

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Amolin 100mg Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100mg atenolol.

Each tablet also contains 61.80mg lactose monohydrate

For a full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Tablet.

White, round, biconvex scored tablet with inscription on the upper side: "C25".

The scoreline allows the tablet to be divided into equal halves.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

- Management of hypertension
- Management of angina pectoris
- Management of cardiac dysrhythmias
- Myocardial infarction: early intervention in the acute phase.

### 4.2 Posology and method of administration

The dosage should be individually determined, based mainly on the pulse rate or the therapeutical effectiveness. It is advisable to start the therapy with the lowest possible dosage in order to be able to identify cardiac decompensation or bronchial phenomena at an early stage; this is especially important in the elderly. With Amolin a stepwise increase up to the fully effective dose is possible. Subsequent increases in dose should take place slowly (e.g. once a week) under control or on the basis of clinical effect.

#### Adults

##### – Hypertension:

While some patients will respond to a single daily dose of 50 mg, the usual daily dosage is 100 mg as a single dose. The effect will be fully established after one to two weeks. A further reduction in blood pressure may be achieved by combining Amolin with other antihypertensive agents, e.g. a diuretic.

##### – Angina pectoris:

The usual daily dose is 100 mg given once daily or 50 mg twice daily. It is unlikely that additional benefit will be gained by increasing the dose.

##### – Dysrhythmias:

Following control of the dysrhythmia with intravenous atenolol, a suitable oral maintenance dosage is 50 – 100 mg daily, given as a single dose.

– **Acute myocardial infarction:**

For suitable patients presenting within 12 hours of the onset of the chest pain, atenolol 5-10 mg should be given by slow intravenous injection (1mg/ml) followed by atenolol 50 mg orally about 15 minutes after the intravenous injection provided no untoward effects occur from the intravenous dose. This should be followed by 50 mg orally 12 hours after the intravenous dose and then 12 hours later by 100 mg orally to be given once daily.

Amolin 100 mg Tablets must be discontinued immediately in the event of heart rate and/or blood pressure falls or any other complications requiring therapeutic intervention.

Children:

There is no paediatric experience with atenolol and for this reason it is not recommended for use in children.

Elderly:

Dosage may need to be reduced especially in patients with impaired renal function.

Renal failure:

Patients with renal dysfunction need to have their atenolol dose adjusted to renal clearance of the drug. No significant accumulation of atenolol occurs in patients who have a creatinine clearance greater than 35 ml/min. If the creatinine clearance is decreased to 15-35 ml/min (equivalent to serum creatinine < 3-6 mg/dl) the oral dose should be 50 mg daily. For patients with a creatinine clearance < 15 ml/min (equivalent to serum creatinine > 6mg/dl) the oral dose should be 25 mg daily or 50 mg on alternate days. Patients on haemodialysis should be given 50 mg orally after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur.

Type and duration of administration

The tablets should be ingested whole with some liquid before meals.

### 4.3 Contraindications

Amolin 100 mg is contraindicated in patients with:

- Overt heart failure
- Shock
- Second and third degree AV block
- Sick sinus syndrome
- SA block
- Bradycardia (heart rate at rest < 50 beats/minute before therapy)
- Hypotension (systolic blood pressure < 90mmHg)
- Metabolic Acidosis
- Bronchial hyperreactivity (e.g. in bronchial asthma)
- Advanced stages of peripheral arterial occlusive disease
- Concurrent MAO inhibitor therapy (except MAO-B inhibitor)
- Hypersensitivity to atenolol or other beta-adrenergic receptor blocking agents

Intravenous verapamil-type or diltiazem-type calcium antagonists and other intravenous anti-arrhythmics (such as disopyramide) are contra-indicted in patients on atenolol therapy (except in an intensive care setting).

### 4.4 Special warnings and precautions for use

If Amolin 100 mg therapy is to be interrupted or discontinued after prolonged use, this should always be done by gradual downward titration, since abrupt withdrawal may give rise to myocardial ischaemia with exacerbation of

angina pectoris or to myocardial infarction, or may cause exacerbation of hypertension.

Particularly careful medical monitoring is necessary when using this medicinal product in:

- Patients with first-degree AV block
- Diabetics with highly unstable blood glucose concentrations (because of the risk of severe hypoglycemic episodes).
- Patients following an absolute diet for prolonged periods of time and those subject to great physical exertion (because of the risk of severe hypoglycaemic episodes)
- Patients with pheochromocytoma (tumour of the adrenal medulla: prior alpha-blocker therapy is indicated)
- Patients with impaired kidney function

Beta-receptor blocking drugs should be used only after carefully weighing expected benefits against potential risks in patients with a history or family history of psoriasis.

Beta receptor blocking drugs may increase susceptibility to allergens and the severity of anaphylactic reactions. Beta-receptor blocking drugs should therefore be used only if clearly needed in patients with a history of severe hypersensitivity reactions and those receiving specific hyposensitisation therapy (because of the risk of exaggerated anaphylactic reactions).

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

#### *Special Labelling Requirement:*

*Do not take this medicine without consulting your doctor if you have a history of wheezing or asthma.*

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

In case of a concomitant use of Amolin and other drugs the following interactions should be taken into consideration.

### Not recommended association

*Calcium antagonists of the verapamil or diltiazem type:*

negative influence on contractility and auriculo-ventricular conduction. Neither drug should be administered intravenously within 48 hours of discontinuing the other.

*Clonidine:*

increases the risk of "rebound hypertension".

Upon abrupt withdrawal of clonidine while Amolin is given concurrently, there may be an exaggerated increase in blood pressure. Clonidine must therefore not be discontinued unless Amolin therapy has been stopped several days previously. Only then can clonidine be withdrawn gradually.

### Precautions for use

*Class I antiarrhythmic drugs (e.g. disopyramide, quinidine) and amiodarone:*

may have potentiating effect on atrial-conduction time and induce negative inotropic effect.

*Insulin or oral antidiabetic:*

may intensify the blood sugar lowering effect. Beta-adrenergic blockade may prevent the appearance of signs of hypoglycaemia (tachycardia). Regular blood sugar determinations are therefore necessary.

*Anaesthetics, peripheral muscle relaxants:*

Anaesthetics may attenuate the reflex tachycardia and increase the risk of hypotension. Continuation of beta-blockades reduce the risk of arrhythmia during induction and intubation. Anaesthetic drugs causing myocardial depression, such as

cyclopropane and trichlorethylene, are best avoided.

Neuromuscular blockade induced by peripheral muscle relaxants (e.g. succinylcholine, tubocurarine) may be enhanced by beta-adrenergic receptor blockade of atenolol.

If atenolol cannot be discontinued before a surgical procedure under general anaesthesia or prior to the use of peripheral muscle relaxant, the anaesthetist/anaesthesiologist must be informed about atenolol therapy beforehand.

#### Take into account

*Calcium antagonist: dihydropyridine derivatives such as nifedipine:*

the risk of hypotension may be increased. In patients with latent cardiac insufficiency, treatment with beta-blocking agents may lead to cardiac failure.

*Indomethacin:*

may decrease the hypotensive effect of atenolol.

*Norepinephrine or epinephrine:*

may counteract the effect of beta-adrenergic blocking agents.

*Tricyclic antidepressants, barbiturates or phenothiazines, or diuretics, vasodilators or other antihypertensive drugs:*

may increase the blood pressure lowering effect.

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

Atenolol crosses the placental barrier and appears in the cord blood. No studies have been performed on the use of Atenolol in the first trimester and the possibility of foetal injury cannot be excluded. Atenolol has been used under close supervision for the treatment of hypertension in the third trimester. Administration of Atenolol to pregnant women in the management of mild to moderate hypertension has been associated with the intra-uterine growth retardation. The use of Atenolol in women who are, or may become, pregnant requires that the anticipated benefit be weighed against the possible risks, particularly in the first and second trimesters.

There is significant accumulation of Atenolol in breast milk.

Neonates born to mothers who are receiving Atenolol at parturition or breast-feeding may be at risk for hypoglycemia. Caution should be exercised when Atenolol is administered during pregnancy or to a woman who is breast-feeding.

## **4.7 Effects on ability to drive and use machines**

Since there are only rare reports of beta-blockers causing symptomatic hypotension and bradycardia, the use of Amolin is unlikely to result in any impairment of the ability of patients to drive or operate machinery.

## **4.8 Undesirable effects**

In this section undesirable effects are defined as follows:

Very common ( $>1/10$ ), common ( $>1/100 - <1/10$ ), uncommon ( $\geq 1/1,000 - <1/100$ ), rare ( $\geq 1/10,000 - <1/1,000$ ), very rare ( $<1/10,000$ ).

*Immune system disorders*

Common: Allergic skin reactions (erythema, pruritus, exanthema).

*Endocrine disorders*

In patients with hyperthyroidism, the clinical signs of thyrotoxicosis (e.g. tachycardia, tremor) may be masked during atenolol therapy.

*Metabolism and nutrition disorders*

Uncommon: Latent diabetes mellitus becoming manifest or manifest diabetes mellitus becoming worse.

Patients following an absolute diet for prolonged periods of time and those subject to great physical exertion may experience hypoglycaemic episodes when using atenolol at the same time. The warning signs of hypoglycaemia (tachycardia and tremor in particular) may be masked.

Atenolol therapy may be associated with lipid metabolism disruptions. While total cholesterol was usually normal, HDL cholesterol was reduced and plasma triglycerides were elevated.

*Nervous system disorders*

Common: disturbances of the central nervous system such as fatigue, dizziness, headache, visual disturbances, sweating, drowsiness, confusion, hallucinations, psychosis, nightmares or increased dream activity, sleep disturbances and depressive disorders (especially at the start of therapy); paresthesias; cold sensations in the extremities.

*Eye disorders*

Common: Conjunctivitis; reduced lacrimation (this should be borne in mind by patients wearing contact lenses).

*Cardiac and vascular disorders*

Common: Excessive hypotension, bradycardia, syncope, atrioventricular conduction disturbances or exacerbation of cardiac insufficiency.

In patients with angina pectoris, worsening of anginal attacks cannot be ruled out to occur in isolated instances.

There have been reports of worsening complaints in patients with peripheral arterial occlusive disease (including those with Raynaud's syndrome).

*Respiratory, thoracic and mediastinal disorders*

Patients with bronchospastic disease (especially those with obstructive airway disease) may experience breathlessness because this drug may increase airway resistance.

*Gastrointestinal disorders*

Common: Transient gastro-intestinal symptoms (nausea, vomiting, constipation, diarrhoea).

Uncommon: Dry mouth.

*Skin and subcutaneous tissue disorders*

Very rare (incl. Isolated reports): Beta-receptor blocking drugs may precipitate or worsen psoriasis or produce psoriasiform skin eruptions.

*Musculoskeletal and connective tissue disorders*

Uncommon: Muscle weakness, muscle cramps.

*Reproductive system and breast disorders*

Very rare (incl. isolated reports): Reduced libido, impotence.

*Precautionary notes*

As patients with pre-existing severe renal insufficiency have, in isolated instances, experienced deterioration of kidney function during treatment with other beta-receptor blocking drugs, atenolol therapy should be accompanied by appropriate kidney function monitoring.

Reports of elevated liver enzymes have been noted with the use of atenolol but they are rare. Other beta-blocking drugs have been associated with severe liver damage.

As other beta receptor blocking drugs have been associated with thrombocytopenic or non-thrombocytopenic purpura, patients on atenolol therapy should be watched for signs of purpura.

**4.9 Overdose****(a) Symptoms of an overdose**

Depending on the extent of intoxication, the clinical picture typically includes cardiovascular and CNS symptoms. Overdosage may cause hypotension, bradycardia, acute cardiac insufficiency, and cardiogenic shock. Additional signs and symptoms may include difficulty breathing, bronchospasm, vomiting, disturbed consciousness, as well as generalized convulsions in the occasional patient.

(b) Management of an overdose

In the event of an overdose or a life-threatening fall in the heart rate and/or blood pressure, Amolin 100 mg therapy must be discontinued.

Apart from general measures (primary detoxification by gastric lavage, administration of activated charcoal and a laxative), the vital signs must be monitored and, if necessary, treated in an intensive care ward.

The following agents may be useful antidotes:

- Atropine: 0.5 - 2 mg intravenously as bolus,
- Glucagon: initially 8 - 10 mg intravenously, afterwards 1 - 3 mg per hour as prolonged infusion
- $\beta$ -sympathomimetics, depending on body weight and effect: Dobutamine, isoprenaline, orciprenaline or adrenaline.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Atenolol is a hydrophilic relatively beta 1-selective (i.e., "cardioselective") beta-adrenergic receptor blocking agent without intrinsic sympathomimetic activity (ISA) and without a membrane-stabilizing effect.

Atenolol lowers the heart rate, myocardial contractility, AV conduction velocity, and plasma renin activity as a function of sympathetic tone. Atenolol may increase smooth muscle tone by inhibiting beta 2-receptors.

### 5.2 Pharmacokinetic properties

Orally administered atenolol is approx. 50% absorbed out of the gastro-intestinal tract. Because there is no "first-pass effect", the systemic availability is approx. 50% as well. A maximal plasma count is reached in 2-4 hours. The plasma protein bound fraction is approximately 3%; relative volume of distribution: 0.7 l/kg. Atenolol is metabolized in minimal amounts. No active metabolites with clinical relevance arise. Within 48 hours, approximately 90% of the systemic available atenolol is eliminated by the kidneys unchanged. The half life of the elimination is 6-10 hours. In end-stage renal failure patients, the elimination half-life may be as long as 140 hours.

#### Bioavailability

*Amolin 100 mg:*

The bioavailability ( $AUC_{0-t}$ ) of Amolin 100 mg is 92% in comparison to the reference preparation.

### 5.3 Preclinical safety data

#### Acute toxicity

See point 4.9 overdosage (symptoms, emergency measures, antidote).

#### Chronic toxicity

Rats and dogs which were given Atenolol in various dosages over longer periods of time (3-12 months) showed no significant biochemical, morphological or haematological changes. When the dosage was very high, weight gains in the heart and spleen were observed.

#### Tumorigenic and mutagenic potential

#### *Tumorigenicity:*

Long-term studies in rats and mice yielded no evidence of a tumorigenic potential of atenolol.

***Mutagenicity:***

Atenolol has not been studied extensively in mutagenicity tests. However, both in vitro and in vivo tests conducted to date have given clearly negative results.

**Reproduction toxicology**

The embryotoxic potential of Atenolol has been examined on two types of animals (rats and rabbits). Embryo absorption was observed when the doses were below the maternal toxic range. Malformations were not observed. A detrimental effect on fertility has not been determined.

**6 PHARMACEUTICAL PARTICULARS****6.1 List of excipients**

Maize starch  
Pregelatinised maize starch  
Lactose monohydrate  
Povidone  
Sodium lauril sulfate  
Colloidal anhydrous silica  
Magnesium stearate

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

5 years.

The medication should not be used after the printed expiration date.

**6.4 Special precautions for storage**

Keep in original container. Do not store above 25°C.

**6.5 Nature and contents of container**

Blister packs consisting of aluminium foil and PVC/PVDC film. Blisters are packed, along with a package leaflet, in a folded cardboard box.

Pack sizes: 20, 30, 50 and 100 tablets

Not all pack sizes may be marketed.

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

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Stada Arzneimittel AG  
Stadastraße 2-18  
D-61118 Bad Vilbel

Germany

**8 MARKETING AUTHORISATION NUMBER**

PA 593/4/3

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

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Date of last renewal: 16<sup>th</sup> May 2009

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