SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Filnarine SR 30 mg prolonged release film coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release tablet contains:
30 mg morphine sulphate corresponding to 22.5 mg morphine

Each prolonged release tablet contains:
87.74 mg lactose monohydrate and 0.001 mg Ponceau 4R (E124)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablet.
Greyish blue film-coated tablets with inscription “30”

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of severe pain, particularly cancer pain and post-operative pain.

4.2 Posology and method of administration

The prolonged release film-coated tablets are for oral use. They should be swallowed completely with some liquid. Filnarine SR prolonged release tablets

must not be divided or dissolved before administration. Dissolving or parting the Filnarine SR prolonged release tablets will damage the sustained release system and lead to rapid release of morphine which may entail substantial undesirable effects.
The treatment is initiated by titration with an immediate release morphine formulation to a morphine dose which gives adequate pain control. Thereafter, the patient is transferred to the same daily dose of Filnarine SR prolonged release tablets. Breakthrough pain should be treated with immediate release morphine.

Filnarine SR 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 after initiated treatment with an immediate release morphine formulation:
A patient presenting with severe pain should normally be started on 10-30 mg morphine sulphate 12-hourly, patients with low body-weight requiring a small starting dose.

Patient presenting with severe pain, uncontrolled by weaker opioids (e.g. dihydrocodeine), should normally be started on 30 mg morphine sulphate 12-hourly, patients with low body-weight requiring a small starting dose. However, a starting dose as low as 10 mg bd may be appropriate for the elderly who may be susceptible to morphine and patients with low body-weight requiring a small starting dose, in hypothyroidism and in patients with significantly impaired renal or hepatic function. (See section 4.4 and 5.2).

Increasing severity of pain will require an increased dosage of morphine. An incremental increase of 30%-50% in the daily dose may be appropriate. The correct dosage for any individual patient is that which is sufficient to control pain with no, or tolerable, undesirable effects for a full 12 hours.

Patients receiving Filnarine SR 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. As a result of the replacement, there may be a reduction in the analgesic effect. Normally a dose increase is required of the order of 100% of the parenteral morphine dose.
It should be emphasised that patients, once titrated to an effective dose of a certain opioid drug, should not be changed to other slow, sustained or controlled release morphine or other narcotic analgesic preparations without retitration and clinical assessment. Otherwise a continuing analgesic action is not ensured.

Children:
6 years and older: A starting dosage in the range of 0.2 mg – 0.8 mg morphine/kg 12-hourly with dose titration as for adults is recommended.

If it is not possible to give the recommended dosage with this formulation (prolonged release tablet) another pharmaceutical form should be chosen.

Special patient populations:
A reduction in dosage may be advisable in elderly, in hypothyroidism, and in patients with significantly impaired renal or hepatic function (see section 5.2).

Post operative pain:
Filnarine SR prolonged release tablets are not recommended in the first 24 hours post operatively or until normal bowel function has returned. Thereafter it is suggested that the following dosage schedule be observed at the physician's discretion:
- 20 mg 12 hourly to patients under 70 kg
- 30 mg 12 hourly to patients over 70 kg
– in elderly patients a reduction in dosage may be advisable
- use in children is not recommended

4.3 Contraindications

- Hypersensitivity to morphine or to any of the excipients.
- Children under 6 years of age, because swallowing tablets as a whole requires oro-pharyngeal control.
- Respiratory depression
- Airway obstruction caused by mucus
- Obstructive airways disease
- Convulsive disorders
- Head injury
- Raised intracranial pressure
- Paralytic ileus
- "Acute abdomen"
- Delayed gastric emptying
- Acute hepatic disease
- Post-operative after biliary surgery
- 24 hours before cordotomy
- Concurrent administration of monoamine oxidase inhibitors or within two weeks of discontinuation of their use.
- Concomitant use of morphine agonists/antagonists (see section 4.5)
- Agitation states in patients affected by alcohol or hypnotics.

4.4. Special warnings and precautions for use

Filnarine SR Prolonged Release Film-coated Tablets should be used with caution in opiate-dependent patients and in patients with hypotension with hypovolaemia, disorders of consciousness, diseases of the biliary tract, biliary or urinary colic, pancreatitis, obstructive and inflammatory bowel disorders, prostatic hypertrophy and adrenocortical insufficiency.

Pre-operative administration of Filnarine SR Prolonged Release Film-coated Tablets is not recommended.

The effects of morphine have led to its abuse and dependence may develop with regular, inappropriate use. Physical and psychic dependence may develop after administration of therapeutic doses for 1-2 weeks. Daily 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. Isolated cases of dependence have been reported even after 2-3 days of therapy. The risk may be reduced by observing an exact timetable of administration. Abrupt withdrawal after long term treatment with morphine may lead to a withdrawal syndrome within a few hours. This syndrome usually reaches its maximum 36 to 72 hours after withdrawal.
There is cross-tolerance with other opioids.
Should paralytic ileus be suspected or occur during use, Filnarine SR Prolonged Release Film-coated Tablets should be discontinued immediately.
As with all morphine preparations, Filnarine SR Prolonged Release Film-coated Tablets should be used with caution post-operatively and following abdominal surgery as morphine impairs intestinal motility and should not be used until the physician is assured of normal bowel function.

Concomitant use of alcohol and morphine sulphate prolonged release tablets may increase the undesirable effects of morphine; concomitant use should be avoided, since it may result in the rapid release and absorption of a potentially fatal dose of morphine. Additionally, patients must not use prescription or non-prescription medications containing alcohol while on morphine sulphate therapy.

A reduction in dosage may be advisable in the elderly, in hypothyroidism and in patients with significantly impaired renal or hepatic function (see section 5.2).

The Filnarine SR Prolonged Release Film-coated Tablets contain lactose monohydrate. They should not be administered to patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

Morphine potentiates the effect of tranquillisers, anaesthetics, hypnotics, sedatives, alcohol, muscle relaxants and antihypertensives. Alcohol may enhance the pharmacodynamic effects of Filnarine SR Prolonged Release Film-Coated Tablets; concomitant use should be avoided, since it may result in the rapid release and absorption of a potentially fatal dose of morphine.
Cimetidine inhibits the metabolism of morphine. The clinical relevance of the interaction is unknown.
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. An adjustment of the dose may be necessary.

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 (see section 4.3).

4.6 Pregnancy and lactation

Morphine is not recommended during pregnancy because animal experiments indicated damage to offspring and morphine is not recommended during labour due to the risk of neonatal respiratory depression. Morphine sulphate should be used during pregnancy only when the potential benefits justify the possible risks to the foetus. Administration to breast-feeding mothers is not recommended as morphine is excreted in breast milk. Withdrawal symptoms may be observed in the new born infant of mothers undergoing chronic treatment.

4.7 Effects on ability to drive and use machines

Morphine has major influence on the ability to drive and use machines. Morphine may reduce attention and reaction time. This should be anticipated particularly at the beginning of treatment, when dosage is increased or when associated with concomitant alcohol or other sedative medicines.

4.8. Undesirable Effects

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1000 to < 1/100)
Rare (≥ 1/10000 to < 1/1000)
Very rare (< 1/10000), not known (cannot be estimated from the available data)

	Very common (≥ 1/10)	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥ 1/10000 to < 1/1000)**	**Very rare (< 1/10000)**
Immune system disorders				Anaphylactic and anaphylactoid	

				reactions, uticaria and pruritus	
Psychiatric disorders			Agitation, disorientation, sedation, mood changes and hallucinations		
Nervous system disorders		Drowsiness	Vertigo and headache	Insomnia and raised intracranial pressure	
Eye disorders		Miosis		Blurred vision	
Cardiac disorders			Palpitations	Bradycardia, tachycardia	
Vascular disorders				Reductions in blood pressure	
Respiratory, thoracic and mediastinal disorders			Respiratory depression and broncospasm	Asthma attacks in susceptible patients	
Gastrointestinal disorders		Nausea vomiting and constipation	Colic, dry mouth		
Skin and subcutaneous tissue disorders			Sweating and facial flushing	Chill	
Renal and urinary disorders			Colic, urinary retention and biliary or ureteric spasm		
General disorders and administration site conditions				General asthenia up to syncope	

4.9 Overdose

Signs of morphine toxicity and overdose 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 overdose:
Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation.
In the case of massive overdose the intravenous administration of naloxone is recommended. Intravenous administration of 0,4-0,8 mg naloxone is recommended. Administration should be repeated at 2 to 3 minute intervals as necessary, or by infusion of 2 mg in 500 ml of sodium chloride 0.9 mg/ml (0.9%) solution or 0.004 mg/ml glucose (5%). The infusion should be run at a rate related to the previous bolus dose 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. Filnarine SR 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 overdose should be modified accordingly.
Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose. 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 active substance, particularly when a modified release formulation has been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioids, natural opium alkaloids

ATC-code: NO2AA01

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

5.2 Pharmacokinetic properties

The maximum peak concentration is reached approximately 2 hours after dosing. After oral administration morphine is subject to a high and variable first-pass metabolism. The bioavailability of morphine is 30%, with a range between 10 and 50%. The bioavailability of morphine may be increased in patients with liver cancer. When the prolonged release tablets were taken with food, t_{max} of morphine was not changed. C_{max} of morphine was slightly raised after the prolonged release tablets were taken with food (from 9,73 to 10,0 ng/ml).

Morphine is eliminated mainly by metabolism. In the liver morphine is metabolised to the inactive morphine-3-glucuronide and to the active morphine-6-glucuronide. This metabolite is more potent than morphine itself.

The metabolites are mainly excreted in the urine (90% in 24 hours). Morphine and its metabolites are recirculated interohepatically. About 7-10% is excreted through the bile in the faeces. The half-life is about 3 hours. Circa 20-30% of morphine is bound to plasma proteins.

The volume of distribution is 1-3,8 l/kg. The pharmacokinetics of morphine is independent of dose. The plasma levels of the active morphine-6-glucuronide may be markedly increased in patients with decreased renal function.

Morphine-6-glucuronide passes the blood-brain barrier.

Morphine passes the placenta and is excreted into breastmilk.

5.3 Preclinical safety data

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

Tablet core:
Hypromellose

Stearic acid
Magnesium stearate
Colloidal anhydrous silica
Lactose monohydrate

Tablet coating:
Hypromellose
Macrogol 400
Titanium dioxide (E171)
Ferric oxide yellow (E172)
Ferric oxide brown (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Keep blister card in the outer cartoon in order to protect from light.

6.5 Nature and contents of container

PVC/PVDC/Al blisters containing 7 and 10 prolonged release film-coated tablets.

Pack sizes:
Blisters of 10, 14, 20, 28, 30, 50, 56, 60 or 100 prolonged release film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

TEVA UK Limited
Brampton Road, Hampden Park
Eastbourne, East Sussex, BN22 9AG

8 MARKETING AUTHORISATION NUMBER(S)

PL 0289/0383

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 June 2001/18 January 2007

10 DATE OF REVISION OF THE TEXT

26/10/2012