SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Libradin 10, 10 mg modified release capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Libradin contains barnidipine hydrochloride. Libradin 10 modified release capsules, hard, contain 10 mg barnidipine hydrochloride, equivalent to 9.3 mg barnidipine per capsule.

Excipients with known effect: sucrose 95 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified release capsules, hard.
Libradin 10 modified release capsules are yellow and marked: 155 10

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mild to moderate essential hypertension.

4.2 Posology and method of administration

Posology
The recommended starting dosage is 10 mg once daily, in the morning. It may be increased to 20 mg once daily if necessary. The decision to increase the dosage should only be taken after complete stability is achieved on the initial dosage. This usually takes at least 3-6 weeks.

Paediatric population
As there are no data in children (under 18 years) barnidipine should not be administered to children.

Elderly patients
The dosage need not be adjusted in elderly patients. Extra care at the start of treatment is advisable.

Patients with renal impairment
In patients with mild to moderate renal impairment, care should be taken when increasing the dosage from 10 to 20 mg once daily. See the “Contraindications” and “Special warnings and precautions for use” sections.

Patients with hepatic impairment
See the “Contraindications” section.

Method of administration
Take the capsules preferably with a glass of water. Libradin can be taken before, during and after a meal.

4.3 Contraindications

Hypersensitivity to the active substance (or to any dihydropyridine) or to any of the excipients..
Hepatic impairment.
Severe renal impairment (creatinine clearance < 10 ml/min).
Unstable angina pectoris and acute myocardial infarction (in the first 4 weeks).

Untreated heart failure.
Blood levels of barnidipine may be increased when used in combination with strong CYP3A4 inhibitors (results in vitro interaction studies). Therefore, antiproteases, ketoconazole, itraconazole, erythromycin and clarithromycin should not be used concomitantly.

4.4 Special warnings and precautions for use

Libradin should be used with caution in patients with mild to moderate renal impairment (creatinine clearance between 10 and 80 ml/min) (see section 4.2 “Posology and method of administration”).

The combination of a calcium antagonist with a drug that exerts a negative inotropic effect may lead to cardiac decompensation, hypotension or an (additional) myocardial infarction in high-risk patients (e.g. patients with a history of myocardial infarction).

As with all other dihydropyridines, Libradin should be used with caution in patients with left ventricular dysfunction, in patients suffering from obstruction of the outflow channel of the left ventricle and patients with isolated right-sided cardiac decompensation, e.g. cor pulmonale. Barnidipine has not been studied in NYHA class III or IV patients.

Caution is recommended also when barnidipine is administered to patients with sick sinus (if a pacemaker is not in situ).

In vitro studies indicate that barnidipine is metabolised by cytochrome P450 3A4 (CYP3A4). No in vivo interaction studies on the effect of drugs that inhibit or induce the cytochrome P450 3A4 enzyme on the pharmacokinetics of barnidipine, have been carried out. Based on the results of in vitro interaction studies, care should be taken when barnidipine is prescribed concomitantly with mild CYP3A4 inhibitors or inducers (see the “Interactions with other medicinal products and other forms of interaction” section).

The capsules contain 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

The concurrent administration of barnidipine and other antihypertensive drugs may result in an additional antihypertensive effect.

Libradin can be used concurrently with betablockers or ACE inhibitors.

The pharmacokinetic interaction profile of barnidipine has not been studied in full. In vitro studies show that barnidipine is metabolised by cytochrome P450 3A4 (CYP3A4).

No elaborate in vivo interaction studies on the effect of drugs which inhibit or induce the CYP3A4 enzyme on the pharmacokinetics of barnidipine, have been carried out.

In vitro data show that cyclosporin may inhibit the metabolism of barnidipine. Until in vivo information is available, barnidipine should not be prescribed concomitantly with the strong CYP3A4 inhibitors: antiproteases, ketoconazole, itraconazole, erythromycin and clarithromycin (see section 4.3 Contraindications). Care should be taken with concomitant use of mild CYP3A4 inhibitors or inducers. In case of concomitant use of CYP3A4 inhibitors it is discouraged to increase the dosage of barnidipine to 20 mg.

Concurrent dosing of cimetidine in a specific interaction study led on average to a doubling of barnidipine plasma levels. Care should therefore be exercised when using barnidipine concomitantly with cimetidine.

A higher dose of barnidipine may be necessary when barnidipine is administered concomitantly with enzyme inducing drugs, such as phenytoin, carbamazepine and rifampicin. Should a patient stop using an enzyme inducing drug, lowering the dosage of barnidipine should be considered.

Based on the results of in vitro interaction studies with, among other things, simvastatin, metoprolol, diazepam and terfenadine, it is considered unlikely that barnidipine has any effect on the pharmacokinetics of other drugs which are metabolised by cytochrome P450 isoenzymes.

An in vivo interaction study showed that barnidipine does not influence the pharmacokinetics of digoxin.
In a specific interaction study alcohol led to an increase of barnidipine plasma levels (40%), which increase may be considered clinically not relevant. As with all vasodilating and antihypertensive agents, caution should be exercised when alcohol is taken concomitantly as it may potentiate their effect.
Although barnidipine kinetics was not significantly altered by administration with grapefruit juice, a modest effect was observed.

4.6 Fertility, pregnancy and lactation

Pregnancy
No clinical experience with barnidipine in pregnancy or lactation is present. Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal or postnatal development. Only indirect effects are observed (see 5.3). The class of dihydropyridines has shown the potential to prolong delivery and parturition, which was not observed with barnidipine. As a consequence, barnidipine could be used in pregnancy only if the benefit justifies the potential risk to the fetus.

Breast-feeding
The results of animal tests have shown that barnidipine (or its metabolites) is excreted in human milk. Therefore, breast feeding is not advised during use of barnidipine.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed Libradin. However, caution should be exercised because dizziness/vertigo may occur during antihypertensive treatment.

4.8 Undesirable effects

System organ class	10 mg dosage	20 mg dosage
Immune system disorders • Anaphylactoid reaction	Not known (frequency cannot be estimated from the available data)	Not known (frequency cannot be estimated from the available data)
Nervous system disorders • Headache • Dizziness/vertigo	Common (≥1/100 to <1/10) Common (≥1/100 to <1/10)	Very common (≥1/10) Common (≥1/100 to <1/10)
Cardiac disorders • Palpitations • Tachycardia, sinus tachycardia, heart rate increased	Common (≥1/100 to <1/10) Not known (frequency cannot be estimated from the available data)	Common (≥1/100 to <1/10) Not known (frequency cannot be estimated from the available data)
Vascular disorders • Flushing	Common (≥1/100 to <1/10)	Very common (≥1/10)
Hepato-biliary disorders • Liver function test abnormal	Not known (frequency cannot be estimated from the available	Not known (frequency cannot be estimated from the available

	data)	data)
Skin and subcutaneous tissue disorders • Rash	Not known (frequency cannot be estimated from the available data)	Not known (frequency cannot be estimated from the available data)
General and administration site conditions • Peripheral oedema	Common (≥1/100 to <1/10)	Very common (≥1/10)

The symptoms tend to diminish or disappear during treatment (within one month for peripheral oedema and two weeks for flushing, headache and palpitations).

Although never observed, the following adverse event may be of interest, as it is in the use of other dihydropyridines: gingival hyperplasia.

Some dihydropyridines may rarely lead to precordial pain or angina pectoris. Very rarely patients with pre-existing angina pectoris may experience increased frequency, duration or severity of these attacks. Isolated cases of myocardial infarction may be observed.

4.9 Overdose

Symptoms of intoxication
In general, clinical symptoms following an overdose of calcium antagonists develop within 30 to 60 minutes after administration of a dose five to ten times higher than the therapeutic dose.

Hypotension, electrophysiological effects (sinus bradycardia, prolonged AV conduction, second and third degree AV block, tachycardia), effects on the central nervous system (drowsiness, confusion and, rarely, convulsions), gastrointestinal symptoms (nausea and vomiting) and metabolic effects (hyperglycaemia) can theoretically be expected.

Intoxication treatment
Hospital treatment is necessary in the event of intoxication. Symptomatic treatment and continuous ECG monitoring are indicated.

In the event of an overdose a gastric lavage should be performed as soon as possible.

An intravenous (dosage 0.2 ml/kg body weight) injection of calcium (preferably 10 ml of a calcium chloride solution of 10%) should be given over a period of 5 minutes, up to a total dose of 10 ml 10%. Contractility of the myocardium, sinus rhythm and atrioventricular conduction will thus be improved. The treatment can be repeated every 15 to 20 minutes (up to a total of 4 doses) based on the patient's response. Calcium levels should be checked.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihypertensives. ATC code C08CA12.

Mechanism of action
Barnidipine (pure S,S isomer) is a lipophilic 1,4-dihydropyridine calcium antagonist showing high affinity for the calcium channels of the smooth muscle cells in the vascular wall. Receptor kinetics of barnidipine are characterised by a slow onset of action and a strong and long-lasting binding. The reduction in peripheral

resistance brought about by barnidipine results in blood pressure lowering. When using Libradin, the antihypertensive effect remains during the entire 24-hour dose interval.

Use of Libradin in chronic treatment does not lead to an increase in basic heart frequency.
The impact of barnidipine on cardiovascular morbidity or mortality has not been studied. However, recently completed, controlled studies of other long acting dihydropyridines indicate similar beneficial effects on morbidity and mortality compared to other antihypertensives in hypertension of the elderly.

Metabolic effects
Barnidipine does not exert any negative effect on serum lipids profile, glucose level or blood electrolytes.

5.2 Pharmacokinetic properties

Absorption
After repeated administration of Libradin 20 to healthy individuals, the concomitant intake of food did not have a statistically significant effect on AUC, C_{max}, T_{max} or $t_{½}$.
Maximum plasma levels are obtained 5 to 6 hours after oral administration of Libradin 20.
Libradin shows an absolute bioavailability of 1.1%.
Barnidipine plasma concentrations may show considerable interpersonal variation.

Distribution
In vitro studies show that barnidipine binds at the rate of 26-32% to human erythrocytes and to a high extent (89-95%) to plasma proteins. In vitro analysis of protein components indicates that barnidipine mainly binds to serum albumin, followed by α_1 acid glycoprotein and high density lipoproteins. To a much lesser extent binding to γ globulin takes place.
No drug interactions based on elimination of plasma protein binding have been observed in in-vitro studies.

Biotransformation
Barnidipine is to a great extent metabolised into inactive metabolites. No in vivo chiral inversion of the pure S,S isomer takes place. Main reactions are N-debenzylisation of the side chain, hydrolysis of the N-benzylpyrrolidine ester, oxidation of the 1,4-dihydropyridine ring, hydrolysis of the methyl ester and reduction of the nitro group. The metabolism of barnidipine seems mainly mediated by the CYP3A isoenzyme family.

Elimination
The median terminal elimination plasma half-life of Libradin was 20 hours after repeated administration, according to a two-compartment analytical model.
Elimination mainly takes place through metabolism. Barnidipine and/or its metabolites are excreted in faeces (60%), urine (40%) and breath (less than 1%). No unmetabolised barnidipine is excreted in urine.

Special patient groups
After a single dose, barnidipine plasma levels are 3 to 4 times higher in patients with mild to moderate hepatic impairment than in healthy volunteers. The variability in plasma levels is also increased.
Barnidipine plasma levels are on average twice as high in patients with renal impairment not needing haemodialysis than in healthy volunteers. The average plasma level in patients needing haemodialysis is more than 3 times as high as in healthy volunteers, accompanied by increased variability.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The excipients of Libradin capsules are:
capsule content: carboxymethylethylcellulose, polysorbate 80, sucrose, ethylcellulose, talc.
capsule shell: titanium dioxide (E171), yellow iron oxide (E172) and gelatine.
printing ink: shellac, propylene glycol (E1520), black iron oxide (E172), ammonia.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

Libradin modified release capsules are packed in boxes containing 10, 14, 20, 28, 30, 50, 56, 98 or 100 capsules in aluminium-aluminium (with PVC and polyamide coating) blisters. A blister contains 7, 10 or 14 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

Do not remove granules from the capsules.

7. MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<{DD/MM/YYYY}> <{DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>

<[To be completed nationally]>

1. NAME OF THE MEDICINAL PRODUCT

Libradin 20, 20 mg modified release capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Libradin contains barnidipine hydrochloride. Libradin 20 modified release capsules, hard, contain 20 mg barnidipine hydrochloride, equivalent to 18.6 mg barnidipine per capsule.

Excipients with known effect: sucrose 190 mg.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified release capsules, hard.
Libradin 20 modified release capsules are yellow and marked: 155 20

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mild to moderate essential hypertension.

4.2 Posology and method of administration

Posology
The recommended starting dosage is 10 mg once daily, in the morning. It may be increased to 20 mg once daily if necessary. The decision to increase the dosage should only be taken after complete stability is achieved on the initial dosage. This usually takes at least 3-6 weeks.

Paediatric population
As there are no data in children (under 18 years) barnidipine should not be administered to children.

Elderly patients
The dosage need not be adjusted in elderly patients. Extra care at the start of treatment is advisable.

Patients with renal impairment
In patients with mild to moderate renal impairment, care should be taken when increasing the dosage from 10 to 20 mg once daily. See the “Contraindications” and “Special warnings and precautions for use” sections.

Patients with hepatic impairment
See the “Contraindications” section.

Method of administration
Take the capsules preferably with a glass of water. Libradin can be taken before, during and after a meal.

4.3 Contraindications

Hypersensitivity to the active substance (or to any dihydropyridine) or to any of the excipients..
Hepatic impairment.
Severe renal impairment (creatinine clearance < 10 ml/min).
Unstable angina pectoris and acute myocardial infarction (in the first 4 weeks).

Untreated heart failure.
Blood levels of barnidipine may be increased when used in combination with strong CYP3A4 inhibitors (results in vitro interaction studies). Therefore, antiproteases, ketoconazole, itraconazole, erythromycin and clarithromycin should not be used concomitantly.

4.4 Special warnings and precautions for use

Libradin should be used with caution in patients with mild to moderate renal impairment (creatinine clearance between 10 and 80 ml/min) (see section 4.2 “Posology and method of administration”).

The combination of a calcium antagonist with a drug that exerts a negative inotropic effect may lead to cardiac decompensation, hypotension or an (additional) myocardial infarction in high-risk patients (e.g. patients with a history of myocardial infarction).

As with all other dihydropyridines, Libradin should be used with caution in patients with left ventricular dysfunction, in patients suffering from obstruction of the outflow channel of the left ventricle and patients with isolated right-sided cardiac decompensation, e.g. cor pulmonale. Barnidipine has not been studied in NYHA class III or IV patients.

Caution is recommended also when barnidipine is administered to patients with sick sinus (if a pacemaker is not in situ).

In vitro studies indicate that barnidipine is metabolised by cytochrome P450 3A4 (CYP3A4). No in vivo interaction studies on the effect of drugs that inhibit or induce the cytochrome P450 3A4 enzyme on the pharmacokinetics of barnidipine, have been carried out. Based on the results of in vitro interaction studies, care should be taken when barnidipine is prescribed concomitantly with mild CYP3A4 inhibitors or inducers (see the “Interactions with other medicinal products and other forms of interaction” section).

The capsules contain 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

The concurrent administration of barnidipine and other antihypertensive drugs may result in an additional antihypertensive effect.

Libradin can be used concurrently with betablockers or ACE inhibitors.

The pharmacokinetic interaction profile of barnidipine has not been studied in full. In vitro studies show that barnidipine is metabolised by cytochrome P450 3A4 (CYP3A4).

No elaborate in vivo interaction studies on the effect of drugs which inhibit or induce the CYP3A4 enzyme on the pharmacokinetics of barnidipine, have been carried out.

In vitro data show that cyclosporin may inhibit the metabolism of barnidipine. Until in vivo information is available, barnidipine should not be prescribed concomitantly with the strong CYP3A4 inhibitors: antiproteases, ketoconazole, itraconazole, erythromycin and clarithromycin (see section 4.3 Contraindications). Care should be taken with concomitant use of mild CYP3A4 inhibitors or inducers. In case of concomitant use of CYP3A4 inhibitors it is discouraged to increase the dosage of barnidipine to 20 mg.

Concurrent dosing of cimetidine in a specific interaction study led on average to a doubling of barnidipine plasma levels. Care should therefore be exercised when using barnidipine concomitantly with cimetidine.

A higher dose of barnidipine may be necessary when barnidipine is administered concomitantly with enzyme inducing drugs, such as phenytoin, carbamazepine and rifampicin. Should a patient stop using an enzyme inducing drug, lowering the dosage of barnidipine should be considered.

Based on the results of in vitro interaction studies with, among other things, simvastatin, metoprolol, diazepam and terfenadine, it is considered unlikely that barnidipine has any effect on the pharmacokinetics of other drugs which are metabolised by cytochrome P450 isoenzymes.

An in vivo interaction study showed that barnidipine does not influence the pharmacokinetics of digoxin.
In a specific interaction study alcohol led to an increase of barnidipine plasma levels (40%), which increase may be considered clinically not relevant. As with all vasodilating and antihypertensive agents, caution should be exercised when alcohol is taken concomitantly as it may potentiate their effect.
Although barnidipine kinetics was not significantly altered by administration with grapefruit juice, a modest effect was observed.

4.6 Fertility, pregnancy and lactation

Pregnancy
No clinical experience with barnidipine in pregnancy or lactation is present. Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal or postnatal development. Only indirect effects are observed (see 5.3). The class of dihydropyridines has shown the potential to prolong delivery and parturition, which was not observed with barnidipine. As a consequence, barnidipine could be used in pregnancy only if the benefit justifies the potential risk to the fetus.

Breast-feeding
The results of animal tests have shown that barnidipine (or its metabolites) is excreted in human milk. Therefore, breast feeding is not advised during use of barnidipine.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed Libradin. However, caution should be exercised because dizziness/vertigo may occur during antihypertensive treatment.

4.8 Undesirable effects

System organ class	10 mg dosage	20 mg dosage
Immune system disorders • Anaphylactoid reaction	Not known (frequency cannot be estimated from the available data)	Not known (frequency cannot be estimated from the available data)
Nervous system disorders • Headache • Dizziness/vertigo	Common (≥1/100 to <1/10) Common (≥1/100 to <1/10)	Very common (≥1/10) Common (≥1/100 to <1/10)
Cardiac disorders • Palpitations • Tachycardia, sinus tachycardia, heart rate increased	Common (≥1/100 to <1/10) Not known (frequency cannot be estimated from the available data)	Common (≥1/100 to <1/10) Not known (frequency cannot be estimated from the available data)
Vascular disorders • Flushing	Common (≥1/100 to <1/10)	Very common (≥1/10)
Hepato-biliary disorders • Liver function test abnormal	Not known (frequency cannot be estimated from the available	Not known (frequency cannot be estimated from the available

	data)	data)
Skin and subcutaneous tissue disorders • Rash	Not known (frequency cannot be estimated from the available data)	Not known (frequency cannot be estimated from the available data)
General and administration site conditions • Peripheral oedema	Common (≥1/100 to <1/10)	Very common (≥1/10)

The symptoms tend to diminish or disappear during treatment (within one month for peripheral oedema and two weeks for flushing, headache and palpitations).

Although never observed, the following adverse event may be of interest, as it is in the use of other dihydropyridines: gingival hyperplasia.

Some dihydropyridines may rarely lead to precordial pain or angina pectoris. Very rarely patients with pre-existing angina pectoris may experience increased frequency, duration or severity of these attacks. Isolated cases of myocardial infarction may be observed.

4.9 Overdose

Symptoms of intoxication
In general, clinical symptoms following an overdose of calcium antagonists develop within 30 to 60 minutes after administration of a dose five to ten times higher than the therapeutic dose.

Hypotension, electrophysiological effects (sinus bradycardia, prolonged AV conduction, second and third degree AV block, tachycardia), effects on the central nervous system (drowsiness, confusion and, rarely, convulsions), gastrointestinal symptoms (nausea and vomiting) and metabolic effects (hyperglycaemia) can theoretically be expected.

Intoxication treatment
Hospital treatment is necessary in the event of intoxication. Symptomatic treatment and continuous ECG monitoring are indicated.

In the event of an overdose a gastric lavage should be performed as soon as possible.

An intravenous (dosage 0.2 ml/kg body weight) injection of calcium (preferably 10 ml of a calcium chloride solution of 10%) should be given over a period of 5 minutes, up to a total dose of 10 ml 10%. Contractility of the myocardium, sinus rhythm and atrioventricular conduction will thus be improved. The treatment can be repeated every 15 to 20 minutes (up to a total of 4 doses) based on the patient's response. Calcium levels should be checked.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihypertensives. ATC code C08CA12.

Mechanism of action
Barnidipine (pure S,S isomer) is a lipophilic 1,4-dihydropyridine calcium antagonist showing high affinity for the calcium channels of the smooth muscle cells in the vascular wall. Receptor kinetics of barnidipine are characterised by a slow onset of action and a strong and long-lasting binding. The reduction in peripheral

resistance brought about by barnidipine results in blood pressure lowering. When using Libradin, the antihypertensive effect remains during the entire 24-hour dose interval.

Use of Libradin in chronic treatment does not lead to an increase in basic heart frequency.
The impact of barnidipine on cardiovascular morbidity or mortality has not been studied. However, recently completed, controlled studies of other long acting dihydropyridines indicate similar beneficial effects on morbidity and mortality compared to other antihypertensives in hypertension of the elderly.

Metabolic effects
Barnidipine does not exert any negative effect on serum lipids profile, glucose level or blood electrolytes.

5.2 Pharmacokinetic properties

Absorption
After repeated administration of Libradin 20 to healthy individuals, the concomitant intake of food did not have a statistically significant effect on AUC, C_{max}, T_{max} or $t_{½}$.
Maximum plasma levels are obtained 5 to 6 hours after oral administration of Libradin 20.
Libradin shows an absolute bioavailability of 1.1%.
Barnidipine plasma concentrations may show considerable interpersonal variation.

Distribution
In vitro studies show that barnidipine binds at the rate of 26-32% to human erythrocytes and to a high extent (89-95%) to plasma proteins. In vitro analysis of protein components indicates that barnidipine mainly binds to serum albumin, followed by α_1 acid glycoprotein and high density lipoproteins. To a much lesser extent binding to γ globulin takes place.
No drug interactions based on elimination of plasma protein binding have been observed in in-vitro studies.

Biotransformation
Barnidipine is to a great extent metabolised into inactive metabolites. No in vivo chiral inversion of the pure S,S isomer takes place. Main reactions are N-debenzylisation of the side chain, hydrolysis of the N-benzylpyrrolidine ester, oxidation of the 1,4-dihydropyridine ring, hydrolysis of the methyl ester and reduction of the nitro group. The metabolism of barnidipine seems mainly mediated by the CYP3A isoenzyme family.

Elimination
The median terminal elimination plasma half-life of Libradin was 20 hours after repeated administration, according to a two-compartment analytical model.
Elimination mainly takes place through metabolism. Barnidipine and/or its metabolites are excreted in faeces (60%), urine (40%) and breath (less than 1%). No unmetabolised barnidipine is excreted in urine.

Special patient groups
After a single dose, barnidipine plasma levels are 3 to 4 times higher in patients with mild to moderate hepatic impairment than in healthy volunteers. The variability in plasma levels is also increased.
Barnidipine plasma levels are on average twice as high in patients with renal impairment not needing haemodialysis than in healthy volunteers. The average plasma level in patients needing haemodialysis is more than 3 times as high as in healthy volunteers, accompanied by increased variability.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The excipients of Libradin capsules are:
capsule content: carboxymethylethylcellulose, polysorbate 80, sucrose, ethylcellulose, talc.
capsule shell: titanium dioxide (E171), yellow iron oxide (E172) and gelatine.
printing ink: shellac, propylene glycol (E1520), black iron oxide (E172), ammonia.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

Libradin modified release capsules are packed in boxes containing 10, 14, 20, 28, 30, 50, 56, 98 or 100 capsules in aluminium-aluminium (with PVC and polyamide coating) blisters. A blister contains 7, 10 or 14 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

Do not remove granules from the capsules.

7. MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<{DD/MM/YYYY}> <{DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>

<[To be completed nationally]>

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Libradin 10 modified release capsules 10 mg

barnidipine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each Libradin 10 capsule contains 10 mg barnidipine hydrochloride corresponding to 9.3 mg barnidipine.

3. LIST OF EXCIPIENTS

Also contains sucrose.

4. PHARMACEUTICAL FORM AND CONTENTS

30 capsules
10 capsules
14 capsules
20 capsules
28 capsules
50 capsules
56 capsules
98 capsules
100 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp.:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>
<[See Annex I - To be completed nationally]> *[For referral procedures]*

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

<[To be completed nationally]>

<Medicinal product subject to medical prescription.>

15. INSTRUCTIONS ON USE

<[To be completed nationally]> *[For referral procedures]*

16. INFORMATION IN BRAILLE

<[To be completed nationally]> *[For referral procedures]*

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Libradin 10 modified release capsule

10 mg barnidipine HCl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Astellas

3. EXPIRY DATE

Exp:

4. BATCH NUMBER

Batch:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Libradin 20 modified release capsules 20 mg

barnidipine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each Libradin 20 capsule contains 20 mg barnidipine hydrochloride corresponding to 18.6 mg barnidipine.

3. LIST OF EXCIPIENTS

Also contains sucrose.

4. PHARMACEUTICAL FORM AND CONTENTS

30 capsules
10 capsules
14 capsules
20 capsules
28 capsules
50 capsules
56 capsules
98 capsules
100 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp.:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>
<[See Annex I - To be completed nationally]> *[For referral procedures]*

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

<[To be completed nationally]>

<Medicinal product subject to medical prescription.>

15. INSTRUCTIONS ON USE

<[To be completed nationally]> *[For referral procedures]*

16. INFORMATION IN BRAILLE

<[To be completed nationally]> *[For referral procedures]*

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Libradin 20 modified release capsule

20 mg barnidipine HCl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Astellas

3. EXPIRY DATE

Exp:

4. BATCH NUMBER

Batch:

5. OTHER

PACKAGE LEAFLET

Package leaflet: Information for the patient

Libradin 10, 10 mg modified release capsules
Libradin 20, 20 mg modified release capsules
barnidipine hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects , talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

What Libradin is and what it is used for
The active substance of Libradin belongs to the group of medicines called calcium antagonists. Libradin causes blood vessels to dilate thereby lowering blood pressure. Libradin capsules are made in a 'prolonged-release' form. This means that the active substance gets absorbed into your system gradually and has a longer lasting effect. That is why taking the dose once daily is sufficient.

Libradin is used to treat high blood pressure.

2. What you need to know before you take Libradin

Do not take Libradin
- if you are allergic to barnidipine or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to dihydropyridines (found in medicines to treat high bloodpressure)
- if you suffer from liver disease.
- if you suffer from severe kidney disease.
- if you suffer from these specific heart diseases: untreated heart failure, certain forms of pain on the chest (unstable angina pectoris) or acute cardiac arrest.
- if you use one of the following other medicines: protease blockers (medicines used to treat AIDS), ketoconazole or itraconazole (medicines to treat yeast infections), erythromycin or claritromycin (antibiotics).

Warnings and precautions
Talk to your doctor or pharmacist before taking Libradin
- if you suffer from a kidney disease.
- if you suffer from a heart disease.

Children and adolescents
Libradin is not to be used in children or adolescents under 18 years.

Other medicines and Libradin
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines.

This is especially important if you use one of the following medicines as they MUST not be used together with Libradin:
- protease blockers (medicines used to treat AIDS),
- ketoconazole or itraconazole (medicines to treat yeast infections),
- erythromycin or claritromycin (antibiotics).

Also inform your doctor if you are taking:
- other medicines to treat high blood pressure as they may cause your blood pressure to fall even more.
- cimetidine (medicine against stomach problems) as they may increase the effect of Libradin.
- phenytoin or carbamazepine (medicines used to treat epilepsy), or rifampicin (an antibiotic) as higher dose of Libradin may be needed. If you stop treatment with these medicines, your doctor may lower the dose of Libradin.

Libradin with drink and alcohol
Take special care when drinking alcohol or grapefruit juice, as these may cause an increase in the effect of Libradin.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

You should not use Libradin during pregnancy unless clearly necessary.
Do not use Libradin if you breast feed. Barnidipine may get into your breast milk.

Driving and using machines
There is no information to suggest that Libradin affects your ability to drive or use machines. However Libradin may cause dizziness, so make sure you know how this medicine affects you before you drive or use machines

Libradin capsules contain sucrose. If you have been told by your doctor that you have an intolerance to some sugars, please contact your doctor before taking this medicine.

3. How to take Libradin

Dosage
Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The usual starting dose is 1 capsule Libradin 10 mg once daily. Your doctor may increase this dose to 1 capsule of Libradin 20 mg, once daily or 2 capsules of Libradin 10 mg, once daily.

If you are older you can use the normal dosage. Your doctor will most likely monitor you more closely at the start of the treatment.

Instructions for proper use
- Take the capsule once daily, in the morning. It is advisable to associate taking the capsule with something you do on a daily basis, like brushing your teeth or having breakfast
- Swallow the capsules whole, preferably with a glass of water. You can take Libradin before, during or after a meal, according to your preference.
- Even though you may not feel any signs or symptoms of high blood pressure, it is important to continue to take Libradin every day to get the full benefits of blood pressure reduction.

If you take more Libradin than you should
If you have accidentally taken a large amount of capsules at once, you should immediately contact your doctor or have someone bring you to the hospital emergency room. Possible symptoms followed by an overdose are weakness, slow or faster heart rate, drowsiness, confusion, nausea, vomiting and convulsions.

If you forget to take Libradin
If you forget to take Libradin at your usual time take the capsule as soon as possible on that same day.
If you only remember the following day do not take a double dose to make up for the forgotten capsule,.
Simply continue with your regular daily dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you experience serious allergic reaction which causes difficulty in breathing or dizziness, you must inform your doctor or nurse immediately

Libradin may cause the following:
Very common: may affect more than 1 in 10 people
- headache
- facial redness
- fluid accumulation (edema) in arms or legs

Common: may affect up to 1 in 10 people- dizziness
- palpitations

Not known: frequency cannot be estimated from the available data
- faster heart beat
- blood tests which show changes in the way the liver is working
- rash

These side effects usually lessen or disappear during treatment (within one month for fluid accumulation and within two weeks for facial redness, headache and palpitations).

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Libradin

Keep this medicine out of the sight and reach of children.

Store Libradin capsules below 25 ºC.
Do not use Libradin after the expiry date which is stated on the packaging after “EXP”. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to dispose of medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Libradin contains
- The active substance is 10 mg or 20 mg barnidipine hydrochloride equivalent to 9.3 and 18.6 mg barnidipine per capsule, respectively.
- Other ingredients are
  capsule content: carboxymethylethylcellulose, polysorbate 80, sucrose, ethylcellulose and talc.

capsule case: titanium dioxide (E171), yellow iron oxide (E172) and gelatine.
print ink: shellac, propylene glycol (E1520), black iron oxide (E172), ammonia.

What Libradin looks like and contents of the pack
The capsules are yellow.
Libradin 10 carries the code 155 10.
Libradin 20 carries the code 155 20.

Libradin capsules are packaged in aluminium-aluminium blister packs (with PVC and polyamide coating) in cardboard boxes of 10, 14, 20, 28, 30, 50, 56, 98 or 100. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands
Telephone: 071-5455745

This medicinal product is authorised in the Member States of the EEA under the following names: Netherlands, Italy: Libradin

This leaflet was last revised in January 2013