Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ticinan 60 mg prolonged release tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains 60 mg morphine hydrochloride trihydrochlroide equivalent to 45.6 mg morphine.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablet.

Yellow tablets, round and biconvex.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the prolonged relief of severe and most severe pain (such as cancer pain), resistant to lower level analgesics.

4.2 Posology and method of adminstration

The prolonged release tablets should be swallowed completely with some liquid.

Ticinan prolonged release tablets must not be divided or dissolved before administration. Dissolving or parting of the Ticinan prolonged release tablets will damage the prolonged release system and lead to rapid release of morphine which may entail substantial side effects.

The treatment is initiated by titration with an immediate release morphine formulation (tablets or mixture) to a morphine dose which gives adequate pain control. Thereafter, the patient is transferred to the same daily dose of Ticinan prolonged release tablets. Breakthrough pain should be treated with immediate release morphine.

Ticinan prolonged release tablets should be used at 12-hourly intervals. The dosage is dependent upon the severity of the pain, the patient’s age and previous history of analgesic requirements.

For adults and adolescents from the age of 12 years:

A patient presenting with severe pain should normally be started on 10-30 mg morphine hydrochloride 12-hourly, patients with low body-weight (weighing less than 70 kg) requiring a small starting dose.

Caution should be exercised and the initial dose should be reduced in elderly patients and patients with impaired hepatic or renal function.

Increasing severity of pain will require an increased dosage of morphine. The correct dosage for any individual patient is that which is sufficient to control pain with no, or tolerable, side effects for a full 12 hours.

Generally a 200 mg tablet is intended for relief of, in particular, cancer pain in patients who tolerate morphine and

require a daily dose of morphine more than 200 mg.

Patients receiving Ticinan prolonged release tablets in place of parenteral morphine should be treated cautiously, based on individually different sensitivity, that means that the dose requirement per day should not be overestimated.

Children:

For administration of Ticinan prolonged release tablets in children younger than 12 years of age no sufficiently documented experience is available.

4.3 Contraindications

Known hypersensitivity to morphine or to excipients of Ticinan prolonged release tablets. Respiratory depression, mucus secretion stagnation, obstructive airways disease, convulsive disorders, head injury, paralytic ileus, “acute abdomen”, delayed gastric emptying, acute hepatic disease, concurrent administration of monoamine oxidase inhibitors or within two weeks of discontinuation of their use. Agitation states in patients affected by alcohol or hypnotics.

Ticinan prolonged release tablets are not recommended during pregnancy or labour or for pre-operative use or for the first 24 hours post operative.

4.4 Special warnings and special precautions for use

Use with caution in opiate dependent patients and in patients with raised intracranial pressure, hypotension with hypovolaemia, disorders of consciousness, diseases of the biliary tract, biliary or ureteric colic, pancreatitis, obstructive and inflammatory bowel disorders, prostatic hypertrophy and adrenocortical insufficiency.

Pre-operative administration of Ticinan prolonged release tablets is not recommended.

The effects of morphine have led to its abuse, and dependence may develop with regular, inappropriate use. Duly administration in patients with chronic pain significantly reduces the risk of physical and psychic addiction, and it is not a major concern in the treatment of patients with severe pain. There is cross-tolerance with other opioids.

Should paralytic ileus be suspected or occur during use, Ticinan prolonged release tablets should be discontinued immediately.

A reduction in dosage may be advisable in the elderly, in hypothyroidism and in patients with significantly impaired renal or hepatic function.

It should be emphasized that patients, once titrated to an effective dose of a certain opioid drug, should not be changed to other slow, prolonged or controlled release morphine or other narcotic analgesic preparations without retitration and clinical assessment.

Otherwise a continuing analgesic action is not ensured.

Chronic use of opioid analgesics may be associated with the development of physical dependence. A withdrawal syndrome may be precipitated when opioid administration is suddenly discontinued or opioid antagonists are administered.

Ticinan 60 mg prolonged release tablets contain the azo colouring agent E 110 which can cause allergic reactions including asthma.

4.5 Interaction with other medicinal products and other forms of interaction

Morphine potentiates the effects of tranquillisers, anaesthetics, hypnotics, sedatives, alcohol, muscle relaxants and antihypertensives. Concurrent administration of antacids may result in a more rapid release of morphine than otherwise

expected; dosing should therefore be separated by a minimum of two hours. Cimetidine inhibits the metabolism of morphine. Monoamine oxidase inhibitors are known to interact with narcotic analgesics producing CNS excitation or depression with hyper- or hypotensive crisis.

Rifampicin induces the metabolism of orally administered morphine to a high degree and therefore higher doses may be needed.

Clomipramine and amitriptyline increase the analgesic effects of morphine, which may partly be due to an increased bioavailability.

Combination with morphine agonists/antagonists (buprenorphine, nalbuphine, pentazocine) is contraindicated because there is reduction of the analgesic effect by competitive blocking of the receptors, with a risk of occurrence of a withdrawal syndrome.

4.6 Pregnancy and lactation

Morphine must not be used during pregnancy because animal experiments indicated damage to offspring and morphine is not recommended during labour due to the risk of neonatal respiratory depression. Administration to breast-feeding mothers is not recommended as morphine is excreted in breast milk. Withdrawal symptoms may be observed in the newborn of mothers undergoing chronic treatment.

4.7 Effects on ability to drive and use machines

Morphine may change attention and ability to react such that the competence to participate actively on traffic or operate machines is impaired or not provided anymore. This has to be expected especially at the beginning of treatment, at any change of dosage as well as in connection with alcohol or tranquillisers.

4.8 Undesirable effects

Common: Miosis, nausea, vomiting, constipation and drowsiness.

Uncommon: Dry mouth, sweating, vertigo, headache, disorientation, facial flushing, mood changes, palpitations, hallucinations, respiratory depression, bronchospasm, colic, urinary retention and biliary or ureteric spasm.

Rare: Blurred vision, nystagmus, diplopia, peripheral edema (reversible after stopping the treatment), insomnia, anaphylactic and anaphylactoid reactions, reductions and increases in blood pressure and heart rate, chill, general asthenia up to syncope and heart failure, asthma attacks in susceptible patients. Morphine has histamine releasing effects which may be responsible in part for reactions such as urticaria and pruritus.

If nausea and vomiting occur with Ticinan prolonged release tablets, the tablets can be combined with an antiemetic if required. Constipation may be treated with appropriate laxatives.

In individual cases non-cardiogenic lung oedema has been observed in patients under intensive care.

4.9 Overdose

Signs of morphine toxicity and overdosage are pin-point pupils, respiratory depression and hypotension. Circulatory failure and deepening coma may occur in more severe cases. In addition tachycardia, vertigo, dropping of body temperature, relaxation of skeletal muscles; in children general convulsions were observed.

Treatment of morphine overdosage:

Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation.

In the case of massive overdosage the intravenous administration of naloxone is recommended. The infusion should be run at a rate related to the previous bolus doses administered and should be in accordance with the patient's response. However, because the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Ticinan prolonged release tablets will continue to release and add to the morphine load for up to 12 hours after administration and the management of morphine overdosage should be modified accordingly.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdosage. Naloxone should be administered cautiously to persons who are known, or suspected, to be physically dependent on morphine. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug, particularly when a modified release formulation has been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: NO2A

Morphine acts as an agonist at opiate receptors in the CNS particularly μ and to a lesser extent κ receptors. μ receptors are thought to mediate supraspinal analgesia, respiratory depression and euphoria, and κ receptors spinal analgesia, miosis and sedation. Morphine also has a direct action on the bowel wall nerve plexuses causing constipation.

In elderly patients, the analgesic effect of morphine is increased.

Other effects of morphine on the central nervous system are nausea, vomiting and release of antidiuretic hormone.

The respiratory depressive effect of morphine can lead to respiratory insufficiency in patients with decreased ventilation capacity due to pulmonary disease or due to effects of other drugs.

The effects of morphine may be increased in patients with encephalitis.

5.2 Pharmacokinetic properties

Oral morphine is well absorbed and undergoes extensive and variable first-pass metabolism in the liver.

The bioavailability of morphine is 30%, with a range between 10% and 50%. The bioavailability may increase in patients with liver cancer. Morphine has dose-linear pharmacokinetics.

In Ticinan tablets morphine hydrochloride is present as a prolonged release formulation, which extends the dosaging interval up to 12 hours, whereas non-prolonged release formulations have a dosing interval of 4-6 hours.

Under fed conditions Tmax increases after application of Ticinan prolonged release tablets from 2.4 (fasted) to 3.4 hours. A large amount metabolises to glucuronides, which undergo enterohepatic recirculation.

The excretion of morphine of which 90% is excreted as metabolites (morphine-3-glucuronide and morphine-6-glucuronide) is for the most part renal and only to small extent biliary. Morphine-6-glucuronide is more active than the parent compound. Morphine passes the placental barrier and enters breast-milk.

5.3 Preclinical safety data

Experimental studies have shown that morphine sulphate induces chromosome damage in animals in somatic and germ

cells and in human somatic cells. A genotoxic potential for humans may be expected. Long-term animal studies on the carcinogenic potential of morphine have not been conducted. Several studies show that morphine can enhance tumor growth.

In animal studies morphine showed a teratogenic potential and neurobehavioural deficiencies in the developing organism, while data in humans do not show evidence of malformations or fetotoxic effects of morphine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Polyacrylate dispersion 30%
Methacrylic acid-ethyl acrylate copolymer (1:1)
Ammonio methacrylate copolymer type B
Hypromellose 4000
Magnesium stearate
Macrogol 6000
Talc
Titanium dioxide (E171)
Hypromellose 5
Silicon antifoaming agent SE2 MC
Colouring agents Quinoline yellow E104/Sunset yellow FeF E110

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Pack type: Blister (PVC and aluminium foil)

Pack size: Boxboard cartons of 10, 14, 20, 30, 50, 56, 60, 100 and 100 x 1 pieces.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Lannacher Heilmittel Ges.m.b.H
8502 Lannach
Austria

8 MARKETING AUTHORISATION NUMBER

PA 947/1/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st January 2000

Date of last renewal: 28th July 2003

10 DATE OF REVISION OF THE TEXT

March 2004