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## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Vendal retard 10 mg film-coated tablets  
Vendal retard 30 mg film-coated tablets  
Vendal retard 60 mg film-coated tablets  
Vendal retard 100 mg film-coated tablets  
Vendal retard 200 mg film-coated tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

10 mg: 1 tablet contains 10 mg morphine hydrochloride trihydrate equivalent to 7.59 mg morphine.  
30 mg: 1 tablet contains 30 mg morphine hydrochloride trihydrate equivalent to 22.78 mg morphine.  
60 mg: 1 tablet contains 60 mg morphine hydrochloride trihydrate equivalent to 45.55 mg morphine.  
100 mg: 1 tablet contains 100 mg morphine hydrochloride trihydrate equivalent to 75.92 mg morphine.  
200 mg: 1 tablet contains 200 mg morphine hydrochloride trihydrate equivalent to 151.84 mg morphine.

Excipients with known effect:

10 mg: Lactose monohydrate ..... 8 mg per tablet.  
30 mg: Lactose monohydrate ..... 24.74 mg per tablet.  
60 mg: Lactose monohydrate ..... 49.48 mg per tablet.  
Colouring agent Sunset yellow (E 110) ..... 0.00128 mg per tablet.  
100 mg: Lactose monohydrate ..... 82.20 mg per tablet.  
Colouring agent Sunset yellow (E 110) ..... 0.0332 mg per tablet.  
200 mg: Lactose monohydrate ..... 164.40 mg per tablet.  
Colouring agent Ponceau 4R (E 124) ..... 0.0225 mg per tablet.  
Colouring agent Sunset yellow (E 110) ..... 0.01375 mg per tablet.

For the full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Prolonged-release film-coated tablet.

10 mg: White round and biconvex tablets  
30 mg: Blue to green round and biconvex tablets  
60 mg: Yellow round and biconvex tablets  
100 mg: Yellow to orange round and biconvex tablets  
200 mg: Red round and biconvex tablets

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

For the prolonged relief of severe and most severe pain (such as cancer pain) that is resistant to other analgesics.

### **4.2 Posology and method of administration**

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

Vendal retard prolonged-release tablets should be used at 12-hour intervals. The dose has to be adjusted according to the severity of the pain, the patient's age and previous history of analgesic requirements.

#### **Posology**

##### ***Paediatric population***

Vendal retard prolonged-release tablets are not recommended for the use in children below 12 years due to insufficient data on safety and efficacy.

The use of morphine is contraindicated in children below 1 year.

##### ***Adults and adolescents >12 years***

In patients with severe pain the usual initial dose is 10-30 mg morphine hydrochloride at 12-hour intervals. Patients with low body weight (less than 70 kg) require a lower starting dose. Caution should be exercised and the initial dose should be reduced in elderly patients and patients with impaired hepatic or renal function.

Increased intensity of pain requires an increased dose of morphine. The correct dose for every patient is a dose that is sufficient to control pain with no or tolerable side effects for 12 hours.

Usually, Vendal retard 200 mg prolonged-release tablets are intended for the relief of particularly cancer pain in patients who tolerate morphine and require a daily morphine dose of more than 200 mg.

Patients receiving Vendal retard 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.

#### **Method of administration**

The tablets should be swallowed as a whole with a sufficient amount of liquid.

Vendal retard prolonged-release tablets must not be divided or dissolved before administration. Dissolving or dividing of the tablets will damage the prolonged-release system, leading to a rapid release of morphine which may cause substantial side effects.

### **4.3 Contraindications**

- Known hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Respiratory depression
- Impaired mucus secretion of the airways
- Obstructive airways disease

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- Convulsive disorders or head injury
  - Paralytic ileus
  - Acute abdomen or delayed gastric emptying
  - Acute hepatic disease
  - Concurrent administration of monoamine oxidase inhibitors or within two weeks of their discontinuation
  - Agitation states in patients affected by alcohol or hypnotics
  - Children < 1 year

#### 4.4 Special warnings and precautions for use

The major risk of opioid excess is respiratory depression.

Vendal retard must be used with caution in patients with

- opiate dependency
- increased intracranial pressure
- hypotension with hypovolaemia
- disorders of consciousness
- diseases of the biliary tract
- biliary or uretric colic
- pancreatitis
- obstructive and inflammatory bowel disorders
- prostatic hypertrophy
- adrenocortical insufficiency

Hyperalgesia that will not respond to a further dose increase of morphine may very rarely occur in particular in high doses. A morphine dose reduction or change in opioid may be required.

##### ***Abuse potential:***

The effects of morphine may lead to 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 therefore not a major concern in the treatment of patients with severe pain. There is cross-tolerance with other opioids.

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.

The film-coated tablets must not be dissolved and must not be given parenteral. This may lead to respiratory depression, necrosis of local tissue and to granulomatous inflammation of organs (esp. lungs).

##### ***Not recommended use:***

Concomitant use of alcohol and Vendal retard may increase the undesirable effects of Vendal retard; concomitant use should be avoided.

Because of its mutagenic properties, men and women of procreative or child-bearing age should receive morphine, only if the use of effective contraceptive measures is ensured (see sections 4.6 and 5.3).

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

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

***Dose titration:***

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

Patients 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.

***Doping tests:***

Vendal retard prolonged-release tablets may produce positive results in doping controls.

***Excipients:***

This medicine contains lactose.

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

Vendal retard 60 mg and 100 mg prolonged-release tablets contain the colouring agent Sunset Yellow (E 110) which can cause allergic reactions including asthma.

Vendal retard 200 mg prolonged-release tablets contain the colouring agents Sunset Yellow (E 110) and Ponceau 4R (E 124) which can cause allergic reactions including asthma.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Alcohol may enhance the pharmacodynamic effects of Vendal retard prolonged-release tablets; concomitant use should be avoided.

***The CNS depressant effects, e.g. sedation and respiratory depression, of***

- anaesthetics
- tranquilisers, hypnotics and sedatives
- neuroleptics
- antidepressants
- antiemetics
- antihistamines
- other opioids or

**may be enhanced by Vendal retard prolonged-release tablets.**

***Vendal retard prolonged-release tablets enhance the effects of***

- anaesthetics,
- tranquilizers, hypnotics, sedatives,
- muscle relaxants and
- antihypertensives.

In case of possible misuse, patients should be informed, that concomitant abuse of alcohol, and also uncontrolled combination with other centrally depressant pharmaceuticals may lead to respiratory depression with possible lethal outcome.

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### **The effects of Vendal retard prolonged-release tablets are affected by**

- antacids. The concomitant use may result in a more rapid release of morphine than otherwise expected. An at least two-hours interval is recommended between the intakes.
- cimetidine. It inhibits the metabolism of morphine and may therefore potentiate its effects.
- monoamine oxidase inhibitors. They are known to interact with narcotic analgesics producing CNS excitation or depression with hyper- or hypotensive crisis (see section 4.3).
- Rifampicin. It induces the metabolism of orally administered morphine to a high degree, and therefore higher doses may be needed.
- clomipramine and amitriptyline. They increase the analgesic effects of morphine, which may partly be due to an increased bioavailability.

The combination with morphine agonists/antagonists (buprenorphine, nalbuphine, pentazocine) is contraindicated due to the competitive receptor block leading to a reduction of the analgesic effect, with a risk of occurrence of a withdrawal syndrome.

### **4.6 Fertility, pregnancy and lactation**

#### ***Pregnancy***

There are insufficient data in humans to permit evaluation of the teratogenic risks. There have been reports of a possible connection with increased incidence of hernias. Morphine passes the placental barrier. Animal studies showed damaging potential for the offspring during the entire duration of pregnancy (see section 5.3). Morphine may therefore only be used during pregnancy, if the benefit for the mother clearly outweighs the risk for the child; other therapeutic options should be taken into account before. Because of its mutagenic properties, it is recommended that men and women of procreative or child bearing age use morphine only when the use of effective contraceptive measures is ensured.

The administration of morphine is not recommended during labour due to the risk of neonatal respiratory depression.

#### ***Breast feeding***

The administration in breast-feeding mothers is not recommended as morphine is excreted into breast milk. Withdrawal symptoms may be observed in the newborns 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. It may change attention, influence concentration and the ability to react in such manner that the ability to actively participate in traffic or to operate machines is impaired or not provided anymore.

### **4.8 Undesirable effects**

Undesirable effects are classified according to their severity and frequency:

Very common ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1\ 000$  to  $< 1/100$ )

Rare ( $\geq 1/10\ 000$  to  $< 1/1\ 000$ )

Very rare ( $< 1/10\ 000$ )

Not known (cannot be estimated from the available data).

The most common side effects are nausea, vomiting, constipation, miosis, and drowsiness.

***Psychiatric disorders***

Uncommon: hallucinations

Rare: insomnia

***Nervous system disorders***

Common: drowsiness

Uncommon: sweating, vertigo, headache, confusion, mood changes. Overdose may lead to breathing disorders

Very rare: hyperalgesia (see section 4.4)

Not known: cognitive disorders, myoclonus

***Eye disorders***

Common: miosis

Rare: blurred vision, diplopia, nystagmus

***Cardiac disorders***

Uncommon: palpitations

Rare: increased or decreased heart rate

***Vascular disorders***

Rare: increase or decrease of blood pressure

***Respiratory, thoracic and mediastinal disorders***

Uncommon: bronchospasm, respiratory depression

Rare: attacks of asthma in predisposed patients

Very rare: lung oedema has been reported from intensive care patients

***Gastrointestinal disorders***

Common: nausea, vomiting, constipation

Uncommon: gastrointestinal spasms, dry mouth

***Hepatobiliary disorders***

Uncommon: bile tract spasms

***Skin and subcutaneous tissue disorders***

Uncommon: flush

Rare: urticaria, pruritus

***Renal and urinary disorders***

Uncommon: problems passing urine, urinary tract spasms

***Reproductive system and breast disorders***

Not known: Amenorrhoea, decreased libido, erectile dysfunction

***General disorders***

Rare: peripheral oedema (reversible after stopping the treatment), hypersensitivity reactions, general asthenia up to syncope, chill

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

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### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:

Bundesamt für Sicherheit im Gesundheitswesen  
Traisengasse 5  
1200 WIEN  
ÖSTERREICH  
Fax: + 43 (0) 50 555 36207  
Website: <http://www.basg.gv.at/>

## **4.9 Overdose**

### **Symptoms**

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, decrease of body temperature, relaxation of skeletal muscles have been reported. In children general convulsions were observed.

### **Treatment**

Primary attention should be given to establishing a patent airway and 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. Vental retard prolonged-release film-coated tablets will continue to release morphine 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**

**Pharmacotherapeutic group:** Natural opium alkaloids.

**ATC-Code:** N02AA01

Morphine acts as an agonist at opiate receptors in the CNS, particularly  $\mu$  and, to a lesser extent,  $\kappa$  receptors.  $\mu$  receptors are thought to mediate supraspinal analgesia, respiratory depression and euphoria, and  $\kappa$  receptors spinal analgesia, miosis and sedation. Morphine also directly affects the nerve plexuses in the intestinal wall, 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.

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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

### ***Absorption and distribution***

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

Under fed conditions  $T_{max}$  increases from 2.4 (fasted) to 3.4 hours.

Morphine passes the placental barrier and is excreted into breast-milk.

### ***Biotransformation***

A large amount of the active substance is metabolised to glucuronides, which undergo enterohepatic recirculation.

### ***Elimination***

Morphine, 90 % of which is excreted as metabolites (morphine-3-glucuronide and morphine-6-glucuronide), is excreted mainly renal, and only to a small extent biliary. Morphine-6-glucuronide is more active than the parent compound.

## 5.3 Preclinical safety data

There are clear positive findings on mutagenicity, which indicate that morphine has a clastogenic effect and performs this effect also in germ cells. Therefore morphine is to be regarded as a mutagenic effective substance; such an effect must also be assumed in humans. Morphine should only be used with safe contraceptive measures.

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

10 mg:

Lactose monohydrate, polyacrylate dispersion 30 per cent, methacrylic acid-ethyl acrylate copolymer (1:1), ammonio methacrylate copolymer type B, hypromellose 4000, colloidal anhydrous silica, magnesium stearate, macrogol 6000, talc, titanium dioxide (E 171), hypromellose 5.

30 mg:

Lactose monohydrate, polyacrylate dispersion 30 per cent, methacrylic acid-ethyl acrylate copolymer (1:1), ammonio methacrylate copolymer type B, hypromellose 4000, magnesium



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stearate, macrogol 6000, talc, titanium dioxide (E 171), hypromellose 5, Indigo carmine aluminium lake (E 132), Quinoline yellow aluminium lake (E 104).

60 mg:

Lactose monohydrate, polyacrylate dispersion 30 per cent, methacrylic acid-ethyl acrylate copolymer (1:1), ammonio methacrylate copolymer type B, hypromellose 4000, magnesium stearate, macrogol 6000, talc, titanium dioxide (E 171), hypromellose 5, Quinoline yellow aluminium lake (E 104), Sunset yellow aluminium lake (E 110).

100 mg:

Lactose monohydrate, polyacrylate dispersion 30 per cent, methacrylic acid-ethyl acrylate copolymer (1:1), ammonio methacrylate copolymer type B, hypromellose 4000, magnesium stearate, macrogol 6000, talc, titanium dioxide (E 171), hypromellose 5, Quinoline yellow aluminium lake (E 104), Sunset yellow aluminium lake (E 110).

200 mg:

Lactose monohydrate, polyacrylate dispersion 30 per cent, methacrylic acid-ethyl acrylate copolymer (1:1), ammonio methacrylate copolymer type B, hypromellose 4000, magnesium stearate, macrogol 6000, talc, hypromellose 5, Ponceau 4 R aluminium lake (E 124), Sunset yellow aluminium lake (E 110).

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

10 mg: 3 years

30 mg, 60 mg, 100 mg, 200 mg: 5 years

## 6.4 Special precautions for storage

Do not store above 25°C.

## 6.5 Nature and contents of container

10, 14, 20, 30, 50, 60, 100, and 100x1 tablets in PCV/aluminium blisters.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

No special requirements.

Any unused product or waste should be disposed of in accordance with local requirements

## 7. MARKETING AUTHORISATION HOLDER

G.L. Pharma GmbH, 8502 Lannach

## 8. MARKETING AUTHORISATION NUMBER(S)

10 mg: 1-19834

30 mg: 1-19837

60 mg: 1-19833

100 mg: 1-19835

200 mg: 1-19836

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: November 02<sup>nd</sup>, 1992

Date of the last renewal: July 28<sup>th</sup>, 2008

**10. DATE OF REVISION OF THE TEXT**

May 2016

**PRESCRIPTION/PHARMACY ONLY**

Narcotic substance, dispensing with narcotic prescription only, available only in pharmacies