

KENZEM SR 60MG CAPSULES (DILTIAZEM HYDROCHLORIDE)

PL 08215/0059

KENZEM SR 90MG CAPSULES (DILTIAZEM HYDROCHLORIDE)

PL 08215/0060

KENZEM SR 120MG CAPSULES (DILTIAZEM HYDROCHLORIDE)

PL 08215/0061

UKPAR

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KENZEM SR CAPSULES (DILTIAZEM HYDROCHLORIDE)

PL 08215/0059-61

LAY SUMMARY

The MHRA granted Kent Pharmaceuticals Limited Marketing Authorisations (licences) on the 8th March 2006, for Kenzem SR 60mg, 90mg and 120mg Capsules. These Prescription Only Medicines (POM) are used to treat angina and high blood pressure.

Kenzem SR Capsules contain the active ingredient diltiazem hydrochloride, which is a calcium channel blocker, and works to relax the muscles surrounding the blood vessels, to enable the heart to work properly.

These applications are duplicates of previously granted applications for Diltiazem SR Capsules 60mg, 90mg and 120mg (PL 06934/0054-6) and, as such, these products can be used interchangeably.

No new or unexpected safety concerns arose from these simple applications and it was, therefore, judged that the benefits of taking Kenzem SR 60mg, 90mg and 120mg Capsules outweigh the risks, hence Marketing Authorisations have been granted.

KENZEM SR CAPSULES (DILTIAZEM HYDROCHLORIDE)

PL 08215/0059-61

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted marketing authorisations for the medicinal products Kenzem SR 60mg, 90mg and 120mg Capsules (PL 08215/0059, PL 08215/0060 and PL 08215/0061) to Kent Pharmaceuticals Ltd on 8 March 2006. This medicinal product is available as a Prescription Only Medicine (POM).

The applications were submitted as informed consent abridged applications according to article 10.1(a)(i) of Directive 2001/83/EC, cross-referring to Diltiazem SR Capsules 60mg, 90mg and 120mg (PL 06934/0054-6), which were granted marketing authorisations on 23 February 2001.

No new data was submitted nor was it necessary for these simple applications, as the data is identical to that of the previously granted cross-reference products. As the cross-reference products were granted prior to the introduction of current legislation, no public assessment report was generated for them.

The products contain the active ingredient diltiazem hydrochloride which is a calcium-channel blocking agent. Diltiazem Capsules are indicated for the treatment of angina pectoris and mild to moderate hypertension.

These applications for Kenzem SR 60mg, 90mg and 120mg Capsules were submitted at the same time and were assessed concurrently. Consequently, all sections of this Scientific Discussion refer to all products.

PHARMACEUTICAL ASSESSMENT

1. INTRODUCTION & BACKGROUND

These are national 'informed consent applications' (Article 10.1(a)(i) Directive 2001/83/EC) for SR capsules containing 60, 90 and 120mg, respectively of diltiazem hydrochloride, and are claimed to be identical to Diltiazem SR capsules 60mg, 90mg and 120mg PL 06934/0054-56 (trade names: Bi-Carzem SR capsules, Horizem SR capsules, Zildil SR capsules and Disogram SR capsules), which were granted to Ethypharm SA on 23 February 2001.

A letter of authorisation from Kent Pharmaceuticals Limited (giving the appropriate PL numbers) has been supplied, confirming that Athlone Laboratories Limited has been given consent to apply on their behalf.

The applicant has confirmed that they have access to Module 3 data concerning these products (letter dated 26 June 2003 from Athlone Laboratories Limited), and a letter of informed consent has been provided by Ethypharm SA dated 16 June 2003 concerning these products. Ethypharm SA, in a letter, dated 11 June 2003, also confirm their willingness to manufacture for Kent Pharmaceuticals Limited, and agree to inform them of any modifications relative to the manufacturing process.

2. COMPOSITION

The qualitative composition of the modified release capsules is listed below, and is identical to the reference products.

Name of active substances	Reference/Monograph Standard
Diltiazem Hydrochloride	EP

Name of excipient	Reference/Monograph Standard
1. Sugar Spheres	HSE
2. Povidone	EP
3. Metacrylic acid copolymer	EP
4. Ethylcellulose	EP
5. Diethyl Phthalate	EP
6. Talc	EP
7. Red iron oxide E172	None
8. Titanium dioxide E171	None
9. Yellow iron oxide E172	None
10. Hard gelatine capsule (size 3)	

METHOD OF PREPARATION

The licensing particulars are identical to the respective strengths of the reference products involving pack sizes; shelf life; storage; finished product specification; and method of manufacture.

Suitable ML certificates have been provided naming the same site(s) of manufacture and assembly, and a suitable flow-chart indicating the different sites involved in the manufacturing process has also been provided.

CONTROL OF STARTING MATERIALS

ACTIVE SUBSTANCE

An acceptable certificate of suitability has been provided for the active substance.

OTHER INGREDIENTS

The excipients meet Ph. Eur. requirements, where monographs exist, and acceptable specifications have been provided.

PACKAGING MATERIAL (IMMEDIATE PACKAGING)

The pack sizes, stated in the MAA form (56 and 100), are identical to the current PL holder.

EXPERT REPORT

The pharmaceutical expert report was compiled by a suitably qualified person and a CV has been provided.

The clinical, toxicological and pharmacological expert report was compiled by a suitably qualified person

An assurance has been provided that the applicants product will be manufactured and controlled in accordance with the reference product already licensed in the UK (PL 06934/0054-0056).

SUMMARY OF PRODUCT CHARACTERISTICS

The SPC's are consistent with those of the reference products.

PATIENT INFORMATION LEAFLET

The PIL is acceptable.

14. LABELLING

The blister foil(s) is acceptable.

15. DISCUSSION

These are simple product licence applications, which are identical to the reference products.

CONCLUSIONS

A product licence can be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.

CLINICAL ASSESSMENT

As these are duplicate applications for PL 06934/0054-56, no new clinical data have been supplied and none are required.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for these applications is consistent with that previously assessed for the cross-reference products and as such has been judged to be satisfactory.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Diltiazem hydrochloride is a well known drug and has been used as a peripheral and coronary vasodilator for many years. These applications are identical to the approved marketing authorisations for Diltiazem SR Capsules 60mg, 90mg and 120mg (PL 06934/0054-6).

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference products.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's products are identical to the cross-reference products and, as such, can be used interchangeably. Extensive clinical experience with diltiazem hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

KENZEM SR CAPSULES (DILTIAZEM HYDROCHLORIDE)

PL 08215/0059-61

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation applications on 30/06/2003.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 16/09/2003.
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 03/09/2004, 07/12/2004, 16/12/2004, 17/06/2005, 04/07/2005, 05/07/2005, 23/11/05, 10/02/2006, 17/02/2006 and 09/03/2006.
4	The applicant responded to the MHRA's requests, providing further information on 18/10/2004, 15/12/2004, 21/06/2005, 04/07/2005, 05/07/2005, 12/07/2005, 08/09/2005, 10/11/2005, 23/11/2005, 02/02/2006, 10/02/2006, 16/02/06, 17/02/2006 and 09/03/2006.
5	The application was determined on 08/03/2006.

KENZEM SR CAPSULES (DILTIAZEM HYDROCHLORIDE)

PL 08215/0059-61

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

KENZEM SR 60MG CAPSULES (DILTIAZEM HYDROCHLORIDE)

PL 08215/0059

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Kenzem SR 60mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 60mg of diltiazem hydrochloride

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Modified release capsule

4 CLINICAL PARTICULARS

4.1 *Therapeutic indications*

The treatment of angina pectoris.

The treatment of mild to moderate hypertension.

4.2 *Posology and method of administration*

The method of administration is by oral use.

Adult Dosage

For all indications the usual dose is 90mg twice daily. Depending on clinical response, the patient's dosage may be increased to 180mg twice daily if required.

Dosage in children

Not recommended

Dosage in the elderly and patients with impaired hepatic or renal function

Dosage should commence at the lower level of 60mg twice daily and be increased slowly in order to achieve the required level of control. The daily dose should not

exceed 90mg twice daily. Do not increase the dose if the heart rate falls below 50 beats per minute.

4.3 *Contraindications*

In women of child bearing potential.

Inpatients with bradycardia (less than 50 beats per minute), second or third degree heart block or sick sinus syndrome.

In patients with impaired renal function.

In patients with moderate to severe hepatic dysfunction.

In patients with cardiac failure after myocardial infarction; left ventricular failure with stasis. Concomitant administration of dantrolene infusion.

4.4 *Special warnings and precautions for use*

Rare instances of hyperglycaemia have been reported in association with diltiazem hydrochloride. The use of diltiazem hydrochloride in diabetic patients may require adjustment of their control. The product should be used with caution in patients with mild hepatic dysfunction. Cautions should be taken in patients with reduced left ventricular function. Patients should be observed closely if they have mild bradycardia, first degree atrio-ventricular block or prolonged PR interval. Do not suck or chew capsules.

This product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

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

Diltiazem hydrochloride should be administered with great care to patients receiving concurrent treatment with anti-hypertensives or other hypotensive agents or drugs with moderate protein binding. Diltiazem hydrochloride will not protect against effects of withdrawal of beta-adrenoceptor blocking agents, nor the rebound effects seen with various antihypertensives. Combination with beta- adrenoceptor blockers having significant 'first pass' loss, e.g. propranolol, may require a decrease in their dose. There may be an additive effect when used with drugs which may induce bradycardia or with other antihypertensives or other antiarrhythmic drugs; since diltiazem exerts an antiarrhythmic effect, its co-prescription with other antiarrhythmic drugs must be subjected to the highest caution and under close clinical surveillance and ECG monitoring. Diltiazem may increase the blood levels of concomitant carbamazepine, theophylline, cyclosporin and digoxin. Concomitant H₂ antagonist therapy (specifically cimetidine and, to a lesser extent, ranitidine) may increase diltiazem blood levels. Patients receiving beta blockers, diuretics, ACE inhibitors or other antihypertensive agents should be regularly monitored. Use with alpha blockers should be strictly monitored. Diltiazem hydrochloride has been continued in anaesthesia without problems, but the anaesthetist should be made aware that the patient is taking this medication because of the potential for synergism or interactions with other agents used in anaesthesia.

4.6 *Pregnancy and lactation*

Diltiazem should not be given during pregnancy and lactation. Diltiazem must not be used at any time during pregnancy as it is teratogenic in some animal species. There is no experience of its effects in humans. As diltiazem is known to readily enter the breast milk and there is no experience of possible effects in infants, infants should be weaned if treatment with diltiazem is necessary.

4.7 *Effects on ability to drive and use machines*

None known. Presumed to be safe or unlikely to produce an effect.

4.8 *Undesirable effects*

Diltiazem is generally well tolerated. Side effects include anorexia, nausea, bradycardia, rash, flushing, ankle oedema, malaise, headache, gastrointestinal disturbance, sinoatrial and atrio-ventricular block, elevation of liver transaminases. In rare cases, gingival hyperplasia, depression, insomnia, tremors and paraesthesia have been reported.

4.9 *Overdose*

Experience of overdosage in man is limited, but cases of spontaneous recovery have been reported. However, it is recommended that patients with suspected overdose should be placed under observation in a coronary care unit with facilities available for treatment of any possible hypotension and conduction disturbances that may occur.

Most patients suffering from overdosage of diltiazem become hypotensive within 8 hours of ingestion. With bradycardia and first to third degree atrioventricular block also developing, cardiac arrest may be ensue. Hyperglycaemia is also a recognised complication. The elimination half-life of diltiazem after overdosage is estimated to be about 5.5 – 10.2 hours. If a patient presents early after overdose, gastric lavage should be performed and activated charcoal administered to reduce diltiazem absorption.

Hypotension should be corrected with plasma expanders, intravenous calcium gluconate and inotropic agents (dopamine, dobutamine or isoprenaline). Symptomatic bradycardia and high grade AV block may respond to atropine, isoprenaline or occasionally cardiac pacing which may be useful if cardiac standstill occurs.

Diltiazem SR Capsules are extended release capsules and effects may be slow in onset and prolonged, therefore, monitoring should be carried out for longer periods than following overdose with immediate release dosage forms.

5 PHARMACOLOGICAL PROPERTIES

5.1 *Pharmacodynamic properties*

Diltiazem hydrochloride is a calcium-channel blocking agent. It is a peripheral and coronary vasodilator with some negative inotropic activity. Diltiazem inhibits cardiac conduction particularly at the sino-atrial and atrioventricular nodes. It is used in the management of classical and vasospastic angina pectoris and it is also used in the treatment of essential hypertension.

5.2 *Pharmacokinetic properties*

Diltiazem is rapidly and almost completely absorbed from the gastro-intestinal tract following oral administration, but undergoes extensive first-pass hepatic metabolism. The bioavailability has been reported to be about 40%, although there is considerable inter-individual variation in plasma concentrations. Diltiazem is about 80% bound to plasma proteins. It is extensively metabolised in the liver; one of the metabolites, desacetyl diltiazem has been reported to have 25 to 50% of the activity of the parent compound. The half-life is reported to be about 3 to 4 hours. Approximately 60% of the dose is excreted in the bile and 35 to 40% in the urine, and 2 to 4% as unchanged diltiazem.

The sustained-release formulation is designed for twice daily dosage.

5.3 *Preclinical safety data*

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 *List of excipients*

Sugar spheres (75% sucrose; 25% corn starch)

Povidone

Methacrylic acid copolymer

Ethylcellulose

Diethyl phthalate

Talc

Hard gelatin capsules:

- Containing E171 (Titanium dioxide), E172 (red iron oxide), E172 (yellow iron oxide)

6.2 *Incompatibilities*

No known incompatibilities.

6.3 *Shelf life*

The shelf-life of the product, as packaged for sale, is four years.

There are no recommendations for dilution or reconstitution.

There are no data available on the shelf-life of the product after first opening the container.

6.4 *Special precautions for storage*

Store below 25°C in a dry place away from heat and moisture.

6.5 *Nature and contents of container*

PVC/aluminium foil blister strips supplied in packs of 56 capsules.

High density, white polyethylene 'tablet containers' with white polypropylene screw caps containing 100 capsules.

Both containers are enclosed in outer cardboard cartons, which also contain a patient information leaflet.

6.6 *Special precautions for disposal*

No special requirements.

7 **MARKETING AUTHORISATION HOLDER**

Kent Pharmaceuticals Limited,
Wotton Road,
Ashford,
Kent TN23 6LL
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**

PL 08215/0059

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/03/2006

10 DATE OF REVISION OF THE TEXT

08/03/2006

KENZEM SR 90MG CAPSULES (DILTIAZEM HYDROCHLORIDE)

PL 08215/0060

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Kenzem SR 90mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 90mg of diltiazem hydrochloride

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Modified release capsule

4 CLINICAL PARTICULARS

4.1 *Therapeutic indications*

The treatment of agina pectoris.

The treatment of mild to moderate hypertension.

4.2 *Posology and method of administration*

The method of administration is by oral use

Adult Dosage

For all indications the usual dose is 90mg twice daily. Depending on clinical response, the patient's dosage may be increased to 180mg twice daily if required.

Dosage in children

Not recommended

Dosage in the elderly and patients with impaired hepatic or renal function

Dosage should commence at the lower level of 60mg twice daily and be increased slowly in order to achieve the required level of control. The daily dose should not exceed 90mg twice daily. Do not increase the dose if the heart rate falls below 50 beats per minute.

4.3 *Contraindications*

In women of child bearing potential.

In patients with bradycardia (less than 50 beats per minute), second or third degree heart block or sick sinus syndrome.

In patients with impaired renal function.

In patients with moderate to severe hepatic dysfunction.

In patients with cardiac failure after myocardial infarction; left ventricular failure with stasis. Concomitant administration of dantrolene infusion.

4.4 *Special warnings and precautions for use*

Rare instances of hyperglycaemia have been reported in association with diltiazem hydrochloride. The use of diltiazem hydrochloride in diabetic patients may require adjustment of their control. The product should be used with caution in patients with mild hepatic dysfunction. Cautions should be taken in patients with reduced left ventricular function. Patients should be observed closely if they have mild bradycardia, first degree atrio-ventricular block or prolonged PR interval. Do not suck or chew capsules.

This product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

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

Diltiazem hydrochloride should be administered with great care to patients receiving concurrent treatment with anti-hypertensives or other hypotensive agents or drugs with moderate protein binding. Diltiazem hydrochloride will not protect against effects of withdrawal of beta-adrenoceptor blocking agents, nor the rebound effects seen with various antihypertensives. Combination with beta- adrenoceptor blockers having significant 'first pass' loss, e.g. propranolol, may require a decrease in their dose. There may be an additive effect when used with drugs which may induce bradycardia or with other antihypertensives or other antiarrhythmic drugs; since diltiazem exerts an antiarrhythmic effect, its co-prescription with other antiarrhythmic drugs must be subjected to the highest caution and under close clinical surveillance and ECG monitoring. Diltiazem may increase the blood levels of concomitant carbamazepine, theophylline, cyclosporin and digoxin. Concomitant H₂ antagonist therapy (specifically cimetidine and, to a lesser extent, ranitidine) may increase diltiazem blood levels. Patients receiving beta blockers, diuretics, ACE inhibitors or other antihypertensive agents should be regularly monitored. Use with

alpha blockers should be strictly monitored. Diltiazem hydrochloride has been continued in anaesthesia without problems, but the anaesthetist should be made aware that the patient is taking this medication because of the potential for synergism or interactions with other agents used in anaesthesia.

4.6 *Pregnancy and lactation*

Diltiazem should not be given during pregnancy and lactation. Diltiazem must not be used at any time during pregnancy as it is teratogenic in some animal species. There is no experience of its effects in humans. As diltiazem is known to readily enter the breast milk and there is no experience of possible effects in infants, infants should be weaned if treatment with diltiazem is necessary.

4.7 *Effects on ability to drive and use machines*

None known. Presumed to be safe or unlikely to produce an effect.

4.8 *Undesirable effects*

Diltiazem is generally well tolerated. Side effects include anorexia, nausea, bradycardia, rash, flushing, ankle oedema, malaise, headache, gastrointestinal disturbance, sinoatrial and atrio-ventricular block, elevation of liver transaminases. In rare cases, gingival hyperplasia, depression, insomnia, tremors and paraesthesia have been reported.

4.9 *Overdose*

Experience of overdosage in man is limited, but cases of spontaneous recovery have been reported. However, it is recommended that patients with suspected overdose should be placed under observation in a coronary care unit with facilities available for treatment of any possible hypotension and conduction disturbances that may occur.

Most patients suffering from overdosage of diltiazem become hypotensive within 8 hours of ingestion. With bradycardia and first to third degree atrioventricular block also developing, cardiac arrest may be ensue. Hyperglycaemia is also a recognised complication. The elimination half-life of diltiazem after overdosage is estimated to be about 5.5 – 10.2 hours. If a patient presents early after overdose, gastric lavage should be performed and activated charcoal administered to reduce diltiazem absorption.

Hypotension should be corrected with plasma expanders, intravenous calcium gluconate and inotropic agents (dopamine, dobutamine or isoprenaline). Symptomatic bradycardia and high grade AV block may respond to atropine,

isoprenaline or occasionally cardiac pacing which may be useful if cardiac standstill occurs.

Diltiazem SR Capsules are extended release capsules and effects may be slow in onset and prolonged, therefore, monitoring should be carried out for longer periods than following overdose with immediate release dosage forms.

5 PHARMACOLOGICAL PROPERTIES

5.1 *Pharmacodynamic properties*

Diltiazem hydrochloride is a calcium-channel blocking agent. It is a peripheral and coronary vasodilator with some negative inotropic activity. Diltiazem inhibits cardiac conduction particularly at the sino-atrial and atrioventricular nodes. It is used in the management of classical and vasospastic angina pectoris and it is also used in the treatment of essential hypertension.

5.2 *Pharmacokinetic properties*

Diltiazem is rapidly and almost completely absorbed from the gastro-intestinal tract following oral administration, but undergoes extensive first-pass hepatic metabolism. The bioavailability has been reported to be about 40%, although there is considerable inter-individual variation in plasma concentrations. Diltiazem is about 80% bound to plasma proteins. It is extensively metabolised in the liver; one of the metabolites, desacetyl diltiazem has been reported to have 25 to 50% of the activity of the parent compound. The half-life is reported to be about 3 to 4 hours. Approximately 60% of the dose is excreted in the bile and 35 to 40% in the urine, and 2 to 4% as unchanged diltiazem.

The sustained-release formulation is designed for twice daily dosage.

5.3 *Preclinical safety data*

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 *List of excipients*

Sugar spheres (75% sucrose; 25% corn starch)
Povidone
Methacrylic acid copolymer

Ethylcellulose
Diethyl phthalate
Talc
Hard gelatin capsules:
- Containing E171 (Titanium dioxide), E172 (red iron oxide), E172 (yellow iron oxide)

6.2 *Incompatibilities*

No known incompatibilities.

6.3 *Shelf life*

The shelf-life of the product, as packaged for sale, is four years.

There are no recommendations for dilution or reconstitution.

There are no data available on the shelf-life of the product after first opening the container.

6.4 *Special precautions for storage*

Store below 25°C in a dry place away from heat and moisture.

6.5 *Nature and contents of container*

PVC/aluminium foil blister strips supplied in packs of 56 capsules.

High density, white polyethylene 'tablet containers' with white polypropylene screw caps containing 100 capsules.

Both containers are enclosed in outer cardboard cartons, which also contain a patient information leaflet.

6.6 *Special precautions for disposal*

No special requirements.

7 **MARKETING AUTHORISATION HOLDER**

Kent Pharmaceuticals Limited,
Wotton Road,
Ashford,

Kent TN23 6LL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 08215/0060

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

08/03/2006

10 DATE OF REVISION OF THE TEXT

KENZEM SR 120MG CAPSULES (DILTIAZEM HYDROCHLORIDE)

PL 08215/0061

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Kenzem SR 120mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 120mg of diltiazem hydrochloride

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Modified release capsule

4 CLINICAL PARTICULARS

4.1 *Therapeutic indications*

The treatment of agina pectoris.

The treatment of mild to moderate hypertension.

4.2 *Posology and method of administration*

The method of administration is by oral use

Adult Dosage

For all indications the usual dose is 90mg twice daily. Depending on clinical response, the patient's dosage may be increased to 180mg twice daily if required.

Dosage in children

Not recommended

Dosage in the elderly and patients with impaired hepatic or renal function

Dosage should commence at the lower level of 60mg twice daily and be increased slowly in order to achieve the required level of control. The daily dose should not exceed 90mg twice daily. Do not increase the dose if the heart rate falls below 50 beats per minute.

4.3 *Contraindications*

In women of child bearing potential.

Inpatients with bradycardia (less than 50 beats per minute), second or third degree heart block or sick sinus syndrome.

In patients with impaired renal function.

In patients with moderate to severe hepatic dysfunction.

In patients with cardiac failure after myocardial infarction; left ventricular failure with stasis. Concomitant administration of dantrolene infusion.

4.4 *Special warnings and precautions for use*

Rare instances of hyperglycaemia have been reported in association with diltiazem hydrochloride. The use of diltiazem hydrochloride in diabetic patients may require adjustment of their control. The product should be used with caution in patients with mild hepatic dysfunction. Cautions should be taken in patients with reduced left ventricular function. Patients should be observed closely if they have mild bradycardia, first degree atrio-ventricular block or prolonged PR interval. Do not suck or chew capsules.

This product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

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

Diltiazem hydrochloride should be administered with great care to patients receiving concurrent treatment with anti-hypertensives or other hypotensive agents or drugs with moderate protein binding. Diltiazem hydrochloride will not protect against effects of withdrawal of beta-adrenoceptor blocking agents, nor the rebound effects seen with various antihypertensives. Combination with beta- adrenoceptor blockers having significant 'first pass' loss, e.g. propranolol, may require a decrease in their dose. There may be an additive effect when used with drugs which may induce bradycardia or with other antihypertensives or other antiarrhythmic drugs; since diltiazem exerts an antiarrhythmic effect, its co-prescription with other antiarrhythmic drugs must be subjected to the highest caution and under close clinical surveillance and ECG monitoring. Diltiazem may increase the blood levels of concomitant carbamazepine, theophylline, cyclosporin and digoxin. Concomitant H₂ antagonist therapy (specifically cimetidine and, to a lesser extent, ranitidine) may increase diltiazem blood levels. Patients receiving beta blockers, diuretics, ACE

inhibitors or other antihypertensive agents should be regularly monitored. Use with alpha blockers should be strictly monitored. Diltiazem hydrochloride has been continued in anaesthesia without problems, but the anaesthetist should be made aware that the patient is taking this medication because of the potential for synergism to interactions with other agents used in anaesthesia.

4.6 *Pregnancy and lactation*

Diltiazem should not be given during pregnancy and lactation. Diltiazem must not be used at any time during pregnancy as it is teratogenic in some animal species. There is no experience of its effects in humans. As diltiazem is known to readily enter the breast milk and there is no experience of possible effects in infants, infants should be weaned if treatment with diltiazem is necessary.

4.7 *Effects on ability to drive and use machines*

None known. Presumed to be safe or unlikely to produce an effect.

4.8 *Undesirable effects*

Diltiazem is generally well tolerated. Side effects include anorexia, nausea, bradycardia, rash, flushing, ankle oedema, malaise, headache, gastrointestinal disturbance, sinoatrial and atrio-ventricular block, elevation of liver transaminases. In rare cases, gingival hyperplasia, depression, insomnia, tremors and paraesthesia have been reported.

4.9 *Overdose*

Experience of overdosage in man is limited, but cases of spontaneous recovery have been reported. However, it is recommended that patients with suspected overdose should be placed under observation in a coronary care unit with facilities available for treatment of any possible hypotension and conduction disturbances that may occur.

Most patients suffering from overdosage of diltiazem become hypotensive within 8 hours of ingestion. With bradycardia and first to third degree atrioventricular block also developing, cardiac arrest may be ensue. Hyperglycaemia is also a recognised complication. The elimination half-life of diltiazem after overdosage is estimated to be about 5.5 – 10.2 hours. If a patient presents early after overdose, gastric lavage should be performed and activated charcoal administered to reduce diltiazem absorption.

Hypotension should be corrected with plasma expanders, intravenous calcium gluconate and inotropic agents (dopamine, dobutamine or isoprenaline).

Symptomatic bradycardia and high grade AV block may respond to atropine,

isoprenaline or occasionally cardiac pacing which may be useful if cardiac standstill occurs.

Diltiazem SR Capsules are extended release capsules and effects may be slow in onset and prolonged, therefore, monitoring should be carried out for longer periods than following overdose with immediate release dosage forms.

5 PHARMACOLOGICAL PROPERTIES

5.1 *Pharmacodynamic properties*

Diltiazem hydrochloride is a calcium-channel blocking agent. It is a peripheral and coronary vasodilator with some negative inotropic activity. Diltiazem inhibits cardiac conduction particularly at the sino-atrial and atrioventricular nodes. It is used in the management of classical and vasospastic angina pectoris and it is also used in the treatment of essential hypertension.

5.2 *Pharmacokinetic properties*

Diltiazem is rapidly and almost completely absorbed from the gastro-intestinal tract following oral administration, but undergoes extensive first-pass hepatic metabolism. The bioavailability has been reported to be about 40%, although there is considerable inter-individual variation in plasma concentrations. Diltiazem is about 80% bound to plasma proteins. It is extensively metabolised in the liver; one of the metabolites, desacetyl diltiazem has been reported to have 25 to 50% of the activity of the parent compound. The half-life is reported to be about 3 to 4 hours. Approximately 60% of the dose is excreted in the bile and 35 to 40% in the urine, and 2 to 4% as unchanged diltiazem.

The sustained-release formulation is designed for twice daily dosage.

5.3 *Preclinical safety data*

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 *List of excipients*

Sugar spheres (75% sucrose; 25% corn starch)
Povidone
Methacrylic acid copolymer

Ethylcellulose
Diethyl phthalate
Talc
Hard gelatin capsules:
- Containing E171 (Titanium dioxide), E172 (red iron oxide), E172 (yellow iron oxide)

6.2 *Incompatibilities*

No known incompatibilities.

6.3 *Shelf life*

The shelf-life of the product, as packaged for sale, is four years.

There are no recommendations for dilution or reconstitution.

There are no data available on the shelf-life of the product after first opening the container.

6.4 *Special precautions for storage*

Store below 25°C in a dry place away from heat and moisture

6.5 *Nature and contents of container*

PVC/aluminium foil blister strips supplied in packs of 56 capsules.

High density, white polyethylene 'tablet containers' with white polypropylene screw caps containing 100 capsules.

Both containers are enclosed in outer cardboard cartons, which also contain a patient information leaflet.

6.6 *Special precautions for disposal*

No special requirements.

7 **MARKETING AUTHORISATION HOLDER**

Kent Pharmaceuticals Limited,
Wotton Road,
Ashford,

Kent TN23 6LL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 08215/0061

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

08/03/2006

10 DATE OF REVISION OF THE TEXT

KENZEM SR CAPSULES (DILTIAZEM HYDROCHLORIDE)

PL 08215/0059-61

PRODUCT INFORMATION LEAFLET

Patient Information Leaflet

KENZEM SR 60mg, 90mg AND 120mg CAPSULES

(Diltiazem hydrochloride)



INFORMATION ABOUT

Kenzem SR 60mg, 90mg and 120mg Capsules. Your doctor wants you to take Kenzem SR 60mg, 90mg or 120mg Capsules. This leaflet will help you to get to know your medicine. If you have any questions, or you are not sure about anything, please ask your doctor or pharmacist.

ABOUT YOUR MEDICINE

Your medicine is called Kenzem SR 60mg, 90mg or 120mg Capsules. The ingredient which makes your medicine work is diltiazem hydrochloride. Kenzem SR comes in 3 strengths: 60 milligrams, 90 milligrams and 120 milligrams.

Your medicine also contains sugar spheres (sucrose and maize starch), povidone, methacrylic acid copolymer, ethylcellulose, talc and diethyl phthalate. The capsule is made of gelatin and contains titanium dioxide (E171), iron oxide red (E172) and iron oxide yellow (E172).

Kenzem SR 60mg, 90mg and 120mg Capsules come in packs of 56 capsules, as follows:

Kenzem SR 60mg: opaque pink and white capsules

Kenzem SR 90mg: opaque pink and yellow capsules

Kenzem SR 120mg: opaque pink and orange capsules

HOW DO KENZEM SR 60mg, 90mg AND 120mg CAPSULES WORK?

Kenzem SR 60mg, 90mg and 120mg Capsules are one of a group of medicines called 'calcium channel blockers'. These relax the muscles around the blood vessels and make it easier for the heart to do its work.

The product licence holder and distributor is:

Kent Pharmaceuticals Limited, Wotton Road, Ashford, Kent, TN23 6LL, UK.

The manufacturer of your medicine is:

Ethypharm, Z.I. Saint Arnoult, 28170 Chateauneuf-en-Thymerais, France.

HOW DO KENZEM SR 60mg, 90mg AND 120mg CAPSULES HELP YOU?

Kenzem SR 60mg, 90mg and 120mg Capsules are used to treat:

- * angina (the pain you feel in your chest, arms or neck when you exert yourself).
- * high blood pressure.

BEFORE TAKING THIS MEDICINE

Do not take this medicine and tell your doctor if:

- * you are pregnant.
- * you are breast-feeding. Because diltiazem passes into breast milk, breast-feeding must be stopped while taking this medicine.
- * women of child-bearing age should exclude the possibility of pregnancy before commencing treatment.
- * you have had an allergic reaction (rash, itching, shortness of breath) to a medicine containing diltiazem or any component listed above.
- * you are suffering from serious problems with your heart rhythm (for example, slow pulse rate, palpitations) or heart failure.
- * you have a kidney disorder or a serious liver disorder.
- * you are being treated with dantrolene injection (for severe muscle spasm).

Take special care and tell your doctor if:

- * you are diabetic.
- * you suffer from a mild liver disorder.
- * you are suffering from mild problems with your heart rhythm or reduced heart function.
- * you are about to have laboratory tests (e.g. blood tests), since the readings may be inaccurate.

Taking other medicines

Some medicines may affect or be affected by diltiazem hydrochloride.

You should tell your doctor if you are taking:

- * anti-hypertensive agents (medicines used to reduce your blood pressure), such as beta blockers

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- (e.g. propranolol), or alpha blockers (e.g. prazosin), diuretics (water tablets) or ACE inhibitors.
- * carbamazepine (used to treat epilepsy).
- * theophylline (for asthma or breathing difficulties).
- * ciclosporin (used after organ transplant to prevent rejection or used to treat psoriasis).
- * digoxin (to treat palpitations or irregular heart beat).
- * cimetidine or ranitidine (used to treat stomach ulcers or acid reflux disorders).
- * anaesthetic agents at the doctors or dentists.
- * anti-arrhythmic drugs (medicines used to treat abnormal heart rhythms).

Tell your doctor if you are taking other medicines (including those you can buy without prescription). Rare cases of increased sugar levels have been reported in association with diltiazem hydrochloride. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

HOW TO TAKE KENZEM SR 60mg, 90mg AND 120mg CAPSULES

Kenzem SR 60mg, 90mg and 120mg Capsules are sustained release capsules, which means the drug is released over a longer period of time. The usual dose is one capsule twice a day. Allow 12 hours between each dose. During the first few weeks, your doctor may change your dose of Kenzem SR 60mg, 90mg or 120mg Capsules until it is exactly right. It is important to follow your doctor's instructions carefully. If you are not sure about anything, always ask your doctor. The usual dose is between 180mg and 360mg a day. For elderly people and those with liver or kidney disease, the usual dose is between 120mg and 180mg a day. The dose should not be increased if you have a slow heart-rate. You should check with your doctor if you are concerned or have previously suffered from slow heart-rate.

Kenzem SR 60mg, 90mg and 120mg Capsules are easy to take. Simply swallow the capsule whole with a drink of water. Do not chew the capsule. Try and take Kenzem SR 60mg, 90mg or 120mg Capsules at the same time each day. If you forget to take the capsule, but remember within 6 hours of the usual time, take Kenzem SR 60mg, 90mg or 120mg Capsules when you remember. If you remember after more than 6 hours, don't take it. Take the next capsule when it is due. If you miss several days, tell your doctor at your next visit.

Kenzem SR 60mg, 90mg and 120mg Capsules are not recommended for use in children.

IF YOU TAKE TOO MANY CAPSULES

If you take too many capsules, or a child takes any Kenzem SR 60mg, 90mg or 120mg Capsules contact your nearest hospital or doctor immediately. Take this leaflet and any capsules left with you to show the doctor.

ARE THERE ANY SIDE EFFECTS FROM THIS MEDICINE?

Kenzem SR 60mg, 90mg and 120mg Capsules are generally well tolerated, however, like all medicines, they can cause side-effects. If you experience a severe slowing of the heart (which may cause either fainting or dizziness), you should stop taking your medicine and tell your doctor immediately or go to your nearest hospital. You may also suffer from a disturbance in liver function, this is often detectable by a blood test. You may also suffer from excessive growth of the gums, depression, difficulty in sleeping, shakiness or the sensation of pins and needles. Other side effects include loss of appetite, feeling sick, skin rashes, hot flushes, swelling of the ankles, weakness, headache and stomach upsets. If any of the above side effects become troublesome or if you notice any other effects not mentioned in this leaflet, please inform your doctor or pharmacist.

STORING AND DISPOSING OF YOUR MEDICINE

KEEP YOUR MEDICINE AWAY FROM CHILDREN.

- * Store below 25°C in a dry place away from heat and moisture.
- * Do not use after the date on the pack, which appears after the letters "EXP".
- * If you have any medicine left which you do not need, return it to your pharmacist.

REMEMBER

This medicine is only for you. Only a doctor can prescribe it. Never give it to anyone else as it may harm them, even if their symptoms are the same as yours.

This leaflet was revised in June 2005.

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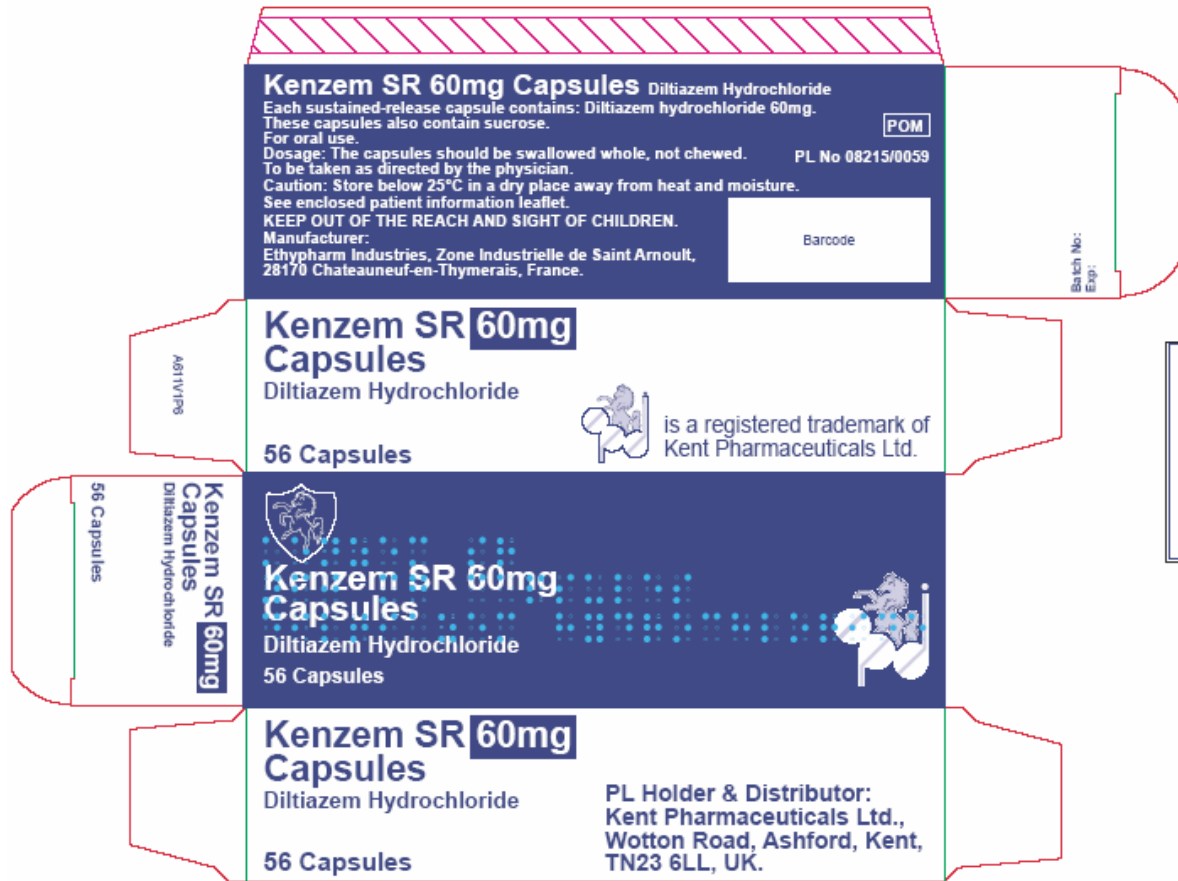
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KENZEM SR 60MG CAPSULES (DILTIAZEM HYDROCHLORIDE)

PL 08215/0059

LABELLING

CARTON



LABEL



KENZEM SR 90MG CAPSULES (DILTIAZEM HYDROCHLORIDE)

PL 08215/0060

CARTON



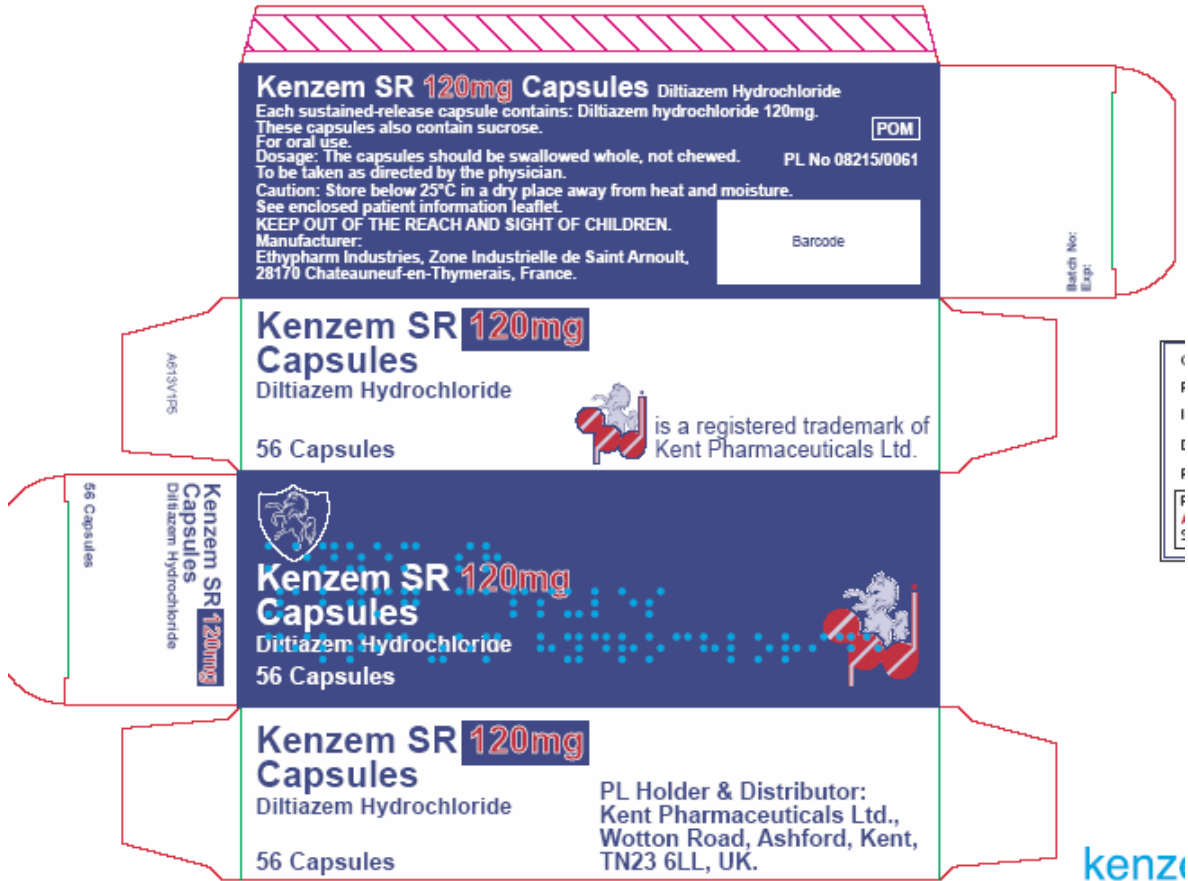
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KENZEM SR 120MG CAPSULES (DILTIAZEM HYDROCHLORIDE)

PL 08215/0061

CARTON



LABEL

