter Strasse 25, 4020 Linz, Austria	Xefo	4 mg/ml	Powder and solvent for solution for injection	Intravenous use Intramuscular use	8 mg
Spain	Laboratorios Andromaco SA, Doctor Zamenhof 36, 29027 Madrid, Spain	Acabel	4 mg	Film-coated tablet	Oral	4 mg

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content**
Spain	Tedec Meiji Farma, S.A., Ctra. M-300, Km 30,500. 28802 Alcalá de Henares, Madrid, Spain	Bosporon	4 mg	Film-coated tablet	Oral	4 mg
	Laboratorios Andromaco SA, Doctor Zamenhof 36, 29027 Madrid, Spain	Acabel	8 mg	Film-coated tablet	Oral	8 mg
	Tedec Meiji Farma, S.A., Ctra. M-300, Km 30,500. 28802 Alcalá de Henares, Madrid, Spain	Bosporon	8 mg	Film-coated tablet	Oral	8 mg
	Laboratorios Andromaco SA, Doctor Zamenhof 36, 29027 Madrid, Spain	Acabel Rapid	8 mg	Film-coated tablet	Oral	8 mg
	Tedec Meiji Farma, S.A., Ctra. M-300, Km 30,500. 28802 Alcalá de Henares, Madrid, Spain	Bosporon Rapid	8 mg	Film-coated tablet	Oral	8 mg
	Laboratorios Andromaco SA, Doctor Zamenhof 36, 29027 Madrid, Spain	Acabel	4 mg/ml	Powder and solvent for solution for injection	Intravenous use Intramuscular use	8 mg
Sweden	Nycomed AB, Tegeluddsvägen 17-21, 102 53 Stockholm, Sweden	Xefo	4 mg	Film-coated tablet	Oral	4 mg
	Nycomed AB, Tegeluddsvägen 17-21, 102 53 Stockholm, Sweden	Xefo	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed AB, Tegeluddsvägen 17-21, 102 53 Stockholm, Sweden	Xefo Akut	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed AB, Tegeluddsvägen 17-21, 102 53 Stockholm, Sweden	Xefo	4 mg/ml	Powder and solvent for solution for injection	Intravenous use Intramuscular use	8 mg
United Kingdom	Nycomed UK Ltd., The Magdalen Centre Oxford Science Park, OX4 4GA Oxford, United Kingdom	Xefo	4 mg	Film-coated tablet	Oral	4 mg
	Nycomed UK Ltd., The Magdalen Centre Oxford Science Park, OX4 4GA Oxford, United Kingdom	Xefo	8 mg	Film-coated tablet	Oral	8 mg
	Nycomed UK Ltd., The Magdalen Centre Oxford Science Park, OX4 4GA Oxford, United Kingdom	Xefo	4 mg/ml	Powder and solvent for solution for injection	Intravenous use Intramuscular use	8 mg

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF XEFO AND ASSOCIATED NAMES (see Annex I)

Lornoxicam (Xefo and its associated names) is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class approved and marketed for treatment of moderate to severe pain. Lornoxicam is available as film coated tablets 4 mg and 8 mg, rapid release film-coated tablets 8 mg, and as powder and solvent for solution for injection 4 mg/ml for intramuscular and intravenous injection.

The above mentioned product Xefo and its associated names, do not have the same Product Information (Summary of Product Characteristics (SPC), package leaflet (PL) and labelling) across all EU Member States with respect to e.g. Indications, Posology, Contraindications, Undesirable effects and sections dealing with recommendations for use.

Due to the divergent national decisions taken by the Member States concerning the authorisation of the above-mentioned product, Nycomed Danmark ApS notified the EMEA of an official referral under Article 30 of Directive 2001/83/EC as amended in order to resolve divergences amongst the nationally authorised Product Information (SPCs, PLs and labellings) for the above-mentioned product and thus to harmonise the Product Information (SPCs, PLs and labellings) and Quality documentation across the EU

- **Quality issues**

In addition, to reaching an agreement on the main quality part of the SPC (shelf-life, storage conditions), the CHMP also took the opportunity to harmonise the Quality documentation concerning a number of minor issues related to the Drug Substance and Finished Product manufacturing and control.

- **Efficacy issues**

Therapeutic indication – pain

The clinical development program for the effect of lornoxicam against pain consisted of 27 studies. The submitted efficacy data on pain focus on meta-analyses from 12 placebo-controlled pain studies (including partly also active controls) [See Table below].

Table 4 Studies included in meta-analyses

Study reference no.	Route of administration	Parameters used			Included in analysis		
		TOTPAR	SPID	IMP	1.	2.	3.
CT01	Oral	X	X	X	X	X	X
CT02	Oral	X	X	X		X	X
CT03	Oral	X	X	X		X	X
CT14	Oral	X	X	X	X	X	X
CT25-2	IM			X			X
CT32	Oral	X		X		X	X
CT50	Oral			X			X
CT51	Oral			X			X
CT70	IV		X	X			X
CT78	Oral	X	X	X	X	X	X
CT85	IM/oral	X	X			X	X
CT87	IM	X	X	X			X

TOTPAR = total pain relief, SPID = sum of pain intensity differences, IMP = overall impression

A meta-analysis consisting of three parts was performed to assess the overall analgesic effect of lornoxicam. As outlined by the MAH this meta-analysis was restricted to placebo-controlled studies as the purpose of the analysis was to estimate a difference to placebo [Tab. 4].

Overall discussion on the meta-analyses

Meta-analysis 1

The meta-analysis included only 3 studies on third molar surgery (CT01, CT14, CT78) with orally applied lornoxicam. Two studies on third molar surgery were excluded from meta-analysis 1. The reason for exclusion of study CT32 is not clear (it was included in meta-analysis 2; single doses were applied post surgery). Study CTX 87 was excluded since single doses of 4-20 mg LNX were administered i.m.

For the dose-relationship up to 32 mg only a single study (CT78) included the 16 mg and 32 mg dose, which reduces the relevance of the dose-relationship, i.g. the dose-response relationship above 8 mg LNX p.o. is based on a single study.

The effect on TOTPAR and PPRA with 2 mg and 4 mg in study CT01 was not significantly different from placebo. A clear reduction in pain intensity vs. placebo was only obtained at ≥8 mg LNX p.o. (8 mg dose in study CT01). No differences were observed regarding the SPID parameter.

Meta-analysis 2

The second meta-analysis included seven studies (CT01, CT02, CT03, CT14, CT32, CT78 and CT85) with orally applied lornoxicam including a total of 1581 patients. 4 of 7 studies investigated the efficacy in third molar surgery pain (and three of these studies were already included in meta-analysis 1).

Only 2/7 studies included a 16 mg dose and only 1/7 study included a 32 mg dose. The construction of a dose-dependence up to 16 mg depends on 2 studies. Study CT85 used only a single oral dose of 8 mg LNX p.o.

TOTPAR in the meta-analysis was significantly different from placebo at 4 mg LNX p.o. and doses >4 mg LNX p.o., however it should be noted that in 2/7 studies (CT01, CT03) the effect of 4 mg LNX on total pain relief was not significantly different from the placebo group. In study CT02 there was no significant difference in TOTPAR between groups in the ITT population, but between placebo and active treatment in the PP-population.

A comparison of significance levels in the original data and in meta-analysis 2 was not performed and is missing in the response.

Meta-analysis 3:

The third meta-analysis on the overall impression of the 12 placebo-controlled double blind lornoxicam efficacy studies included 1 study with parenteral (i.m.) application of LNX (CT87) and 2 studies with multiple doses i.v. (CT25-2, CT70). Because of different pharmacokinetics between oral application and i.m. or i.v. application the pooling of the data is questionable and does not support the oral application. In addition, the use of the endpoint overall impression, which was used as a secondary endpoint in all studies in meta-analysis 3 can not convincingly support the MAH approach for a general indication for pain relief. Thus meta-analysis 3 does not essentially contribute to the MAH's claim for an unrestricted use of lornoxicam in the treatment of pain.

The justification for combining data from lornoxicam administered p.o. and i.m. in meta-analysis 3 is weak. Since lornoxicam is more rapidly absorbed and reaches a higher Cmax after i.m. application than after oral application, a pooling of efficacy data from i.m. and p.o. applications appears not to be justified. On the other hand the parameter IMP (general impression) analysed in meta-analysis 3 is a week efficacy parameter, which can only be considered as supportive to the TOTPAR analysis and the judgement on efficacy has to be based mainly on meta-analysis 1 and 2. For this reason a new meta-analysis 3 with the p.o. data alone will not add much to the discussion.

Therapeutic indication – rheumatic pain (RA)
Eleven studies with lornoxicam were performed in patients suffering from rheumatoid arthritis **(**RA) including nine controlled and 2 uncontrolled clinical phase II or III studies in RA patients.

Difficulties with data interpretation due to differences in the applied methodology such as dose regimens, study designs and durations of treatment, resulted in only 4 of these studies being considered applicable for a scientifically sound overall analysis of efficacy data – meta analysis. Studies not investigating the recommended doses of either 4 mg tid or 8 mg bid were excluded from the analysis.

The aim of the overall analysis (meta-analysis) was to compare the efficacy of different dosages of lornoxicam with comparator drugs or placebo, in a cohort of RA patients.

Overall discussion on RA
With respect to RA, the following can be summarised:

Lornoxicam at dosages 4mg tid and 8mg bid is effective in the symptomatic treatment of RA.

A plateau of efficacy was obtained with 8mg bid; this dosage regimen is thus considered the maximum dose for lornoxicam in RA.

Lornoxicam 4mg tid or 8mg bid is at least as effective as diclofenac 50mg tid and naproxen 500mg bid.

Treatment of rheumatoid arthritis has been approved by 16/16 Member States (AT, BE, CZ, DE, DK, EE, ES, GR, HU, IT, LT, LV, PT, SE, UK). The dose-recommendations in the SPC for the 8 mg film-coated tablets are supported by the presented data.

Therapeutic indication – osteoarthritis (OA)
Eight placebo- and/or reference drug controlled clinical studies were performed in patients suffering from OA. Due to differences in study designs and dosage regimens, only 4 of these studies (CT18, CT33, CT63, CT80) were selected for a retrospective comprehensive evaluation. The duration of blinded treatment was 4 weeks for studies CT18 and CT80 and 12 weeks for CT33 and CT63. Statistical analysis was therefore limited to a 4 week treatment phase which, based on international guidelines, is appropriate to assess therapeutic efficacy of NSAIDs in OA. In case of premature termination, data of last observation were chosen.

The MAH considered study CT80, comparing 4 mg bid and 8 mg bid to placebo, and study CT63, comparing 4 mg tid to 8 mg bid, and to 50mg diclofenac tid, as pivotal.

Overall discussion on OA
With respect to OA, the following can be summarised:
Lornoxicam 8mg bid (16 mg) is more efficacious than placebo.

Lornoxicam 8mg bid is at least as effective as diclofenac 50mg tid and naproxen 500mg bid.

Treatment of osteoarthritis has been approved by 14/16 Member States (AT, BE, CZ, DE, DK, ES, GR, HU, LT, LV, PT, SE, UK). Treatment of osteoarthritis has not been approved by 2/16 Member States (EE, IT). The dose-recommendations in the SPC for the 8 mg film-coated tablets are supported by the presented data.

SPC recommendations
Therapeutic indications – Section 4.1 of the SPC
The Therapeutic Indications were agreed for the following pharmaceutical forms and strengths of lornoxicam

- Lornoxicam, **4 mg & 8mg, film-coated tablets**

- *Short-term relief of acute mild to moderate pain*

- *Symptomatic relief of pain and inflammation in osteoarthritis.*
- *Symptomatic relief of pain and inflammation in rheumatoid arthritis*

- Lornoxicam, **8 mg, Powder and solvent for solution for injection**

Short-term relief of acute mild to moderate pain

- Lornoxicam **Rapid, 8 mg, film coated tablets**

Short-term relief of acute mild to moderate pain

Posology – Section 4.2

- Lornoxicam, **4 & 8 mg, film-coated tablets**

8-16 mg lornoxicam daily divided into 2 or 3 doses. Maximum recommended daily dose is 16 mg.

- Lornoxicam, **8 mg, Powder and solvent for solution for injection**

Recommended dose: 8 mg intravenous or intramuscular. Daily dose should not exceed 16 mg. Some patients may need a further 8 mg given during the first 24 hours.

- Lornoxicam **Rapid, 8 mg, film coated tablets**

Dose recommendation for LNX-QR is based on the following on the results from studies with intramuscular administration of LNX, and the comparative study with diclofenac-potassium in acute low back pain, LO-030-IN. It is common practice when initiating acute pain treatment with NSAIDs to start treatment with a high first dose (e.g., double dose) in order to obtain a significant reduction of the pain from the beginning of the treatment.

That an initial lornoxicam rapid (QR) dose of 16 mg followed by 8 mg 12 hours later on the first treatment day is significantly better than giving lornoxicam rapid 8 mg bid has not been fully demonstrated. (The pharmacokinetic profile of a single dose of 8 mg lornoxicam i.m. is comparable to that of an oral 8 mg dose of lornoxicam – QR).

An initial dose of 16 mg lornoxicam administered i.m., followed by a subsequent dose of 8 mg has shown to be effective and safe in patients with pain after surgery (study CT89). Similarly an initially oral dose of 16 mg lornoxicam given in study LD-030-IN was followed by 8 mg as a second dose on day one and found to be effective and safe in patients with acute low back pain. Based on these data it appears that a higher initial dose of lornoxicam – QR may be justified. The MAH's response is considered acceptable and no further data are requested.

The posology agreed for acute pain is:

8-16 mg lornoxicam given in doses of 8 mg. An initial dose of 16 mg followed by 8 mg 12 hours later can be given on the first treatment day. After the first treatment day the maximum recommended daily dose is 16 mg.

Lornoxicam Rapid film coated tablets are supplied for oral administration and should be taken with a glass of liquid.

- For all the pharmaceutical forms and strengths of lornoxicam

The following wording has been included as agreed by the PhVWP in January 2007:
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4.).

Special warnings and precautions for use – Section 4.4

- For all the pharmaceutical forms and strengths of lornoxicam

The following wording has been included as agreed by the PhVWP in October 2005 and January 2007:

Undesirable effects may be minimised by using lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below)

Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid or other drugs likely to increase gastrointestinal risk (see below and section 4.5). Clinical monitoring at regular intervals is recommended.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetysalicylic acid (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving lornoxicam, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8).

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.3).
……..

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for lornoxicam.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with lornoxicam after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Pregnancy and lactation – Section 4.6

It was agreed that the following statement would be included:
Lornoxicam is contraindicated on the third trimester of pregnancy and should not be used during pregnancy in the first and second trimesters and delivery as no clinical data on exposed pregnancies are available.

Effects on ability to drive and use machines – Section 4.7

It was agreed that the following statement would be included:
Patients showing dizziness and/or sleepiness under treatment with lornoxicam should refrain from driving or operation machinary.

Pharmacodynamic properties – Section 5.1
The divergences between the MS in the wording of the description of the pharmacodynamic properties have been harmonised.

Pharmacokinetic properties – Section 5.2
The divergences between the MS in the wording of the description of the pharmacokinetic properties have been harmonised. The accumulation of lornoxicam in patients with chronic liver disease at higher doses (12 mg/d or 16 mg/d) as observed instudy CT13 has been described in the SPC:
There is no significant change in the kinetic profile of lornoxicam in patients with renal or hepatic failure, except for accumulation in patients with chronic liver disease after 7 days of treatment with daily doses of 12 and 16 mg.

Preclinical safety data – Section 5.3
The divergences between the MS have been harmonised.

- **Safety issues**

Safety database, number of patients & exposure
The safety database (SDB) included all lornoxicam studies under the control of Nycomed Pharma (studies performed by third parties were excluded) comprised a total of 12,570 patients of who 7,427 received lornoxicam.

Data from 103 clinical studies were included in the SDB including 57 double-blind studies, 4 single-blind studies and 50 open studies of which 8 were follow-up to randomised studies.

More than 12,000 patients were included in the 103 studies of which 43 were classified as phase I with 810 patients. Lornoxicam was tested in 34 pain studies with 7,761 patients. The classic rheumatology disorders were investigated in 26 studies with 3,621 patients: 12 studies in rheumatoid arthritis (RA), 8 studies in osteoarthritis (OA), 3 in both indications and 3 in other rheumatology indications (i.e. ankylosing spondylitis (AKS), non-arthritic rheumatism and acute gout). Of the total number of patients 57.8% (7,046/12,192) received lornoxicam (see Table below).

Table Number of Patients by Indication and Treatment

Indication	(#)	Lornoxicam	Placebo	Comparators	Total
Phase I	(43)	626	62	122	810
Pain	(34)	4,065	718	2,978	7,761
Rheumatology	(26)	2,355	474	792	3,621
Total	(103)	7,046	1,254	3,892	12,192

Data from Appendix Table 2.7.4.1.1

Adverse events
The Table below shows the percentages of patients with ADRs in order of incidence by system organ classification (SOC, WHO), lornoxicam dose and indication. A total of 21% of the patients had at least one ADR. Incidence by dose was: 17.0% (8mg), 27.0% (12mg) and 22.7% (16mg). As for all NSAIDs, gastro-intestinal (GI) events were the most frequent (14%) followed by central nervous system (CNS), Peripheral nervous system (PNS), Psychiatric (Psych) (6%), Other (2%), Whole body (2%) and Skin (1%). Reactions relating to other System organs (SOCs) occurred in less than 1% of the patients.

Table Incidence of ADRs reported for lornoxicam by SOC, Indication and Dose

Indication lornoxicam dose	Pain						Rheumatology						Total
	Low	8mg	12mg	16mg	High	Total	Low	8mg	12mg	16mg	High	Total	Total
Exposed # of patients	604	1,265	587	1,054	467	3,908	285	841	575	698	167	2,352	6,260
% of patients with ADR	14	14	24	21	22	18	20	22	30	26	22	26	21
Gastro-intestinal	5	7	19	14	15	11	12	15	21	21	15	18	14
CNS, PNS, Psych.	9	5	6	6	4	6	6	6	8	3	1	6	6
Other	1	1	1	2	4	2	0.4	1	2	2	3	2	2
Whole body	3	2	2	2	1	2	2	1	2	1	2	2	2
Skin	0.2	0.6	0.3	1	1	0.7	3	2	3	2	4	3	1
Cardiovascular	0.5	0.6	0.3	0.4	0.2	0.4		0.5	1	0.6		0.5	0.5
Haematology	0.2	0.2	0.2	0.1	0.4	0.2	0.4	0.2	0.5	1		0.6	0.4
Urinary		0.1	0.2	0.4	0.2	0.2		0.8	0.9	0.3		0.6	0.3
Metabolic/Endocrine			0.2			0.0	0.7	0.6	1	0.6	0.6	0.8	0.3
Respiratory	0.3		0.2	0.2	0.2	0.2		0.4	0.7	0.4	0.6	0.5	0.3
Liver		0.2				0.1		0.5	0.7	0.1	0.6	0.4	0.2

Data from table 2.13 in Clinical Safety Report, dated 21 December 2001

Serious adverse event/deaths/other significant events

- Serious Adverse Drug Reactions

The overall serious ADR (SADR) incidence for lornoxicam was 0.6%. It increased by duration of treatment (0.3%, 0.5% and 1.9% for short-, medium- and long-term treatment, respectively) and was influenced by the vulnerability of patients with chronic diseases in long-term treatment: The majority of patients with SADR had RA or were elderly patients included in post-operative pain studies such as hip replacement.

In the literature, incidences of SADRs for NSAIDs vary between 0.3% and 4.7% indicating that the risk of developing SADRs with lornoxicam is similar to that of other NSAIDs.

Although a considerable number of patients have been treated with lornoxicam so far, only few of the known serious reactions to other NSAIDs have been reported for lornoxicam. Severe urinary, CNS and skin reactions have not been reported. Reactions of liver and haematology have all been mild.

- Deaths

Eight patients died after lornoxicam treatment and three patients after treatment with comparators, and no case was reported after parenteral lornoxicam. The frequency of death per patient year for lornoxicam was 0.007; the corresponding number for active comparator treatment was almost three times as high (0.020).

Three of the lornoxicam patients participated in a study investigating the efficacy of lornoxicam in pain due to bone metastases in prostate cancer, which was the cause of death for two. The third died from myocardial infarction. Another three cases were caused by cardiovascular events and occurred in patients with rheumatological disorders participating in long-term studies. All deaths reported for lornoxicam were considered unrelated to treatment by the responsible investigator and may reflect the multimorbid patients taking part in these studies.

SPC recommendations

Contraindications – Section 4.3

- For all the pharmaceutical forms and strengths of lornoxicam

It was agreed that the following contraindications would be included:

- *The third trimester of pregnancy (see section 4.6)*

In addition the following wording has been included as agreed by the PhVWP in October 2005 and January 2007:
- *History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy*
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- *Severe heart failure*

Interaction with other medicinal products and other forms of interaction – Section 4.5

For several drugs causing interaction and which possibly increase the risk of toxicity in combination with NSAIDs/lornoxicam, the recommendation regarding drug monitoring (for methotrexate, lithium and cyclosporine) has been included in the SPC.

- For all the pharmaceutical forms and strengths of lornoxicam

It was agreed that the following would be included:
- *Methotrexate: Increased serum concentration of methotrexate. Increased toxicity may result. When concomitant therapy has to be used careful monitoring should be undertaken.*
- *Lithium: NSAIDs inhibit renal clearance of lithium, thus the serum concentration of lithium may increase above toxicity limits. Therefore serum lithium levels require monitoring, especially during initiation, adjustment and withdrawal of treatment.*
- *Cyclosporine: Increased serum concentration of cyclosporine. Nephrotoxicity of cyclosporine may be enhanced via renal prostaglandin mediated effects. During combined treatment renal function should be monitored.*

Undesirable effects – Section 4.8

- For all the pharmaceutical forms and strengths of lornoxicam

It was agreed that the following additional undesirable effects: weight changes, ecchymosis, prolonged bleeding time, bronchospasm, rhinitis, perforated peptic ulcer, pupura, increase in blood urea nitrogen and creatinine levels.

In addition the following wording has been included as agreed by the PhVWP in October 2005 and January 2007:

The most commonly observed adverse events of NSAIDs are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4).

Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

- **Conclusions**

Overall the Applicant has responded to the questions raised during the procedure in a satisfactory way, although minor deficits exist in the MAH's efficacy and safety database mainly related to small short-term clinical studies conducted 15-20 years ago.

The MAH has applied the PhVWP core information for NSAIDs in relation to gastrointestinal safety, skin reactions and cardiovascular safety (October 2005). The recent PhVWP core information regarding cardiovascular safety of NSAIDs (January 2007) has also been taken into account.

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics, labelling and package leaflet.

- the Summaries of Products Characteristic, labelling and package leaflet proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CHMP has recommended the amendment of the Marketing Authorisation(s) for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Xefo and associated names (see Annex I).

ANNEX III

SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xefo and associated names (see Annex I) 4 mg film-coated tablets
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 4 mg lornoxicam

Excipients: Lactose 94 mg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
White to yellowish oblong film-coated tablet with imprint “L04”

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Short-term relief of acute mild to moderate pain
- Symptomatic relief of pain and inflammation in osteoarthritis
- Symptomatic relief of pain and inflammation in rheumatoid arthritis

4.2 Posology and method of administration

For all patients the appropriate dosing regimen should be based upon individual response to treatment.

Pain
8-16 mg lornoxicam daily divided into 2 or 3 doses. Maximum recommended daily dose is 16 mg.

Osteoarthritis and Rheumatoid arthritis
Initial recommended dose is 12 mg lornoxicam daily divided into 2 or 3 doses. Maintenance dose should not exceed 16 mg lornoxicam daily.

Xefo film-coated tablets are supplied for oral use and should be taken with a sufficient quantity of liquid.

Additional information on special populations

Children and adolescents
Lornoxicam is not recommended for use in children and adolescents below age 18 due to a lack of data on safety and efficacy.

Elderly
No special dosage modification is required for elderly patients above age 65, but Lornoxicam should be administered with precaution as gastrointestinal adverse effects are less well tolerated in this group (see section 4.4).

Renal impairment
For patients with mild to moderate renal impairment the maximum recommended daily dose is 12 mg divided in 2 or 3 doses (see section 4.4).

Hepatic impairment

For patients with moderate hepatic impairment the maximum recommended daily dose is 12 mg divided in 2 or 3 doses (see section 4.4).

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4.).

4.3 Contraindications

- Hypersensitivity to lornoxicam or to any of the excipients
- Thrombocytopenia
- Hypersensitivity (symptoms like asthma, rhinitis, angioedema or urticaria) to other NSAIDs including acetylsalicylic acid
- Severe heart failure.
- Gastro-intestinal bleeding, cerebrovascular bleeding or other bleeding disorders
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- Severe hepatic impairment
- Severe renal impairment (Serum creatinine > 700 µmol/l)
- The third trimester of pregnancy (see section 4.6)

4.4 Special warnings and precautions for use

For the following disorders, lornoxicam should only be administered after careful risk-benefit assessment:

- Renal impairment: Lornoxicam should be administered with precaution in patients with mild (serum creatinine 150-300 µmol/l) to moderate (serum creatinine 300 – 700 µmol/l) renal impairment due to dependency on renal prostaglandins for maintenance of renal blood flow. Treatment with lornoxicam should be discontinued if renal function deteriorates during treatment.
- Renal functions should be monitored in patients who undergo major surgery, with cardiac failure, receiving treatment with diuretics, receiving concomitant treatment with drugs that are suspected to or known to be able to cause kidney damage.
- Patients with blood coagulation disorders: Careful clinical monitoring and laboratory assessment is recommended (e.g. APTT).
- Hepatic impairment (e.g. liver cirrhosis): Clinical monitoring and laboratory assessments at regular intervals should be considered in patients with hepatic impairment as accumulation of lornoxicam (increase in AUC) may occur after treatment with daily doses of 12-16 mg. Apart from that, hepatic impairment does not seem to affect pharmacokinetic parameters of lornoxicam as compared to healthy subjects.
- Long term treatment (longer than 3 months): Regular laboratory assessments of haematology (haemoglobin), renal functions (creatinine) and liver enzymes are recommended.
- Elderly patients above 65 years: Monitoring of renal and hepatic function is recommended. Precaution is advised in elderly postoperative patients.

The use of lornoxicam with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Undesirable effects may be minimised by using lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be

considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid or other active substances likely to increase gastrointestinal risk (see below and section 4.5). Clinical monitoring at regular intervals is recommended.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.
Caution should be advised in patients receiving concomitant medicinal products which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving lornoxicam, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8).

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.3).

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for lornoxicam.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Lornoxicam after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Concomitant treatment with NSAIDs and heparin in the context of a spinal or epidural anaesthesia increases the risk of spinal/epidural haematoma (see section 4.5).

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Lornoxicam should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Lornoxicam reduces platelet aggregation and prolongs bleeding time and consequently care should be taken when administering to patients with increased bleeding tendency.

Concomitant treatment of NSAIDs and tacrolimus may increase the risk of nephrotoxicity owing to reduced synthesis of prostacyclin in the kidney. Renal function must therefore be monitored closely in patients receiving combination therapy.

As with most NSAIDs occasional increase in serum transaminases level, increase in serum bilirubin or other liver function parameters, as well as increases in serum creatinine and blood urea nitrogen as

well as other laboratory abnormalities have been reported. Should any such abnormality prove significant or persist the administration of lornoxicam should be stopped and appropriate investigations prescribed.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The use of lornoxicam, 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 difficulties conceiving or who are undergoing investigation of infertility, withdrawal of lornoxicam should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of lornoxicam and

- Cimetidine: Increased plasma concentrations of lornoxicam. (No interaction between lornoxicam and ranitidine, or lornoxicam and antacids has been demonstrated).
- Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4). Careful monitoring of INR should be undertaken
- Phenprocoumon: Decreased effect of phenprocoumon treatment.
- Heparin: NSAIDs increase the risk of spinal or epidural haematoma when given concomitantly to heparin in the context of spinal or epidural anaesthesia.
- ACE inhibitors: The antihypertensive effect of the ACE inhibitor may decrease.
- Diuretics: Decreased diuretic and antihypertensive effect of loop diuretics and thiazide diuretics.
- Beta-adrenergic blockers: Decreased antihypertensive efficacy.
- Digoxin: Decreased renal clearance of digoxin.
- Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
- Quinolone antibiotics: Increased risk of seizures.
- Anti-platelet agents: Increased risk of gastrointestinal bleeding (see section 4.4).
- Other NSAIDs: Increased risk of gastrointestinal bleeding.
- Methotrexate: Increased serum concentration of methotrexate. Increased toxicity may result. When concomitant therapy has to be used careful monitoring should be undertaken.
- Selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).
- Lithium: NSAIDs inhibit renal clearance of lithium, thus the serum concentration of lithium may increase above toxicity limits. Therefore serum lithium levels require monitoring, especially during initiation, adjustment and withdrawal of treatment.
- Cyclosporine: Increased serum concentration of cyclosporine. Nephrotoxicity of cyclosporine may be enhanced via renal prostaglandin mediated effects. During combined treatment renal function should be monitored.
- Sulphonylureas: Increased risk of hypoglycaemia.
- Known inducers and inhibitors of CYP2C9 isoenzymes: Lornoxicam (as other NSAIDs depending on the cytochrome P450 2C9 (CYP2C9 isoenzyme)) has interactions with known inducers and inhibitors of CYP2C9 isoenzymes (see section 5.2 Biotransformation).
- Tacrolimus: Increase the risk of nephrotoxicity owing to reduced synthesis of prostacyclin in the kidney. During combined treatment renal function should be monitored.

Food may decrease the absorption with about 20% and increase Tmax.

4.6 Pregnancy and lactation

Pregnancy

Lornoxicam is contraindicated on the third trimester of pregnancy and should not be used during pregnancy in the first and second trimesters and delivery as no clinical data on exposed pregnancies are available.

There are no adequate data from the use of lornoxicam in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post implantation loss and embryo-foetal lethality. During the first and second trimester of pregnancy, prostaglandin synthesis inhibitors should not be given unless clearly necessary.

Prostaglandin synthesis inhibitors administered during the third trimester of pregnancy may expose the foetus to cardiopulmonary toxicity (premature closure of the ductus arteriosus and pulmonary hypertension) and renal dysfunction which may lead to renal failure and hence a reduced quantity of amniotic fluid. At the end of pregnancy, prostaglandin synthesis inhibitors may expose the mother and the foetus to increased bleeding time and inhibition of uterine contractions, which may delay or prolong the labour. Therefore, the use of lornoxicam is contraindicated during the third trimester of pregnancy (see section 4.3).

Lactation
There are no data on the excretion of lornoxicam in human breast milk. Lornoxicam is excreted in milk of lactating rats in relatively high concentrations. Therefore lornoxicam should not be used in breastfeeding women.

4.7 Effects on ability to drive and use machines
Patients showing dizziness and/or sleepiness under treatment with lornoxicam should refrain from driving or operation machinery.

4.8 Undesirable effects
The most commonly observed adverse events of NSAIDs are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration of NSAIDs. Less frequently, gastritis has been observed.

Approximately 20% of patients treated with lornoxicam can be expected to experience adverse reactions. The most frequent adverse effects of lornoxicam include nausea, dyspepsia, indigestion, abdominal pain, vomiting, and diarrhoea. These symptoms have generally occurred in less than 10% of patients in available studies.

Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Listed below are undesirable effects which generally occurred in more than 0.05% of the 6.417 patients treated in clinical phase II, III and IV trials.

Very common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1000, <1/100); rare (≥1/10.000, <1/1.000); Very rare (<1/10.000).

<u>Infections and infestations</u>
Rare: Pharyngitis.

<u>Blood and the lymphatic system disorders</u>
Rare: Anaemia, thrombocytopenia, leucopoenia, prolonged bleeding time
Very rare: Ecchymosis.

Immune system disorders
Rare: Hypersensitivity.

Metabolism and nutrition disorders
Uncommon: Anorexia, weight changes.

Psychiatric disorders
Uncommon: Insomnia, depression.
Rare: Confusion, nervousness, agitation.

Nervous system disorders
Common: Mild and transient headache, dizziness.
Rare: Somnolence, paraesthesia, dysgeusia, tremor, migraine.

Eye disorders
Uncommon: Conjuctivitis
Rare: Visual disturbances.

Ear and labyrinth disorders
Uncommon: Vertigo, tinnitus.

Cardiac disorders
Uncommon: Palpitations, tachycardia, oedema, cardiac failure.

Vascular disorders
Uncommon: Flushing, oedema.
Rare: Hypertension, hot flush, haemorrhage, haematoma.

Respiratory, thoracic and mediastinal disorders
Uncommon: Rhinitis.
Rare: Dyspnoea, cough, bronchospasm.

Gastrointestinal disorders
Common: Nausea, abdominal pain, dyspepsia, diarrhoea, vomiting.
Uncommon: Constipation, flatulence, eructation, dry mouth, gastritis, gastric ulcer, abdominal pain upper, duodenal ulcer, mouth ulceration.
Rare: Melaena, haematemesis, stomatitis, oesophagitis, gastrooesophageal reflux, dysphagia, aphthous stomatitis, glossitis, perforated peptic ulcer.

Hepatobiliary disorders
Uncommon: Increase in liver function tests, SGPT (ALT) or SGOT (AST).
Rare: Hepatic function abnormal.
Very rare: Hepatocellular damage.

Skin and subcutaneous tissue disorders
Uncommon: Rash, pruritus, hyperhidrosis, rash erythematous, urticaria, alopecia.
Rare: Dermatitis, purpura.
Very rare: Oedema and bullous reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders
Uncommon: Arthralgia
Rare: Bone pain, muscle spasms, myalgia.

Renal and urinary disorders
Rare: Nocturia, micturition disorders, increase in blood urea nitrogen and creatinine levels.

General disorders and administration site conditions

Uncommon: Malaise, face oedema.
Rare: Asthenia.

4.9 Overdose
At this time, there is no experience of overdose to permit definition of the consequence of an overdose, or to suggest specific managements. However, it can be expected that after an overdose with lornoxicam, the following symptoms can be seen: Nausea, vomiting, cerebral symptoms (dizziness, disturbances in vision). Severe symptoms are ataxia ascending to coma and cramps, liver and kidney damages and maybe coagulation disorders.

In the case of a real or suspected overdose, the medicinal product should be withdrawn. Due to its short half-life, lornoxicam is rapidly excreted. Lornoxicam is not dialysable. No specific antidote is known to date. The usual emergency measures including gastric lavage should be considered. Based on principles, only administering activated charcoal immediately after the intake of lornoxicam can lead to diminished absorption of the preparation. Gastrointestinal disorders can for example be treated with a prostaglandin analogue or ranitidine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antiinflammatory and antirheumatic products, non-steroids, oxicams
ATC code: M01 AC05

Lornoxicam is a non steroidal anti-inflammatory drug with analgesic properties and belongs to the class of oxicams. Lornoxicams mode of action is mainly related to the inhibition of the prostaglandin synthesis (inhibition of the cyclooxygenase enzyme) leading to desensitisation of peripheral nociceptors and consequently inhibition of inflammation. A central effect on nociception which seems to be independent of anti-inflammatory effects has also been suggested.

Lornoxicam has no effect on vital signs (e.g. body temperature, respiratory rate, heart rate, blood pressure, ECG, spirometry).

The analgesic properties of lornoxicam have been demonstrated successfully in several clinical trials during development of the drug.

Due to a local gastrointestinal irritation and a systemic ulcerogenic effect related to the inhibition of prostaglandin (PG)-synthesis, gastrointestinal sequela are common undesirable effects after treatment with lornoxicam as seen with other NSAIDs.

5.2 Pharmacokinetic properties
Absorption
Lornoxicam is absorbed rapidly and almost completely from the gastrointestinal tract. Maximum plasma concentrations are achieved after approximately 1-2 hours. The absolute bioavailability of lornoxicam is 90-100 %. No first-pass effect has been observed. The mean elimination half-life is 3-4 hours.

Simultaneous intake of lornoxicam with meals reduces C_{max} by approximately 30 % and T_{max} increases from 1.5 to 2.3 hours. The absorption of lornoxicam (calculated on AUC) can be reduced up to 20 %.

Distribution
Lornoxicam is found in the plasma in unchanged form and as its hydroxylated metabolite. The plasma protein binding of lornoxicam is 99 % and not concentration dependent.

Biotransformation
Lornoxicam is extensively metabolised in the liver, primarily to the inactive 5–hydroxylornoxicam by hydroxylation. CYP2C9 is involved in this biotransformation of lornoxicam. Due to genetic

polymorphism, slow and extensive metabolisers exist for this enzyme which could result in markedly increased plasma levels of lornoxicam in slow metabolisers. The hydroxylated metabolite exhibits no pharmacological activity. Lornoxicam is metabolised completely, and approximately 2/3 is eliminated via the liver and 1/3 via the kidneys as inactive substance.

When tested in animal models, lornoxicam did not induce liver enzymes. From clinical trial data there is no evidence of accumulation of lornoxicam after repeated administrations, when given according to recommended dosage. This finding was supported by drug monitoring data from one year studies.

Elimination
The mean elimination half-life of the parent compound is 3 to 4 hours. After oral administration about 50% is excreted in the faeces and 42% through the kidneys, mainly as 5-hydroxylornoxicam. The elimination half-life of 5-hydroxylornoxicam is about 9 hours after a parenteral single or twice daily dose.

In elderly patients above age 65, the clearance is reduced with 30-40%. Apart from reduced clearance, there is no significant change in the kinetic profile of lornoxicam in elderly patients.

There is no significant change in the kinetic profile of lornoxicam in patients with renal or hepatic failure, except for accumulation in patients with chronic liver disease after 7 days of treatment with daily doses of 12 and 16 mg.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Lornoxicam caused renal toxicity and gastrointestinal ulceration single- and repeat-dose toxicity studies in several species.

In animals, administration of prostaglandin synthesis inhibitor has been shown to result in increased pre- and post- implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

In rat, lornoxicam impaired fertility (effects on ovulation and implantation), and affected the pregnancy and delivery. In rabbit and rat, lornoxicam caused premature closure of the ductus arteriosus due to inhibition of cyclooxygenase.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Core:
Lactose monohydrate
Cellulose, microcrystalline
Povidone K 30
Croscarmellose sodium
Magnesium stearate
Film:
Macrogol
Titanium dioxide (E171)
Talc
Hypromellose

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
5 years

6.4 Special precautions for storage
Blister: Do not store above 30 °C
Tablet container: This medicinal product does not require any special storage conditions

6.5 Nature and contents of container
Blister:
Opaque PVC/Aluminium. Each blister strip contains 10 film-coated tablets.
Pack sizes: 10, 20, 30, 50 and 100 film-coated tablets.

Tablet container:
Amber glass, class III (hydrolytic) with aluminium screw cap closures.
Pack sizes: 250 and 500 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Xefo and associated names (see Annex I) 8 mg film-coated tablets
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One film-coated tablet contains 8 mg lornoxicam

Excipients: Lactose 90 mg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
White to yellowish oblong film-coated tablet with imprint “L08”

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Short-term relief of acute mild to moderate pain
- Symptomatic relief of pain and inflammation in osteoarthritis.
- Symptomatic relief of pain and inflammation in rheumatoid arthritis

4.2 Posology and method of administration

For all patients the appropriate dosing regimen should be based upon individual response to treatment.

Pain
8-16 mg lornoxicam daily divided into 2 or 3 doses. Maximum recommended daily dose is 16 mg.

Osteoarthritis and Rheumatoid arthritis
Initial recommended dose is 12 mg lornoxicam daily divided into 2 or 3 doses. Maintenance dose should not exceed 16 mg lornoxicam daily.

Xefo film-coated tablets are supplied for oral use and should be taken with a sufficient quantity of liquid.

Additional information on special populations

Children and adolescents
Lornoxicam is not recommended for use in children and adolescents below age 18 due to a lack of data on safety and efficacy.

Elderly
No special dosage modification is required for elderly patients above age 65 unless renal or hepatic function is impaired. Lornoxicam should be administered with precaution as gastrointestinal adverse effects are less well tolerated in this group (see section 4.4).

Renal impairment
For patients with mild to moderate renal impairment the maximum recommended daily dose is 12 mg divided in 2 or 3 doses (see section 4.4).

Hepatic impairment
For patients with moderate hepatic impairment the maximum recommended daily dose is 12 mg divided in 2 or 3 doses (see section 4.4).

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4.).

4.3 Contraindications

- Hypersensitivity to lornoxicam or any of the excipients
- Thrombocytopenia
- Hypersensitivity (symptoms like asthma, rhinitis, angioedema or urticaria) to other NSAIDs

including acetylsalicylic acid
- Severe heart failure
- Gastro-intestinal bleeding, cerebrovascular bleeding or other bleeding disorders
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- Severe hepatic impairment
- Severe renal impairment (Serum creatinine > 700 µmol/l)
- The third trimester of pregnancy (see section 4.6)

4.4 Special warnings and precautions for use

For the following disorders, lornoxicam should only be administered after careful risk-benefit assessment:

- Renal impairment: Lornoxicam should be administered with precaution in patients with mild (serum creatinine 150-300 µmol/l) to moderate (serum creatinine 300 – 700 µmol/l) renal impairment due to dependency on renal prostaglandins for maintenance of renal blood flow. Treatment with lornoxicam should be discontinued if renal function deteriorates during treatment.
- Renal functions should be monitored in patients who undergo major surgery, with cardiac failure, receiving treatment with diuretics, receiving concomitant treatment with drugs that are suspected to or known to be able to cause kidney damage.
- Patients with blood coagulation disorders: Careful clinical monitoring and laboratory assessment is recommended (e.g. APTT).
- Hepatic impairment (e.g. liver cirrhosis): Clinical monitoring and laboratory assessments at regular intervals should be considered in patients with hepatic impairment as accumulation of lornoxicam (increase in AUC) may occur after treatment with daily doses of 12-16 mg. Apart from that, hepatic impairment does not seem to affect pharmacokinetic parameters of lornoxicam as compared to healthy subjects.
- Long term treatment (longer than 3 months): Regular laboratory assessments of haematology (haemoglobin), renal functions (creatinine) and liver enzymes are recommended.
- Elderly patients above 65 years: Monitoring of renal and hepatic function is recommended. Precaution is advised in elderly postoperative patients.

The use of lornoxicam with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Undesirable effects may be minimised by using lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid or other active substances likely to increase gastrointestinal risk (see below and section 4.5). Clinical monitoring at regular intervals is recommended.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.
Caution should be advised in patients receiving concomitant medicinal products which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving lornoxicam, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8).

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.3).

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for lornoxicam.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Lornoxicam after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Concomitant treatment with NSAIDs and heparin in the context of a spinal or epidural anaesthesia increases the risk of spinal/epidural haematoma (see section 4.5).

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Lornoxicam should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Lornoxicam reduces platelet aggregation and prolongs bleeding time and consequently care should be taken when administering to patients with increased bleeding tendency.

Concomitant treatment of NSAIDs and tacrolimus may increase the risk of nephrotoxicity owing to reduced synthesis of prostacyclin in the kidney. Renal function must therefore be monitored closely in patients receiving combination therapy.

As with most NSAIDs occasional increase in serum transaminases level, increase in serum bilirubin or other liver function parameters, as well as increases in serum creatinine and blood urea nitrogen as well as other laboratory abnormalities have been reported. Should any such abnormality prove significant or persist the administration of lornoxicam should be stopped and appropriate investigations prescribed.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The use of lornoxicam, 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

difficulties conceiving or who are undergoing investigation of infertility, withdrawal of lornoxicam should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of lornoxicam and

- Cimetidine: Increased plasma concentrations of lornoxicam. (No interaction between lornoxicam and ranitidine, or lornoxicam and antacids has been demonstrated).
- Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4). Careful monitoring of INR should be undertaken
- Phenprocoumon: Decreased effect of phenprocoumon treatment.
- Heparin: NSAIDs increase the risk of spinal or epidural haematoma when given concomitantly to heparin in the context of spinal or epidural anaesthesia.
- ACE inhibitors: The antihypertensive effect of the ACE inhibitor may decrease.
- Diuretics: Decreased diuretic and antihypertensive effect of loop diuretics and thiazide diuretics.
- Beta-adrenergic blockers: Decreased antihypertensive efficacy.
- Digoxin: Decreased renal clearance of digoxin.
- Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
- Quinolone antibiotics: Increased risk of seizures.
- Anti-platelet agents: Increased risk of gastrointestinal bleeding (see section 4.4).
- Other NSAIDs: Increased risk of gastrointestinal bleeding.
- Methotrexate: Increased serum concentration of methotrexate. Increased toxicity may result. When concomitant therapy has to be used careful monitoring should be undertaken.
- Selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).
- Lithium: NSAIDs inhibit renal clearance of lithium, thus the serum concentration of lithium may increase above toxicity limits. Therefore serum lithium levels require monitoring, especially during initiation, adjustment and withdrawal of treatment.
- Cyclosporine: Increased serum concentration of cyclosporine. Nephrotoxicity of cyclosporine may be enhanced via renal prostaglandin mediated effects. During combined treatment renal function should be monitored.
- Sulphonylureas: Increased risk of hypoglycaemia.
- Known inducers and inhibitors of CYP2C9 isoenzymes: Lornoxicam (as other NSAIDs depending on the cytochrome P450 2C9 (CYP2C9 isoenzyme)) has interactions with known inducers and inhibitors of CYP2C9 isoenzymes (see section 5.2 Biotransformation).
- Tacrolimus: Increase the risk of nephrotoxicity owing to reduced synthesis of prostacyclin in the kidney. During combined treatment renal function should be monitored.

Food may decrease the absorption with about 20% and increase Tmax.

4.6 Pregnancy and lactation

Pregnancy

Lornoxicam is contraindicated on the third trimester of pregnancy and should not be used during pregnancy in the first and second trimesters and delivery as no clinical data on exposed pregnancies are available.

There are no adequate data from the use of lornoxicam in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post implantation loss and embryo-foetal lethality. During the first and second trimester of pregnancy, prostaglandin synthesis inhibitors should not be given unless clearly necessary.

Prostaglandin synthesis inhibitors administered during the third trimester of pregnancy may expose the foetus to cardiopulmonary toxicity (premature closure of the ductus arteriosus and pulmonary hypertension) and renal dysfunction which may lead to renal failure and hence a reduced quantity of amniotic fluid. At the end of pregnancy, prostaglandin synthesis inhibitors may expose the mother and the foetus to increased bleeding time and inhibition of uterine contractions, which may delay or prolong the labour. Therefore, the use of lornoxicam is contraindicated during the third trimester of pregnancy (see section 4.3).

Lactation
There are no data on the excretion of lornoxicam in human breast milk. Lornoxicam is excreted in milk of lactating rats in relatively high concentrations. Therefore lornoxicam should not be used in breastfeeding women.

4.7 Effects on ability to drive and use machines
Patients showing dizziness and/or sleepiness under treatment with lornoxicam should refrain from driving or operation machinery.

4.8 Undesirable effects
The most commonly observed adverse events of NSAIDs are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration of NSAIDs. Less frequently, gastritis has been observed.

Approximately 20% of patients treated with lornoxicam can be expected to experience adverse reactions. The most frequent adverse effects of lornoxicam include nausea, dyspepsia, indigestion, abdominal pain, vomiting, and diarrhoea. These symptoms have generally occurred in less than 10% of patients in available studies.

Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Listed below are undesirable effects which generally occurred in more than 0.05% of the 6.417 patients treated in clinical phase II, III and IV trials.

Very common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1000, <1/100); rare (≥1/10.000, <1/1.000); Very rare (<1/10.000).

<u>Infections and infestations</u>
Rare: Pharyngitis.

<u>Blood and the lymphatic system disorders</u>
Rare: Anaemia, thrombocytopenia, leucopoenia, prolonged bleeding time
Very rare: Ecchymosis.

<u>Immune system disorders</u>
Rare: Hypersensitivity.

<u>Metabolism and nutrition disorders</u>
Uncommon: Anorexia, weight changes.

<u>Psychiatric disorders</u>
Uncommon: Insomnia, depression.
Rare: Confusion, nervousness, agitation.

Nervous system disorders
Common: Mild and transient headache, dizziness.
Rare: Somnolence, paraesthesia, dysgeusia, tremor, migraine.

Eye disorders
Uncommon: Conjuctivitis
Rare: Visual disturbances.

Ear and labyrinth disorders
Uncommon: Vertigo, tinnitus.

Cardiac disorders
Uncommon: Palpitations, tachycardia, oedema, cardiac failure.

Vascular disorders
Uncommon: Flushing, oedema.
Rare: Hypertension, hot flush, haemorrhage, haematoma.

Respiratory, thoracic and mediastinal disorders
Uncommon: Rhinitis.
Rare: Dyspnoea, cough, bronchospasm.

Gastrointestinal disorders
Common: Nausea, abdominal pain, dyspepsia, diarrhoea, vomiting.
Uncommon: Constipation, flatulence, eructation, dry mouth, gastritis, gastric ulcer, abdominal pain upper, duodenal ulcer, mouth ulceration.
Rare: Melaena, haematemesis, stomatitis, oesophagitis, gastrooesophageal reflux, dysphagia, aphthous stomatitis, glossitis, perforated peptic ulcer.

Hepatobiliary disorders
Uncommon: Increase in liver function tests, SGPT (ALT) or SGOT (AST).
Rare: Hepatic function abnormal.
Very rare: Hepatocellular damage.

Skin and subcutaneous tissue disorders
Uncommon: Rash, pruritus, hyperhidrosis, rash erythematous, urticaria, alopecia.
Rare: Dermatitis, purpura.
Very rare: Oedema and bullous reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders
Uncommon: Arthralgia
Rare: Bone pain, muscle spasms, myalgia.

Renal and urinary disorders
Rare: Nocturia, micturition disorders, increase in blood urea nitrogen and creatinine levels.

General disorders and administration site conditions
Uncommon: Malaise, face oedema.
Rare: Asthenia.

4.9 Overdose

At this time, there is no experience of overdose to permit definition of the consequence of an overdose, or to suggest specific managements. However, it can be expected that after an overdose with lornoxicam, the following symptoms can be seen: Nausea, vomiting, cerebral symptoms (dizziness, disturbances in vision). Severe symptoms are ataxia ascending to coma and cramps, liver and kidney damages and maybe coagulation disorders.

In the case of a real or suspected overdose, the medicinal product should be withdrawn. Due to its short half-life, lornoxicam is rapidly excreted. Lornoxicam is not dialysable. No specific antidote is known to date. The usual emergency measures including gastric lavage should be considered. Based on principles, only administering activated charcoal immediately after the intake of lornoxicam can lead to diminished absorption of the preparation. Gastrointestinal disorders can for example be treated with a prostaglandin analogue or ranitidine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiinflammatory and antirheumatic products, non-steroids, oxicams
ATC code: M01 AC05

Lornoxicam is a non steroidal anti-inflammatory drug with analgesic properties and belongs to the class of oxicams. Lornoxicams mode of action is mainly related to the inhibition of the prostaglandin synthesis (inhibition of the cyclooxygenase enzyme) leading to desensitisation of peripheral nociceptors and consequently inhibition of inflammation. A central effect on nociception which seems to be independent of anti-inflammatory effects has also been suggested.

Lornoxicam has no effect on vital signs (e.g. body temperature, respiratory rate, heart rate, blood pressure, ECG, spirometry).

The analgesic properties of lornoxicam have been demonstrated successfully in several clinical trials during development of the drug.

Due to a local gastrointestinal irritation and a systemic ulcerogenic effect related to the inhibition of prostaglandin (PG)-synthesis, gastrointestinal sequela are common undisirable effects after treatment with lornoxicam as seen with other NSAIDs.

5.2 Pharmacokinetic properties

Absorption

Lornoxicam is absorbed rapidly and almost completely from the gastrointestinal tract. Maximum plasma concentrations are achieved after approximately 1-2 hours. The absolute bioavailability of lornoxicam is 90-100 %. No first-pass effect has been observed. The mean elimination half-life is 3-4 hours.

Simultaneous intake of lornoxicam with meals reduces C_{max} by approximately 30 % and T_{max} increases from 1.5 to 2.3 hours. The absorption of lornoxicam (calculated on AUC) can be reduced up to 20 %.

Distribution

Lornoxicam is found in the plasma in unchanged form and as its hydroxylated metabolite. The plasma protein binding of lornoxicam is 99 % and not concentration dependent.

Biotransformation

Lornoxicam is extensively metabolised in the liver, primarily to the inactive 5–hydroxylornoxicam by hydroxylation. CYP2C9 is involved in this biotransformation of lornoxicam. Due to genetic polymorphism, slow and extensive metabolisers exist for this enzyme which could result in markedly increased plasma levels of lornoxicam in slow metabolisers. The hydroxylated metabolite exhibits no pharmacological activity. Lornoxicam is metabolised completely, and approximately 2/3 is eliminated via the liver and 1/3 via the kidneys as inactive substance.

When tested in animal models, lornoxicam did not induce liver enzymes. From clinical trial data there is no evidence of accumulation of lornoxicam after repeated administrations, when given according to recommended dosage. This finding was supported by drug monitoring data from one year studies.

Elimination
The mean elimination half-life of the parent compound is 3 to 4 hours. After oral administration about 50% is excreted in the faeces and 42% through the kidneys, mainly as 5-hydroxylornoxicam. The elimination half-life of 5-hydroxylornoxicam is about 9 hours after a parenteral single or twice daily dose.

In elderly patients above age 65, the clearance is reduced with 30-40%. Apart from reduced clearance, there is no significant change in the kinetic profile of lornoxicam in elderly patients.

There is no significant change in the kinetic profile of lornoxicam in patients with renal or hepatic failure, except for accumulation in patients with chronic liver disease after 7 days of treatment with daily doses of 12 and 16 mg.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Lornoxicam caused renal toxicity and gastrointestinal ulceration single- and repeat-dose toxicity studies in several species.

In animals, administration of prostaglandin synthesis inhibitor has been shown to result in increased pre- and post- implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

In rat, lornoxicam impaired fertility (effects on ovulation and implantation), and affected the pregnancy and delivery. In rabbit and rat, lornoxicam caused premature closure of the ductus arteriosus due to inhibition of cyclooxygenase.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Core:
Lactose monohydrate
Cellulose, microcrystalline
Povidone K 30
Croscarmellose sodium
Magnesium stearate
Film:
Macrogol
Titanium dioxide (E171)
Talc
Hypromellose

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
5 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions

6.5 Nature and contents of container
Blister:
Opaque PVC/Aluminium. Each blister strip contains 10 film-coated tablets.

Pack sizes: 10, 20, 30, 50 and 100 film-coated tablets.

Tablet container:
Amber glass, class III (hydrolytic) with aluminium screw cap closures.
Pack sizes: 250 and 500 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Xefo Rapid and associated names (see Annex I) 8 mg film-coated tablets
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 8 mg lornoxicam.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
White to yellowish round biconvex film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Short-term relief of acute mild to moderate pain.

4.2 Posology and method of administration

For all patients the appropriate dosing regimen should be based upon individual response to treatment.

Acute pain
8-16 mg lornoxicam given in doses of 8 mg. An initial dose of 16 mg followed by 8 mg 12 hours later can be given on the first treatment day. After the first treatment day the maximum recommended daily dose is 16 mg.

Xefo Rapid film-coated tablets are supplied for oral administration and should be taken with a sufficient quantity of liquid.

Additional information on special populations

Children and adolescents
Lornoxicam is not recommended for use in children and adolescents below age 18 due to a lack of data on safety and efficacy.

Elderly
No special dosage modification is required for elderly patients above age 65 unless renal or hepatic function is impaired. Lornoxicam should be administered with precaution as gastrointestinal adverse effects are less well tolerated in this group (see section 4.4).

Renal impairment
Reduction of dose frequency of Xefo Rapid to once daily in patients suffering from renal impairment is recommended.

Hepatic impairment
Reduction of dose frequency of Xefo Rapid to once daily in patients suffering from hepatic impairment is recommended.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4.).

4.3 Contraindications

- Hypersensitivity to lornoxicam or to any of the excipients
- Thrombocytopenia
- Hypersensitivity (symptoms like asthma, rhinitis, angioedema or urticaria) to other NSAIDs including acetylsalicylic acid
- Severe heart failure
- Gastro-intestinal bleeding, cerebrovascular bleeding or other bleeding disorders
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- Severe hepatic impairment
- Severe renal impairment (Serum creatinine > 700 µmol/l)
- The third trimester of pregnancy (see section 4.6)

4.4 Special warnings and precautions for use

For the following disorders, lornoxicam should only be administered after careful risk-benefit assessment:

- Renal impairment: Lornoxicam should be administered with precaution in patients with mild (serum creatinine 150-300 µmol/l) to moderate (serum creatinine 300 – 700 µmol/l) renal impairment due to dependency on renal prostaglandins for maintenance of renal blood flow. Treatment with lornoxicam should be discontinued if renal function deteriorates during treatment.
- Renal functions should be monitored in patients who undergo major surgery, with cardiac failure, receiving treatment with diuretics, receiving concomitant treatment with drugs that are suspected to or known to be able to cause kidney damage.
- Patients with blood coagulation disorders: Careful clinical monitoring and laboratory assessment is recommended (e.g. APTT).
- Hepatic impairment (e.g. liver cirrhosis): Clinical monitoring and laboratory assessments at regular intervals should be considered in patients with hepatic impairment as accumulation of lornoxicam (increase in AUC) may occur after treatment with daily doses of 12-16 mg. Apart from that, hepatic impairment does not seem to affect pharmacokinetic parameters of lornoxicam as compared to healthy subjects.
- Long term treatment (longer than 3 months): Regular laboratory assessments of haematology (haemoglobin), renal functions (creatinine) and liver enzymes are recommended.
- Elderly patients above 65 years: Monitoring of renal and hepatic function is recommended. Precaution is advised in elderly postoperative patients.

The use of lornoxicam with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Undesirable effects may be minimised by using lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid or other active substances likely to increase gastrointestinal risk (see below and section 4.5). Clinical monitoring at regular intervals is recommended.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medicinal products which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving lornoxicam, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8).

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.3).

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for lornoxicam.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Lornoxicam after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Concomitant treatment with NSAIDs and heparin in the context of a spinal or epidural anaesthesia increases the risk of spinal/epidural haematoma (see section 4.5).

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Lornoxicam should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Lornoxicam reduces platelet aggregation and prolongs bleeding time and consequently care should be taken when administering to patients with increased bleeding tendency.

Concomitant treatment of NSAIDs and tacrolimus may increase the risk of nephrotoxicity owing to reduced synthesis of prostacyclin in the kidney. Renal function must therefore be monitored closely in patients receiving combination therapy.

As with most NSAIDs occasional increase in serum transaminases level, increase in serum bilirubin or other liver function parameters, as well as increases in serum creatinine and blood urea nitrogen as well as other laboratory abnormalities have been reported. Should any such abnormality prove significant or persist the administration of lornoxicam should be stopped and appropriate investigations prescribed.

The use of lornoxicam, 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

difficulties conceiving or who are undergoing investigation of infertility, withdrawal of lornoxicam should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of lornoxicam and

- Cimetidine: Increased plasma concentrations of lornoxicam. (No interaction between lornoxicam and ranitidine, or lornoxicam and antacids has been demonstrated).
- Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4). Careful monitoring of INR should be undertaken
- Phenprocoumon: Decreased effect of phenprocoumon treatment.
- Heparin: NSAIDs increase the risk of spinal or epidural haematoma when given concomitantly to heparin in the context of spinal or epidural anaesthesia.
- ACE inhibitors: The antihypertensive effect of the ACE inhibitor may decrease.
- Diuretics: Decreased diuretic and antihypertensive effect of loop diuretics and thiazide diuretics.
- Beta-adrenergic blockers: Decreased antihypertensive efficacy.
- Digoxin: Decreased renal clearance of digoxin.
- Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
- Quinolone antibiotics: Increased risk of seizures.
- Anti-platelet agents: Increased risk of gastrointestinal bleeding (see section 4.4).
- Other NSAIDs: Increased risk of gastrointestinal bleeding.
- Methotrexate: Increased serum concentration of methotrexate. Increased toxicity may result. When concomitant therapy has to be used careful monitoring should be undertaken.
- Selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).
- Lithium: NSAIDs inhibit renal clearance of lithium, thus the serum concentration of lithium may increase above toxicity limits. Therefore serum lithium levels require monitoring, especially during initiation, adjustment and withdrawal of treatment.
- Cyclosporine: Increased serum concentration of cyclosporine. Nephrotoxicity of cyclosporine may be enhanced via renal prostaglandin mediated effects. During combined treatment renal function should be monitored.
- Sulphonylureas: Increased risk of hypoglycaemia.
- Known inducers and inhibitors of CYP2C9 isoenzymes: Lornoxicam (as other NSAIDs depending on the cytochrome P450 2C9 (CYP2C9 isoenzyme)) has interactions with known inducers and inhibitors of CYP2C9 isoenzymes (see section 5.2 Biotransformation).
- Tacrolimus: Increase the risk of nephrotoxicity owing to reduced synthesis of prostacyclin in the kidney. During combined treatment renal function should be monitored.

Food may decrease the absorption with about 20% and increase Tmax.

4.6 Pregnancy and lactation

Pregnancy

Lornoxicam is contraindicated on the third trimester of pregnancy and should not be used during pregnancy in the first and second trimesters and delivery as no clinical data on exposed pregnancies are available.

There are no adequate data from the use of lornoxicam in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post implantation loss and embryo-foetal lethality. During the first and second trimester of pregnancy, prostaglandin synthesis inhibitors should not be given unless clearly necessary.

Prostaglandin synthesis inhibitors administered during the third trimester of pregnancy may expose the foetus to cardiopulmonary toxicity (premature closure of the ductus arteriosus and pulmonary hypertension) and renal dysfunction which may lead to renal failure and hence a reduced quantity of amniotic fluid. At the end of pregnancy, prostaglandin synthesis inhibitors may expose the mother and the foetus to increased bleeding time and inhibition of uterine contractions, which may delay or prolong the labour. Therefore, the use of lornoxicam is contraindicated during the third trimester of pregnancy (see section 4.3).

Lactation
There are no data on the excretion of lornoxicam in human breast milk. Lornoxicam is excreted in milk of lactating rats in relatively high concentrations. Therefore lornoxicam should not be used in breastfeeding women.

4.7 Effects on ability to drive and use machines
Patients showing dizziness and/or sleepiness under treatment with lornoxicam should refrain from driving or operation machinery.

4.8 Undesirable effects
The most commonly observed adverse events of NSAIDs are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration of NSAIDs. Less frequently, gastritis has been observed.

Approximately 20% of patients treated with lornoxicam can be expected to experience adverse reactions. The most frequent adverse effects of lornoxicam include nausea, dyspepsia, indigestion, abdominal pain, vomiting, and diarrhoea. These symptoms have generally occurred in less than 10% of patients in available studies.

Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Listed below are undesirable effects which generally occurred in more than 0.05% of the 6.417 patients treated in clinical phase II, III and IV trials.

Very common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1000, <1/100); rare (≥1/10.000, <1/1.000); Very rare (<1/10.000).

<u>Infections and infestations</u>
Rare: Pharyngitis.

<u>Blood and the lymphatic system disorders</u>
Rare: Anaemia, thrombocytopenia, leukopenia, prolonged bleeding time
Very rare: Ecchymosis.

<u>Immune system disorders</u>
Rare: Hypersensitivity.

<u>Metabolism and nutrition disorders</u>
Uncommon: Anorexia, weight changes.

<u>Psychiatric disorders</u>
Uncommon: Insomnia, depression.
Rare: Confusion, nervousness, agitation.

Nervous system disorders
Common: Mild and transient headache, dizziness.
Rare: Somnolence, paraesthesia, dysgeusia, tremor, migraine.

Eye disorders
Uncommon: Conjuctivitis
Rare: Visual disturbances.

Ear and labyrinth disorders
Uncommon: Vertigo, tinnitus.

Cardiac disorders
Uncommon: Palpitations, tachycardia, oedema, cardiac failure.

Vascular disorders
Uncommon: Flushing, oedema.
Rare: Hypertension, hot flush, haemorrhage, haematoma.

Respiratory, thoracic and mediastinal disorders
Uncommon: Rhinitis.
Rare: Dyspnoea, cough, bronchospasm.

Gastrointestinal disorders
Common: Nausea, abdominal pain, dyspepsia, diarrhoea, vomiting.
Uncommon: Constipation, flatulence, eructation, dry mouth, gastritis, gastric ulcer, abdominal pain upper, duodenal ulcer, mouth ulceration.
Rare: Melaena, haematemesis, stomatitis, oesophagitis, gastrooesophageal reflux, dysphagia, aphthous stomatitis, glossitis, perforated peptic ulcer.

Hepatobiliary disorders
Uncommon: Increase in liver function tests, SGPT (ALT) or SGOT (AST).
Rare: Hepatic function abnormal.
Very rare: Hepatocellular damage.

Skin and subcutaneous tissue disorders
Uncommon: Rash, pruritus, hyperhidrosis, rash erythematous, urticaria, alopecia.
Rare: Dermatitis, purpura.
Very rare: Oedema and bullous reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders
Uncommon: Arthralgia.
Rare: Bone pain, muscle spasms, myalgia.

Renal and urinary disorders
Rare: Nocturia, micturition disorders, increase in blood urea nitrogen and creatinine levels.

General disorders and administration site conditions
Uncommon: Malaise, face oedema.
Rare: Asthenia.

4.9 Overdose
At this time, there is no experience of overdose to permit definition of the consequence of an overdose, or to suggest specific managements. However, it can be expected that after an overdose with lornoxicam, the following symptoms can be seen: Nausea, vomiting, cerebral symptoms (dizziness, disturbances in vision). Severe symptoms are ataxia ascending to coma and cramps, liver and kidney damages and maybe coagulation disorders.

In the case of a real or suspected overdose, the medicinal product should be withdrawn. Due to its short half-life, lornoxicam is rapidly excreted. Lornoxicam is not dialysable. No specific antidote is known to date. The usual emergency measures including gastric lavage should be considered. Based on principles, only administering activated charcoal immediately after the intake of lornoxicam can lead to diminished absorption of the preparation. Gastrointestinal disorders can for example be treated with a prostaglandin analogue or ranitidine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinflammatory and antirheumatic products, non-steroids, oxicams
ATC code: M01 AC05

Lornoxicam is a non steroidal anti-inflammatory drug with analgesic properties and belongs to the class of oxicams. Lornoxicams mode of action is mainly related to the inhibition of the prostaglandin synthesis (inhibition of the cyclooxygenase enzyme) leading to desensitisation of peripheral nociceptors and consequently inhibition of inflammation. A central effect on nociception which seems to be independent of anti-inflammatory effects has also been suggested.

Lornoxicam has no effect on vital signs (e.g. body temperature, respiratory rate, heart rate, blood pressure, ECG, spirometry).

The analgesic properties of lornoxicam have been demonstrated successfully in several clinical trials during development of the drug.

Due to a local gastrointestinal irritation and a systemic ulcerogenic effect related to the inhibition of prostaglandin (PG)-synthesis, gastrointestinal sequela are common undesirable effects after treatment with lornoxicam as seen with other NSAIDs.

In a clinical study in patients with pain after surgical removal of an impacted third molar lornoxicam Rapid film-coated tablets showed a faster onset of action compared to lornoxicam film-coated tablets.

5.2 Pharmacokinetic properties

Absorption

Lornoxicam is absorbed rapidly and almost completely from the gastrointestinal tract. Maximum plasma concentrations are achieved after approximately 30 minutes. The C_{max} for Xefo Rapid film-coated tablets is higher than C_{max} for Xefo film-coated tablets and equivalent to C_{max} for the parenteral formulation of lornoxicam. The absolute bioavailability of Xefo Rapid film-coated tablets is 90-100 % which is equivalent to Xefo film-coated tablet. No first-pass effect has been observed. The mean elimination half-life is 3-4 hours.

No data are available on simultaneous intake of Xefo Rapid film-coated tablets with meals, but based on data for Xefo film-coated tablets a reduction of C_{max}, an increase in T_{max}, and a reduction in the absorption (AUC) of lornoxicam may be expected.

Distribution

Lornoxicam is found in the plasma in unchanged form and as its hydroxylated metabolite. The plasma protein binding of lornoxicam is 99 % and not concentration dependent.

Biotransformation

Lornoxicam is extensively metabolised in the liver, primarily to the inactive 5–hydroxylornoxicam by hydroxylation. CYP2C9 is involved in this biotransformation of lornoxicam. Due to genetic polymorphism, slow and extensive metabolisers exist for this enzyme which could result in markedly increased plasma levels of lornoxicam in slow metabolisers. The hydroxylated metabolite exhibits no

pharmacological activity. Lornoxicam is metabolised completely, and approximately 2/3 is eliminated via the liver and 1/3 via the kidneys as inactive substance.

When tested in animal models, lornoxicam did not induce liver enzymes. From clinical trial data there is no evidence of accumulation of lornoxicam after repeated administrations, when given according to recommended dosage. This finding was supported by drug monitoring data from one year studies.

Elimination
The mean elimination half-life of the parent compound is 3 to 4 hours. After oral administration about 50% is excreted in the faeces and 42% through the kidneys, mainly as 5-hydroxylornoxicam. The elimination half-life of 5-hydroxylornoxicam is about 9 hours after a parenteral single or twice daily dose.

In elderly patients above age 65, the clearance is reduced with 30-40%. Apart from reduced clearance, there is no significant change in the kinetic profile of lornoxicam in elderly patients.

There is no significant change in the kinetic profile of lornoxicam in patients with renal or hepatic failure, except for accumulation in patients with chronic liver disease after 7 days of treatment with daily doses of 12 and 16 mg.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Lornoxicam caused renal toxicity and gastrointestinal ulceration single- and repeat-dose toxicity studies in several species.

In animals, administration of prostaglandin synthesis inhibitor has been shown to result in increased pre- and post- implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

In rat, lornoxicam impaired fertility (effects on ovulation and implantation), and affected the pregnancy and delivery. In rabbit and rat, lornoxicam caused premature closure of the ductus arteriosus due to inhibition of cyclooxygenase.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Core:
Cellulose, microcrystalline
Sodium hydrogen carbonate
Calcium hydrogen phosphate, anhydrous
Low substituted hydroxypropylcellulose
Hydroxypropylcellulose
Calcium stearate
Film:
Titanium dioxide (E171)
Talc
Propylene glycol
Hypromellose

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
Aluminium/Aluminium blister.
Pack sizes: 6, 10, 20, 30, 50, 100, 250 film-coated tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal
No special requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Xefo and associated names (see Annex I) 8 mg powder and solvent for solution for injection
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 8 mg lornoxicam. Provides 4 mg lornoxicam per ml when reconstituted as recommended.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder: Yellow, solid substance
Solvent: Clear solution
The osmolarity of the reconstituted solution is about 328 mosmol/kg and pH is about 8.7

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Short-term relief of acute mild to moderate pain.

4.2 Posology and method of administration
For all patients the appropriate dosing regimen should be based upon individual response to treatment.

Pain
Recommended dose: 8 mg intravenous or intramuscular. Daily dose should not exceed 16 mg. Some patients may need a further 8 mg given during the first 24 hours.

The route of administration is intravenous (IV) or intramuscular injection (IM). When given as IV injection, the time of injection should be at least 15 seconds, and for IM injection, at least 5 seconds.

After preparation of the solution, the needle should be changed. For IM injection a sufficiently long needle for a deep intramuscular injection.

For further instructions on handling of the product before administration, see section 6.1.

The medicinal product is for single use only

Additional information on special populations

Children and adolescents
Lornoxicam is not recommended for use in children and adolescents below age 18 due to a lack of data on safety and efficacy.

Elderly
No special dosage modification is required for elderly patients above age 65 unless renal or hepatic function is impaired. Lornoxicam should be administered with precaution as gastrointestinal adverse effects are less well tolerated in this group (see section 4.4).

Renal impairment
For patients with mild to moderate renal impairment dose reduction should be considered (see section 4.4).

Hepatic impairment
For patients with moderate hepatic impairment dose reduction should be considered (see section 4.4).

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4.).

4.3 Contraindications

- Hypersensitivity to lornoxicam or any of the excipients
- Thrombocytopenia
- Hypersensitivity (symptoms like asthma, rhinitis, angioedema or urticaria) to other NSAIDs including acetylsalicylic acid
- Severe heart failure.
- Gastro-intestinal bleeding, cerebrovascular bleeding or other bleeding disorders
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- Severe hepatic impairment
- Severe renal impairment (Serum creatinine > 700 µmol/L)
- The third trimester of pregnancy (see section 4.6)

4.4 Special warnings and precautions for use

For the following disorders, lornoxicam should only be administered after careful risk-benefit assessment:

- Renal impairment: Lornoxicam should be administered with precaution in patients with mild (serum creatinine 150-300 µmol/L) to moderate (serum creatinine 300 – 700 µmol/L) renal impairment due to dependency on renal prostaglandins for maintenance of renal blood flow. Treatment with lornoxicam should be discontinued if renal function deteriorates during treatment.
- Renal functions should be monitored in patients who undergo major surgery, with cardiac failure, receiving treatment with diuretics, receiving concomitant treatment with drugs that are suspected to or known to be able to cause kidney damage.
- Patients with blood coagulation disorders: Careful clinical monitoring and laboratory assessment is recommended (e.g. APTT).
- Hepatic impairment (e.g. liver cirrhosis): Clinical monitoring and laboratory assessments at regular intervals should be considered in patients with hepatic impairment as accumulation of lornoxicam (increase in AUC) may occur after treatment with daily doses of 12-16 mg. Apart from that, hepatic impairment does not seem to affect pharmacokinetic parameters of lornoxicam as compared to healthy subjects.
- Long term treatment (longer than 3 months): Regular laboratory assessments of haematology (haemoglobin), renal functions (creatinine) and liver enzymes are recommended.
- Elderly patients above 65 years: Monitoring of renal and hepatic function is recommended. Precaution is advised in elderly postoperative patients.

The use of lornoxicam with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Undesirable effects may be minimised by using lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid or other drugs likely to increase gastrointestinal risk (see below and section 4.5). Clinical monitoring at regular intervals is recommended.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving lornoxicam, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8).

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.3).

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for lornoxicam.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Lornoxicam after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Concomitant treatment with NSAIDs and heparin in the context of a spinal or epidural anaesthesia increases the risk of spinal/epidural haematoma (see section 4.5).

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Lornoxicam should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Lornoxicam reduces platelet aggregation and prolongs bleeding time and consequently care should be taken when administering to patients with increased bleeding tendency.

Concomitant treatment of NSAIDs and tacrolimus may increase the risk of nephrotoxicity owing to reduced synthesis of prostacyclin in the kidney. Renal function must therefore be monitored closely in patients receiving combination therapy.

As with most NSAIDs occassional increase in serum transaminases level, increase in serum bilirubin or other liver function parameters, as well as increases in serum creatinine and blood urea nitrogen as well as other laboratory abnormalities have been reported. Should any such abnormality prove significant or persist the administration of lornoxicam should be stopped and appropriate investigations prescribed.

The use of lornoxicam, as with any drug known to inhibit cyclooxygenase/prostaglanding synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have

difficulties conceiving or who are undergoing investigation of infertility, withdrawal of lornoxicam should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of lornoxicam and

- Cimetidine: Increased plasma concentrations of lornoxicam. (No interaction between lornoxicam and ranitidine, or lornoxicam and antacids has been demonstrated).
- Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4). Careful monitoring of INR should be undertaken
- Phenprocoumon: Decreased effect of phenprocoumon treatment.
- Heparin: NSAIDs increase the risk of spinal or epidural haematoma when given concomitantly to heparin in the context of spinal or epidural anaesthesia.
- ACE inhibitors: The antihypertensive effect of the ACE inhibitor may decrease.
- Diuretics: Decreased diuretic and antihypertensive effect of loop diuretics and thiazide diuretics.
- Beta-adrenergic blockers: Decreased antihypertensive efficacy.
- Digoxin: Decreased renal clearance of digoxin.
- Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
- Quinolone antibiotics: Increased risk of seizures.
- Anti-platelet agents: Increased risk of gastrointestinal bleeding (see section 4.4).
- Other NSAIDs: Increased risk of gastrointestinal bleeding.
- Methotrexate: Increased serum concentration of methotrexate. Increased toxicity may result. When concomitant therapy has to be used careful monitoring should be undertaken.
- Selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).
- Lithium: NSAIDs inhibit renal clearance of lithium, thus the serum concentration of lithium may increase above toxicity limits. Therefore serum lithium levels require monitoring, especially during initiation, adjustment and withdrawal of treatment.
- Cyclosporine: Increased serum concentration of cyclosporine. Nephrotoxicity of cyclosporine may be enhanced via renal prostaglandin mediated effects. During combined treatment renal function should be monitored.
- Sulphonylureas: Increased risk of hypoglycaemia.
- Known inducers and inhibitors of CYP2C9 isoenzymes: Lornoxicam (as other NSAIDs depending on the cytochrome P450 2C9 (CYP2C9 isoenzyme)) has interactions with known inducers and inhibitors of CYP2C9 isoenzymes (see section 5.2 Biotransformation).
- Tacrolimus: Increase the risk of nephrotoxicity owing to reduced synthesis of prostacyclin in the kidney. During combined treatment renal function should be monitored.

4.6 Pregnancy and lactation

Pregnancy

Lornoxicam is contraindicated on the third trimester of pregnancy and should not be used during pregnancy in the first and second trimesters and delivery as no clinical data on exposed pregnancies are available.

There are no adequate data from the use of lornoxicam in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post implantation loss and embryo-foetal lethality. During the first and second trimester of pregnancy, prostaglandin synthesis inhibitors should not be given unless clearly necessary.

Prostaglandin synthesis inhibitors administered during the third trimester of pregnancy may expose the foetus to cardiopulmonary toxicity (premature closure of the ductus arteriosus and pulmonary hypertension) and renal dysfunction which may lead to renal failure and hence a reduced quantity of

amniotic fluid. At the end of pregnancy, prostaglandin synthesis inhibitors may expose the mother and the foetus to increased bleeding time and inhibition of uterine contractions, which may delay or prolong the labour. Therefore, the use of lornoxicam is contraindicated during the third trimester of pregnancy (see section 4.3).

Lactation
There are no data on the excretion of lornoxicam in human breast milk. Lornoxicam is excreted in milk of lactating rats in relatively high concentrations. Therefore lornoxicam should not be used in breastfeeding women.

4.7 Effects on ability to drive and use machines
Patients showing dizziness and/or sleepiness under treatment with lornoxicam should refrain from driving or operation machinery.

4.8 Undesirable effects
The most commonly observed adverse events of NSAIDs are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration of NSAIDs. Less frequently, gastritis has been observed.

Approximately 20% of patients treated with lornoxicam can be expected to experience adverse reactions. The most frequent adverse effects of lornoxicam include nausea, dyspepsia, indigestion, abdominal pain, vomiting, and diarrhoea. These symptoms have generally occurred in less than 10% of patients in available studies.

Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Listed below are undesirable effects which generally occurred in more than 0.05% of the 6.417 patients treated in clinical phase II, III and IV trials.

Very common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1000, <1/100); rare (≥1/10.000, <1/1.000); Very rare (<1/10.000).

Infections and infestations
Rare: Pharyngitis.

Blood and the lymphatic system disorders
Rare: Anaemia, thrombocytopenia, leukopenia, prolonged bleeding time
Very rare: Ecchymosis.

Immune system disorders
Rare: Hypersensitivity.

Metabolism and nutritional disorders
Uncommon: Anorexia, weight changes.

Psychiatric disorders
Uncommon: Insomnia, depression.
Rare: Confusion, nervousness, agitation.

Nervous system disorders
Common: Mild and transient headache, dizziness.

Rare: Somnolence, paraesthesia, dysgeusia, tremor, migraine.

Eye disorders
Uncommon: Conjuctivitis
Rare: Visual disturbances.

Ear and labyrinth disorders
Uncommon: Vertigo, tinnitus.

Cardiac disorders
Uncommon: Palpitations, tachycardia, oedema, cardiac failure.

Vascular disorders
Uncommon: Flushing, oedema.
Rare: Hypertension, hot flush, haemorrhage, haematoma.

Respiratory, thoracic and mediastinal disorders
Uncommon: Rhinitis.
Rare: Dyspnoea, cough, bronchospasm.

Gastrointestinal disorders
Common: Nausea, abdominal pain, dyspepsia, diarrhoea, vomiting.
Uncommon: Constipation, flatulence, eructation, dry mouth, gastritis, gastric ulcer, abdominal pain upper, duodenal ulcer, mouth ulceration.
Rare: Melaena, haematemesis, stomatitis, oesophagitis, gastrooesophageal reflux, dysphagia, aphthous stomatitis, glossitis, perforated peptic ulcer.

Hepatobiliary disorders
Uncommon: Increase in liver function tests, SGPT (ALT) or SGOT (AST).
Rare: Hepatic function abnormal.
Very rare: Hepatocellular damage.

Skin and subcutaneous tissue disorders
Uncommon: Rash, pruritus, hyperhidrosis, rash erythematous, urticaria, alopecia.
Rare: Dermatitis, purpura.
Very rare: Oedema and bullous reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders
Uncommon: Arthralgia.
Rare: Bone pain, muscle spasms, myalgia.

Renal and urinary disorders
Rare: Nocturia, micturition disorders, increase in blood urea nitrogen and creatinine levels.

General disorders and administrative site conditions
Uncommon: Malaise, face oedema.
Rare: Asthenia.

4.9 Overdose
At this time, there is no experience of overdose to permit definition of the consequence of an overdose, or to suggest specific managements. However, it can be expected that after an overdose with lornoxicam, the following symptoms can be seen: Nausea, vomiting, cerebral symptoms (dizziness, disturbances in vision). Severe symptoms are ataxia ascending to coma and cramps, liver and kidney damages and maybe coagulation disorders.

In the case of a real or suspected overdose, the medication should be withdrawn. Due to its short half-life, lornoxicam is rapidly excreted. Lornoxicam is not dialysable. No specific antidote is known to date. Gastrointestinal disorders can for example be treated with a prostaglandin analogue or ranitidine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinflammatory and antirheumatic products, non-steroids, oxicams
ATC code: M01 AC05

Lornoxicam is a non steroidal anti-inflammatory drug with analgesic properties and belongs to the class of oxicams. Lornoxicams mode of action is mainly related to the inhibition of the prostaglandin synthesis (inhibition of the cyclooxygenase enzyme) leading to desensitisation of peripheral nociceptors and consequently inhibition of inflammation. A central effect on nociception which seems to be independent of anti-inflammatory effects has also been suggested.

Lornoxicam has no effect on vital signs (e.g. body temperature, respiratory rate, heart rate, blood pressure, ECG, spirometry).

The analgesic properties of lornoxicam have been demonstrated successfully in several clinical trials during development of the drug.

Due to a local gastrointestinal irritation and a systemic ulcerogenic effect related to the inhibition of prostaglandin (PG)-synthesis, gastrointestinal sequela are common side effects after treatment with lornoxicam as seen with other NSAIDs.

5.2 Pharmacokinetic properties

Absorption
Lornoxicam 8 mg powder for injection is intended for intravenous (IV) as well as intramuscular (IM) administration. After IM injection, maximum plasma concentrations are achieved after approximately 0.4 hours. The absolute bioavailability (calculated on AUC) after IM administration is 97 %

Distribution
Lornoxicam is found in the plasma in unchanged form and as its hydroxylated metabolite. The plasma protein binding of lornoxicam is 99 % and not concentration dependent.

Biotransformation
Lornoxicam is extensively metabolised in the liver, primarily to the inactive 5–hydroxylornoxicam by hydroxylation. CYP2C9 is involved in this biotransformation of lornoxicam. Due to genetic polymorphism, slow and extensive metabolisers exist for this enzyme which could result in markedly increased plasma levels of lornoxicam in slow metabolisers. The hydroxylated metabolite exhibits no pharmacological activity. Lornoxicam is metabolised completely, and approximately 2/3 is eliminated via the liver and 1/3 via the kidneys as inactive substance.

When tested in animal models, lornoxicam did not induce liver enzymes. From clinical trial data there is no evidence of accumulation of lornoxicam after repeated administrations, when given according to recommended dosage. This finding was supported by drug monitoring data from one year studies.

Elimination
The mean elimination half-life of the parent compound is 3 to 4 hours. After oral administration about 50% is excreted in the faeces and 42% through the kidneys, mainly as 5-hydroxylornoxicam. The elimination half-life of 5-hydroxylornoxicam is about 9 hours after a parenteral single or twice daily dose.

In elderly patients above age 65, the clearance is reduced with 30-40%. Apart from reduced clearance, there is no significant change in the kinetic profile of lornoxicam in elderly patients.

There is no significant change in the kinetic profile of lornoxicam in patients with renal or hepatic failure, except for accumulation in patients with chronic liver disease after 7 days of treatment with daily doses of 12 and 16 mg.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Lornoxicam caused renal toxicity and gastrointestinal ulceration single- and repeat-dose toxicity studies in several species.

In animals, administration of prostaglandin synthesis inhibitor has been shown to result in increased pre- and post- implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

In rat, lornoxicam impaired fertility (effects on ovulation and implantation), and affected the pregnancy and delivery. In rabbit and rat, lornoxicam caused premature closure of the ductus arteriosus due to inhibition of cyclooxygenase.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Mannitol
Trometamol
Disodium edetate

Solvent:
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf life

3 years
Reconstituted solution: Chemical and physical in-use stability has been demonstrated for 24 hours at 21°C (±2°C).
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use is the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C. Keep vial in the outer carton.
For storage conditions of the reconstituted medicinal product, see section 6.3

6.5 Nature and contents of container

1 set contains:
Powder for injection, 8 mg: Amber glass (class I) vial (4R/8R) with rubber stopper, sealed with aluminium snap-off closure.
Water for injection, 2 ml: Clear glass ampoule

Pack sizes: 1, 5, 6, 10 sets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The solution for injection is prepared by dissolving the content of one vial in water for injection from the accompanying ampoule, immediately prior to use. The appearance of the product after reconstitution is a yellow, clear liquid.

If visible signs of deterioration are seen in the medicinal product, the product must be disposed of in accordance with local requirements

Lornoxicam has shown compatibility with 0.9% NaCl, 5% dextrose (glucose) and Ringer's solution.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Xefo and associated names (see Annex I) 4 mg film-coated tablets
[See Annex I - To be completed nationally]

Lornoxicam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One film-coated tablet contains 4 mg lornoxicam

3. LIST OF EXCIPIENTS

Lactose monohydrate
For other excipients, see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets
20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON FOR TABLET CONTAINER AND LABEL OF TABLET CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Xefo and associated names (see Annex I) 4 mg film-coated tablets
[See Annex I - To be completed nationally]

Lornoxicam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One film-coated tablet contains 4 mg lornoxicam

3. LIST OF EXCIPIENTS

Lactose monohydrate
For other excipients, see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

250 film-coated tablets
500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Xefo and associated names (see Annex I) 4 mg film-coated tablets
[See Annex I - To be completed nationally]

Lornoxicam

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name}

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Xefo and associated names (see Annex I) 8 mg film-coated tablets
[See Annex I – to be completed nationally]

Lornoxicam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One film-coated tablet contains 8 mg lornoxicam

3. LIST OF EXCIPIENTS

Lactose monohydrate
For other excipients, see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets
20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON FOR TABLET CONTAINER AND LABEL OF TABLET CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Xefo and associated names (see Annex I) 8 mg film-coated tablets
[See Annex I – to be completed nationally]

Lornoxicam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One film-coated tablet contains 8 mg lornoxicam

3. LIST OF EXCIPIENTS

Lactose monohydrate
For other excipients, see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

250 film-coated tablets
500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Xefo and associated names (see Annex I) 8 mg film-coated tablets
[See Annex I – to be completed nationally]

Lornoxicam

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name}

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Xefo Rapid and associated names (see Annex I) 8 mg film-coated tablets
[See Annex I – to be completed nationally]

Lornoxicam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One film-coated tablet contains 8 mg lornoxicam.

3. LIST OF EXCIPIENTS

For excipients, see package leaflet

4. PHARMACEUTICAL FORM AND CONTENTS

6 film-coated tablets
10 film-coated tablets
20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
100 film-coated tablets
250 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]
[See Annex I – to be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Xefo Rapid and associated names (see Annex I) 8 mg film-coated tablets
[See Annex I – to be completed nationally]

Lornoxicam

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name}

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Xefo and associated names (see Annex I) 8 mg powder and solvent for solution for injection
[See Annex I – To be competed nationally]

Lornoxicam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 8 mg lornoxicam.

Reconstituted solution: One ml contains 4 mg lornoxicam

3. LIST OF EXCIPIENTS

Powder:
Mannitol, Trometamol, Disodium edetate

Solvent:
Water for injection

4. PHARMACEUTICAL FORM AND CONTENTS

1 set contains:
One vial powder for solution for injection
One ampoule solvent for solution for injection

Pack sizes: 1, 5, 6, 10 sets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular or intravenous use
Dissolve lornoxicam 8 mg powder for solution for injection with the accompanying 2 ml solvent for solution for injection before i.v. or i.m. injection. The reconstituted product is a yellow, clear liquid.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Keep vial in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]
[See Annex I – To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

GLASS VIAL FOR LORNOXICAM POWDER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Xefo and associated names (see Annex I) 8 mg powder for solution for injection
[See Annex I – To be completed nationally]

Lornoxicam

i.v.
i.m.

2. METHOD OF ADMINISTRATION

The powder must be dissolved in the accompanying solvent before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

8 mg

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

AMPOULE FOR SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for solution for injection
Water for injections

i.v.
i.m.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Xefo and associated names (see Annex I) 4 mg film-coated tablets
[See Annex I - To be completed nationally]

Lornoxicam

Read all of this leaflet carefully before you start taking 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 gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT XEFO IS AND WHAT IT IS USED FOR

Xefo is a non-steroidal anti-inflammatory drug and antirheumatic drug (NSAID) of the oxicam class. It is intended for short term relief of acute mild to moderate pain and symptomatic relief of pain and inflammation in rheumatoid arthritis and osteoarthritis.

2. BEFORE YOU TAKE XEFO

Do not take Xefo
- if you are allergic (hypersensitive) to lornoxicam or any of the other ingredients of Xefo 4 mg film-coated tablets.
- if you suffer from thrombocytopenia
- if you are hypersensitive to other NSAIDs including acetylsalicylic acid
- if you suffer from severe heart failure.
- if you suffer from gastro-intestinal bleeding, cerebrovascular bleeding or other bleeding disorders
- if you have a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- if you suffer from an active or have a history of recurrent peptic ulcer
- if you suffer from severe liver impairment
- if you suffer form severe renal impairment
- if you are in the last three months of your pregnancy.

Take special care with Xefo
- if you have impaired renal function
- if you have a history of hypertension and/or heart failure as fluid retention and oedema
- if you suffer from ulcerative colitis or Crohn's disease
- if you have a history of bleeding tendency

If you suffer from blood coagulation disorder, impaired liver function, such as liver cirrhosis, are elderly or you will be treated with Xefo for more than 3 months, your doctor may monitor you by laboratory test on a frequent basis.

If you are going to be treated with heparin or tacrolimus concomitantly with Xefo, please inform your doctor about your current medicine.

Xefo should not be used concomitantly with other NSAIDs such as acetylsalicylic acid, ibuprofen and COX-2 inhibitors. Ask your doctor or pharmacist if you ar uncertain.

If you experience any unusual abdominal symptoms such as abdominal bleeding, skin reactions such as skin rash, mucosal lesions or other signs of hypersensitivity, you should stop taking Xefo and contact you doctor immediately.

Medicines such as Xefo may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke. Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose of duration of treatment.

If you have heart problems, previous stroke or think that you might be at risk of theese conditions (for example if you have high blood pressure, diabetes or high cholesterol or are a smoker) you should discuss your treatment with your doctor or pharmacist.

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

Xefo may interfere with other medicines.
Particular care should be taken if you are receiving any of the following substances:
- Cimetidine
- Anticoagulantia as heparin, phenprocoumon
- Corticosteroids
- Methotrexate
- Lithium
- Immunosuppressive agents as ciclosporine, tacrolimus
- Heart medicine as digoxin, ACE-inhibitors, beta-adrenergic blockers
- Diuretics
- Quinolone antibiotics
- Anti-platelet agents
- NSAIDs as ibuprofen, acetylsalicylic acids
- SSRI
- Sulphonylureas
- Inducer and inhibitors of CYP2C9-isoenzymes

Taking Xefo with food and drink
Xefo film-coated tablets are supplied for oral use and should be taken before meals with a sufficient quantity of liquid.

Concomitant intake of food may reduce the uptake of the medicinal product

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.
Xefo should not be taken during the first six months of pregnancy and by breast-feeding women. You must not take Xefo during the last three months of your pregnancy.

The use of Xefo may impair fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of Xefo should be considered.

Driving and using machines
Xefo has no or negligible influence on the ability to drive or use machinery.

Important information about some of the ingredients of Xefo
Xefo 4 mg tablets contain lactose monohydrate.
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking the medicinal product

3. HOW TO TAKE XEFO

Always take Xefo exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
Adults: The usual dose is 8-16 mg divided into 2 or 3 doses. The maximum recommended dose is 16 mg daily.

Xefo tablets must be swallowed with sufficient fluid. The tablets should be taken before meals.

Xefo is not recommended for use in children and adolescents below age 18 due to lack of data

If you take more Xefo than you should
Please contact your doctor or the pharmacist if you have taken more Xefo than prescribed.

In case of an overdose the following symptoms may be expected: Nausea, vomiting, cerebral symptoms (dizziness, disturbances in vision).

If you forget to take Xefo
Do not take a double dose to make up for a forgotten tablet.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Xefo can cause side effects, although not everybody gets them.
Medicines such as Xefo may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke.

The most common side effects of Xefo include nausea, dyspepsia, indigestion, abdominal pain, vomiting, and diarrhoea.

Common (less than 1 in 10, but more than 1 in 100 patients treated)
Mild and transient headache, dizziness, nausea, abdominal pain, dyspepsia, diarrhoea, vomiting.

Uncommon (less than 1 in 100, but more than 1 in 1000 patients treated)
Anorexia, insomnia, depression, conjunctivitis, vertigo, tinnitus, palpitations, tachycardia, flushing, constipation, flatulence, eructation, dry mouth, gastritis, gastric ulcer, abdominal pain upper, duodenal ulcer, mouth ulceration, increase in liver function tests, SGPT (ALT) or SGOT (AST), rash, pruritus, hyperhidrosis, rash erythematous, urticaria, alopecia, arthralgia, rheumatoid arthritis, osteoarthritis, malaise, face oedema, weight changes, oedema, rhinitis.

Rare (less than 1 in 1000, but more than 1 in 10.000 patents treated)
Pharyngitis, anaemia, thrombocytopenia, leucopoenia, hypersensitivity, confusion, nervousness, agitation, somnolence, paraesthesia, dysgeusia, tremor, migraine, visual disturbances, hypertension, hot flush, haemorrhage, haematoma, dyspnoea, cough, melaena, haematemesis, stomatitis, oesophagitis, gastrooesophageal reflux, dysphagia, aphthous stomatitis, glossitis, hepatic function abnormal, dermatitis, bone pain, muscle spasms, myalgia, nocturia, micturition disorders, asthenia, prolonged bleeding time, pupura, bronchospasm, increase in blood urea nitrogen and creatinine levels, perforated peptic ulcer

Very rare (less than 1 in 10.000 patients treated)
Hepatocellular damage, ecchymosis, oedema and bullous reactions, Stevens-Johnson syndrome, Toxic epidermal necrolysis.

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

5. HOW TO STORE XEFO

Keep out of the reach and sight of children.
Blister: Do not store above 30 °C
Tablet container: This medicinal product does not require any special storage conditions
Do not use Xefo after the expiry date which is stated on the carton.

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 Xefo contains
- The active substance is lornoxicam.
- One film-coated tablet contains 4 mg lornoxicam
- The other ingredients are:
  Core: Lactose monohydrate, Cellulose, microcrystalline, Povidone, Croscarmellose sodium, Magnesium stearate
  Film: Macrogol, Titanium dioxide (E171), Talc, Hypromellose

What Xefo looks like and contents of the pack
Xefo 4 mg film-coated tablet is a white to yellowish oblong film-coated tablet with imprint “L04”.

Xefo is distributed in pack sizes of 10, 20, 30, 50, 100, 250 and 500 film-coated tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[See Annex I – To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]

PACKAGE LEAFLET: INFORMATION FOR THE USER

Xefo and associated names (see Annex I) 8 mg film-coated tablets
[see Annex I – To be completed nationally]

Lornoxicam

Read all of this leaflet carefully before you start taking 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 gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT XEFO IS AND WHAT IT IS USED FOR

Xefo is a non-steroidal anti-inflammatory drug and antirheumatic drug (NSAID) of the oxicam class. It is intended for short term treatmet of acute mild to moderate pain and symptoms of rheumatoid arthritis and osteoarthritis such as pain and inflammation of joints.

2. BEFORE YOU TAKE XEFO

Do not take Xefo
- if you are allergic (hypersensitive) to lornoxicam or any of the other ingredients of Xefo 8 mg film-coated tablets.
- if you suffer from thrombocytopenia
- if you are hypersensitive to other NSAIDs including acetylsalicylic acid
- if you suffer from severe heart failure
- if you suffer from gastro-intestinal bleeding, cerebrovascular bleeding or other bleeding disorders
- if you have a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- if you suffer from an active or have a history of recurrent peptic ulcer
- if you suffer from severe liver impairment
- if you suffer form severe renal impairment
- if you are in the last three months of your pregnancy

Take special care with Xefo
- if you have impaired renal function
- if you have a history of hypertension and/or heart failure as fluid retention and oedema
- if you suffer from ulcerative colitis or Crohn's disease
- if you have a history of bleeding tendency

If you suffer from blood coagulation disorder, impaired liver function, are elderly or you will be treated with Xefo for more than 3 months, your doctor may have to monitor you by laboratory test on a frequent basis.

If you are going to be treated with heparin or tacrolimus concomitantly with Xefo, please inform your doctor about your current medicine.

Xefo should not be used concomitantly with other NSAIDs such as acetylsalicylic acid, ibuprofen and COX-2 inhibitors. Ask your doctor or pharmacist if you ar uncertain.

If you experience any unusual abdominal symptoms such as abdominal bleeding, skin reactions such as skin rash, mucosal lesions or other signs of hypersensitivity, you should stop taking Xefo and contact you doctor immediately.

Medicines such as Xefo may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke. Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose of duration of treatment.

If you have heart problems, previous stroke or think that you might be at risk of theese conditions (for example if you have high blood pressure, diabetes or high cholesterol or are a smoker) you should discuss your treatment with your doctor or pharmacist.

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

Xefo may interfere with other medicines.
Particular care should be taken if you are receiving any of the following substances:
- Cimetidine
- Anticoagulantia as heparin, phenprocoumon
- Corticosteroids
- Methotrexate
- Lithium
- Immunosuppresive agents as ciclosporine, tacrolimus
- Heart medicine as digoxin, ACE-inhibitors, beta-adrenergic blockers
- Diuretics
- Quinolone antibiotics
- Anti-platelet agents
- NSAIDs as ibuprofen, acetylsalicylic acids
- SSRI
- Sulphonylureas
- Inducer and inhibitors of CYP2C9-isoenzymes

Taking Xefo with food and drink
Xefo film-coated tablets are supplied for oral use and should be taken before meals with a sufficient quantity of liquid.

Concomitant intake of food may reduce the uptake of the medicinal product

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.
Xefo should not be taken during the first six months of pregnancy and by breast-feeding women. You must not take Xefo during the last three months of your pregnancy.

The use of Xefo may impair fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of Xefo should be considered.

Driving and using machines
Xefo has no or negligible influence on the ability to drive or use machinery.

Important information about some of the ingredients of Xefo
Xefo 8 mg tablets contain lactose monohydrate.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking the medicinal product

3. HOW TO TAKE XEFO

Always take Xefo exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
Adults: The usual dose is 8-16 mg divided Into 2 or 3 doses. The maximum recommended doses is 16 mg daily.
Xefo tablets must be swallowed with sufficient fluid. The tablets should be taken before meals.

Xefo is not recommended for use in children and adolescents below age 18 due to lack of data.

If you take more Xefo than you should
Please contact your doctor or the pharmacist if you have taken more Xefo than prescribed.

In case of an overdose the following symptoms may be expected: Nausea, vomiting, cerebral symptoms (dizziness, disturbances in vision).

If you forget to take Xefo
Do not take a double dose to make up for a forgotten tablet.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Xefo can cause side effects, although not everybody gets them.
Medicines such as Xefo may be associated with a small increased risk of heart attack (“myocardial infarction”) or stroke.

The most common side effects of Xefo include nausea, dyspepsia, indigestion, abdominal pain, vomiting, and diarrhoea.

Common (less than 1 in 10, but more than 1 in 100 patients treated)
Mild and transient headache, dizziness, nausea, abdominal pain, dyspepsia, diarrhoea, vomiting.

Uncommon (less than 1 in 100, but more than 1 in 1000 patients treated)
Anorexia, insomnia, depression, conjunctivitis, vertigo, tinnitus, palpitations, tachycardia, flushing, constipation, flatulence, eructation, dry mouth, gastritis, gastric ulcer, abdominal pain upper, duodenal ulcer, mouth ulceration, increase in liver function tests, SGPT (ALT) or SGOT (AST), rash, pruritus, hyperhidrosis, rash erythematous, urticaria, alopecia, arthralgia, rheumatoid arthritis, osteoarthritis, malaise, face oedema, weight changes, oedema, rhinitis.

Rare (less than 1 in 1000, but more than 1 in 10.000 patents treated)
Pharyngitis, anaemia, thrombocytopenia, leucopoenia, hypersensitivity, confusion, nervousness, agitation, somnolence, paraesthesia, dysgeusia, tremor, migraine, visual disturbances, hypertension, hot flush, haemorrhage, haematoma, dyspnoea, cough, melaena, haematemesis, stomatitis, oesophagitis, gastrooesophageal reflux, dysphagia, aphthous stomatitis, glossitis, hepatic function abnormal, dermatitis, bone pain, muscle spasms, myalgia, nocturia, micturition disorders, asthenia, prolonged bleeding time, purpura, bronchospasm, increase in blood urea nitrogen and creatinine levels, perforated peptic ulcer

Very rare (less than 1 in 10.000 patients treated)
Hepatocellular damage, ecchymosis, oedema and bullous reactions, Stevens-Johnson syndrome, Toxic epidermal necrolysis.

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

5. HOW TO STORE XEFO

Keep out of the reach and sight of children.
This medicinal product does not require any special storage conditions.

Do not use Xefo after the expiry date which is stated on the carton.

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 Xefo contains

- The active substance is lornoxicam.
- One film-coated tablet contain 8 mg lornoxicam
- The other ingredients are:
  Core: Lactose monohydrate, Cellulose, microcrystalline, Povidone, Croscarmellose sodium, Magnesium stearate
  Film: Macrogol, Titanium dioxide (E171), Talc, Hypromellose

What Xefo looks like and contents of the pack
Xefo 8 mg film-coated tablet is a white to yellowish oblong film-coated tablet with imprint “L08”.

Xefo is distributed in pack sizes of 10, 20, 30, 50, 100, 250 and 500 film-coated tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[See Annex I – To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]

PACKAGE LEAFLET: INFORMATION FOR THE USER

Xefo Rapid and associated names (see Annex I) 8 mg film-coated tablets
[see Annex I – to be completed nationally]

Lornoxicam

Read all of this leaflet carefully before you start taking 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 gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT XEFO RAPID IS AND WHAT IT IS USED FOR

Xefo Rapid is a non-steroidal anti-inflammatory drug and antirheumatic drug (NSAID) of the oxicam class. It is intended for short term treatment of acute mild to moderate pain

2. BEFORE YOU TAKE XEFO RAPID

Do not take xefo Rapid
- if you are allergic (hypersensitive) to Xefo or any of the other ingredients of Xefo 8 mg film-coated tablets.
- if you suffer from thrombocytopenia
- if you are hypersensitive to other NSAIDs including acetylsalicylic acid
- if you suffer from severe heart failure.
- if you suffer from gastro-intestinal bleeding, cerebrovascular bleeding or other bleeding disorders
- if you have a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- if you suffer from an active or have a history of recurrent peptic ulcer
- if you suffer from severe liver impairment
- if you suffer form severe renal impairment
- if you are in the last three months of your pregnancy.

Take special care with Xefo Rapid
- if you have impaired renal function
- if you have a history of hypertension and⁄or heart failure as fluid retention and oedema
- if you suffer from ulcerative colitis or Crohn’s disease
- if you have a history of bleeding tendency

If you suffer from blood coagulation disorder, impaired liver function, are elderly or you will be treated with Xefo Rapid for more than 3 months, your doctor may monitor you by laboratory test on a frequent basis.

If you are going to be treated with heparin or tacrolimus concomitantly with Xefo Rapid, please inform your doctor about your current medicine.

Xefo Rapid should not be used concomitantly with other NSAIDs such as acetylsalicylic acid, ibuprofen and COX-2 inhibitors. Ask your doctor or pharmacist if you ar uncertain.

If you experience any unusual abdominal symptoms such as abdominal bleeding, skin reactions such as skin rash, mucosal lesions or other signs of hypersensitivity, you should stop taking Xefo Rapid and contact you doctor immediately.

Medicines such as Xefo may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke. Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose of duration of treatment.

If you have heart problems, previous stroke or think that you might be at risk of theese conditions (for example if you have high blood pressure, diabetes or high cholesterol or are a smoker) you should discuss your treatment with your doctor or pharmacist.

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

Xefo Rapid may interfere with other medicines.
Particular care should be taken if you are receiving any of the following substances:
- Cimetidine
- Anticoagulantia as heparin, phenprocoumon
- Corticosteroids
- Methotrexate
- Lithium
- Immunosuppressive agents as ciclosporine, tacrolimus
- Heart medicine as digoxin, ACE-inhibitors, beta-adrenergic blockers
- Diuretics
- Quinolone antibiotics
- Anti-platelet agents
- NSAIDs as ibuprofen, acetylsalicylic acids
- SSRI
- Sulphonylureas
- Inducer and inhibitors of CYP2C9-isoenzymes

Taking Xefo Rapid with food and drink
Xefo Rapid film-coated tablets are supplied for oral use and should be taken before meals with a glass quantity of liquid.

Concomitant intake of food may reduce the uptake of the medicinal product.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.
Xefo Rapid should not be taken during the first six months of pregnancy and by breast-feeding women. You must not take Xefo during the last three months of your pregnancy.

The use of Xefo may impair fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of Xefo should be considered.

Driving and using machines
Xefo Rapid has no or negligible influence on the ability to drive or use machinery.

3. HOW TO TAKE XEFO RAPID

Always take Xefo Rapid exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
Adults: The usual dose is 8-16 mg divided in doses of 8 mg twice daily. An initial dose of 16 mg followed by 8 mg 12 hours later can be given on the first treatment day. After the first treatment day the maximum recommended daily dose is 16 mg.

Xefo Rapid tablets must be swallowed with sufficient fluid. The tablets should be taken before meals.

Xefo Rapid is not recommended for use in children and adolescents below age 18 due to lack of data

If you take more Xefo Rapid than you should
Please contact your doctor or the pharmacist if you have taken more Xefo Rapid than prescribed.

In case of an overdose the following symptoms may be expected: Nausea, vomiting, cerebral symptoms (dizziness, disturbances in vision).

If you forget to take Xefo Rapid
Do not take a double dose to make up for a forgotten tablet.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Xefo Rapid can cause side effects, although not everybody gets them.
Medicines such as xefo may be associated with a small increased risk of heart attack (“myocardial infarction”) or stroke.

The most common side effects of Xefo include nausea, dyspepsia, indigestion, abdominal pain, vomiting, and diarrhoea.

Common (less than 1 in 10, but more than 1 in 100 patients treated)
Mild and transient headache, dizziness, nausea, abdominal pain, dyspepsia, diarrhoea, vomiting.

Uncommon (less than 1 in 100, but more than 1 in 1000 patients treated)
Anorexia, insomnia, depression, conjunctivitis, vertigo, tinnitus, palpitations, tachycardia, flushing, constipation, flatulence, eructation, dry mouth, gastritis, gastric ulcer, abdominal pain upper, duodenal ulcer, mouth ulceration, increase in liver function tests, SGPT (ALT) or SGOT (AST), rash, pruritus, hyperhidrosis, rash erythematous, urticaria, alopecia, arthralgia, rheumatoid arthritis, osteoarthritis, malaise, face oedema, weight changes, oedema, rhinitis.

Rare (less than 1 in 1000, but more than 1 in 10.000 patents treated)
Pharyngitis, anaemia, thrombocytopenia, leukopenia, hypersensitivity, confusion, nervousness, agitation, somnolence, paraesthesia, dysgeusia, tremor, migraine, visual disturbances, hypertension, hot flush, haemorrhage, haematoma, dyspnoea, cough, melaena, haematemesis, stomatitis, oesophagitis, gastrooesophageal reflux, dysphagia, aphthous stomatitis, glossitis, hepatic function abnormal, dermatitis, bone pain, muscle spasms, myalgia, nocturia, micturition disorders, asthenia, prolonged bleeding time, purpura, bronchospasm, increase in blood urea nitrogen and creatinine levels, perforated peptic ulcer

Very rare (less than 1 in 10.000 patients treated)
Hepatocellular damage, ecchymosis, oedema and bullous reactions, Stevens-Johnson syndrome, Toxic epidermal necrolysis.

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

5. HOW TO STORE XEFO RAPID

Keep out of the reach and sight of children.
Do not store above 30°C.
Do not use Xefo Rapid after the expiry date which is stated on the carton.

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 Xefo Rapid contains
- The active substance is lornoxicam.
- One film-coated tablet contains 8 mg lornoxicam
- The other ingredients are:
  Core: Cellulose, microcrystalline, Sodium hydrogen carbonate, Calcium hydrogen phosphate, anhydrous, Low substituted hydroxypropylcellulose, Hydroxypropylcellulose, Calcium stearate
  Film: Titanium dioxide (E171), Talc, Propylen glycol, Hypromellose.

What Xefo Rapid looks like and contents of the pack
Xefo Rapid 8 mg film-coated tablet is a white to yellowish round biconvex film-coated tablet.

Xefo Rapid is distributed in pack sizes of 6, 10, 20, 30, 50, 100 and 250 film-coated tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]

This leaflet was last approved in {MM/YYYY}.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Xefo and associated names (see Annex I) 8 mg powder and solvent for solution for injection
[See Annex I – To be completed nationally]

Lornoxicam

Read all of this leaflet carefully before you start taking 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 gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT XEFO IS AND WHAT IT IS USED FOR

Xefo is a non-steroidal anti-inflammatory drug and antirheumatic drug (NSAID) of the oxicam class. It is intended for treatment of acute mild to moderate pain when oral administration is inappropriate

2. BEFORE YOU TAKE XEFO

Do not take Xefo
- if you are allergic (hypersensitive) to Xefo or any of the other ingredients of Xefo powder and solvent for solution for injection
- if you suffer from thrombocytopenia
- if you are hypersensitive to other NSAIDs including acetylsalicylic acid
- if you suffer from severe heart failure.
- if you suffer from gastro-intestinal bleeding, cerebrovascular bleeding or other bleeding disorders
- if you have a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- if you suffer from an active or have a history of recurrent peptic ulcer
- if you suffer from severe liver impairment
- if you suffer form severe renal impairment
- if you are in the last three months of your pregnancy

Take special care with Xefo
- if you have impaired renal function
- if you have a history of hypertension and⁄or heart failure as fluid retention and oedema
- if you suffer from ulcerative colitis or Crohn’s disease
- if you have a history of bleeding tendency

If you suffer from blood coagulation disorder, impaired liver function, such as liver cirrhosis are elderly or you will be treated with Xefo for more than 3 months, your doctor may monitor you by laboratory test on a frequent basis.

If you are going to be treated with heparin or tacrolimus concomitantly with Xefo, please inform your doctor about your current medicine.
Xefo should not be used concomitantly with other NSAIDs such as acetylsalicylic acid, ibuprofen and COX-2 inhibitors. Ask your doctor or pharmacist if you ar uncertain.

If you experience any unusual abdominal symptoms such as abdominal bleeding, skin reactions such as skin rash, mucosal lesions or other signs of hypersensitivity, you should stop taking Xefo and contact you doctor immediately.

Medicines such as Xefo may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke. Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose of duration of treatment.

If you have heart problems, previous stroke or think that you might be at risk of theese conditions (for example if you have high blood pressure, diabetes or high cholesterol or are a smoker) you should discuss your treatment with your doctor or pharmacist.

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

Xefo may interfere with other medicines.
Particular care should be taken if you are receiving any of the following substances:
- Cimetidine
- Anticoagulantia as heparin, phenprocoumon
- Corticosteroids
- Methotrexate
- Lithium
- Immunosuppressive agents as ciclosporine, tacrolimus
- Heart medicine as digoxin, ACE-inhibitors, beta-adrenergic blockers
- Diuretics
- Quinolone antibiotics
- Anti-platelet agents
- NSAIDs as ibuprofen, acetylsalicylic acids
- SSRI
- Sulphonylureas
- Inducer and inhibitors of CYP2C9-isoenzymes

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.
Xefo should not be taken during the first six months of pregnancy and by breast-feeding women. You must not take Xefo during the last three months of your pregnancy.

The use of Xefo may impair fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of Xefo should be considered.

Driving and using machines
Xefo has no or negligible influence on the ability to drive or use machinery.

3. HOW TO TAKE XEFO

Always take Xefo exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Adults: The recommended dose is 8 mg i.v. or i.m. The maximum daily dose should not exceed 16 mg. Some patients may need further 8 mg within the first day of treatment
Xefo 8 mg powder for solution for injection must be dissolved with the accompanying 2 ml solvent for solution for injection before use

Xefo 4 mg/ml solution for injection is intended for intramuscular (i.m.) or intravenous (i.v.) injection. The injection should be administered slowly over not less than 15 seconds as an i.v. injection, and over not less than 5 seconds as i.m. injection.

Unless compatibility is proven, Xefo 4 mg/ml solution for injection should always be administered separately.

If you take more Xefo than you should
Please contact your doctor or the pharmacist if you have received more Xefo than prescribed.

In case of an overdose the following symptoms may be expected: Nausea, vomiting, cerebral symptoms (dizziness, disturbances in vision).

If you forget to take Xefo
Do not take a double dose to make up for a forgotten Dose.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Xefo can cause side effects, although not everybody gets them.
Medicines such as Xefo may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke.

The most common side effects of Xefo include nausea, dyspepsia, indigestion, abdominal pain, vomiting, and diarrhoea.

Common (less than 1 in 10, but more than 1 in 100 patients treated)
Mild and transient headache, dizziness, nausea, abdominal pain, dyspepsia, diarrhoea, vomiting.

Uncommon (less than 1 in 100, but more than 1 in 1000 patients treated)
Anorexia, insomnia, depression, conjunctivitis, vertigo, tinnitus, palpitations, tachycardia, flushing, constipation, flatulence, eructation, dry mouth, gastritis, gastric ulcer, abdominal pain upper, duodenal ulcer, mouth ulceration, increase in liver function tests, SGPT (ALT) or SGOT (AST), rash, pruritus, hyperhidrosis, rash erythematous, urticaria, alopecia, arthralgia, rheumatoid arthritis, osteoarthritis, malaise, face oedema, weight changes, oedema, rhinitis.

Rare (less than 1 in 1000, but more than 1 in 10.000 patents treated)
Pharyngitis, anaemia, thrombocytopenia, leukopenia, hypersensitivity, confusion, nervousness, agitation, somnolence, paraesthesia, dysgeusia, tremor, migraine, visual disturbances, hypertension, hot flush, haemorrhage, haematoma, dyspnoea, cough, melaena, haematemesis, stomatitis, oesophagitis, gastrooesophageal reflux, dysphagia, aphthous stomatitis, glossitis, hepatic function abnormal, dermatitis, bone pain, muscle spasms, myalgia, nocturia, micturition disorders, asthenia, prolonged bleeding time, purpura, bronchospasm, increase in blood urea nitrogen and creatinine levels, perforated peptic ulcer

Very rare (less than 1 in 10.000 patients treated)
Hepatocellular damage, ecchymosis, oedema and bullous reactions, Stevens-Johnson syndrome, Toxic epidermal necrolysis.

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

5. HOW TO STORE XEFO

Keep out of the reach and sight of children.
Do not store above 25°C.
Keep the vial in the outer carton

Shelf life after reconstitution: 24 hours at 21°C (±2 °C)

If visible signs of deterioration are seen in the medicinal product, the product must be disposed of in accordance with local requirements

The chemical and physical in-use stability has been demonstrated for 24 hours at 21 °C (±2°C). From a microbiological point of view, the product should be used immediately. If the solution is not used immediately, in-use storage times and conditions prior to use is the responsibility of the user and would not be longer than 24 hours at 2-8 °C taken place in controlled and validated aseptic condition.

Do not use Xefo after the expiry date which is stated on the carton

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 Xefo 4 mg/ml solution for injection contains
The vial:
- The active substance is lornoxicam.
- One vial with powder contains 8 mg lornoxicam
- Reconstituted solution: One ml contains 4 mg lornoxicam
- The other ingredients are mannitol, trometamol, disodium edetate.

The ampoule:
- The solvent contains water for injection.

What Xefo looks like and contents of the pack
The powder is a yellow, solid substance and the solvent a clear liquid.
After reconstitution the solution for injection is a yellow, clear liquid.

Xefo is distributed as set containing 1 vial of powder for solution for injection and 1 ampoule of solvent for solution for injection.
The pack sizes are 1, 5, 6 and 10 sets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax>}
<{e-mail}>

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]

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The following information is intended for medical or healthcare professionals only

Xefo 8 mg powder and solvent for solution for injection:

- The active substance is lornoxicam
  One vial with powder contains 8 mg lornoxicam
  Reconstituted solution: One ml contains 4 mg lornoxicam
- The other ingredients are mannitol, trometamol, disodium edetate.
  Solvent:
  One ampoule contains 2 ml water for injection

Instruction for use and handling

Xefo 4 mg/ml solution for injection is prepared by dissolving the powder in the vial with the 2 ml solvent in the ampoule, immediately prior to use.
The appearance of the solution after reconstitution is a yellow, clear liquid.

After preparation of the solution, change the needle.
For i.m. injection use sufficiently long needle for a deep intramuscular injection.

Compatibilities

Xefo 4 mg/ml solution for injection is compatible with:
Ringer's solution
0.9% sodium chloride solution
5% dextrose (glucose) solutions