Professional information

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE

ZIABETA 2,5/6,25 mg film-coated tablets

ZIABETA 5/6,25 mg film-coated tablets

ZIABETA 10/6,25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ZIABETA 2,5/6,25 mg tablet contains:

Bisoprolol fumarate 2,5 mg

Hydrochlorothiazide 6,25 mg

Each ZIABETA 5/6,25 mg tablet contains:

Bisoprolol fumarate 5 mg

Hydrochlorothiazide 6,25 mg

Each ZIABETA 10/6,25 mg tablet contains:

Bisoprolol fumarate 10 mg

Hydrochlorothiazide 6,25 mg

Sugar-free.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ZIABETA 2,5/6,25 mg: Yellow, round, biconvex film-coated tablet, upper side embossed with a heart, downside embossed with 2,5.

ZIABETA 5/6,25 mg:	Pink, round, biconvex film-coated tablet, upper side embossed with a heart, downside embossed with 5.
ZIABETA 10/6,25 mg:	White, round, biconvex film-coated tablet, upper side embossed with a heart, downside embossed with 10.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZIABETA is indicated for the treatment of mild to moderate essential hypertension.

4.2 Posology and method of administration

Posology

Antihypertensive therapy may be initiated with the lowest dose of ZIABETA, one 2,5 mg/6,25 mg tablet, once daily.

Subsequent dose adjustment may be carried out with ZIABETA tablets up to maximum recommended dose of one 10 mg/6,25 mg tablet once daily, as appropriate.

Dosage adjustment on the basis of age is not usually necessary, unless there is also significant renal or hepatic dysfunction.

Experience with ZIABETA in paediatric patients is limited, therefore its use cannot be recommended in this population.
If withdrawal of ZIABETA therapy is planned, gradual discontinuation of treatment is recommended, since abrupt withdrawal of bisoprolol (as in ZIABETA) may lead to an acute deterioration of the patient's condition, in particular in patients with ischaemic heart disease. Patients should be carefully observed.

Method of administration

ZIABETA should be swallowed in the morning and can be taken with food. The film-coated tablets should be swallowed with some liquid and not be chewed.

4.3 Contraindications

ZIABETA is contra-indicated in patients with:

- hypersensitivity to bisoprolol, hydrochlorothiazide, other thiazides, sulphonamides, or to any of the excipients listed in section 6.1
- acute heart failure or during episodes of heart failure decompensation requiring intravenous inotropic therapy
- cardiogenic shock
- metabolic acidosis
- symptomatic bradycardia or a pulse rate below 50 beats per minute
- second or third degree AV block
- sick sinus syndrome
- sinoatrial block
- bronchial asthma
- severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome
- pheochromocytoma until full alpha blockade has been achieved
- severe renal impairment (creatinine clearance ≤ 30 mL/min)
- severe hepatic impairment
- refractory hypokalaemia
- Concomitant treatment with Lithium

4.4 Special warnings and precautions for use

Treatment with ZIABETA must not be withdrawn abruptly unless clearly indicated, since abrupt withdrawal of bisoprolol (as in ZIABETA) may lead to an acute deterioration of the patient’s condition in particular in patients with ischaemic heart disease. Discontinuation should be gradual,

and patients should be advised to limit the extent of their physical activity during the period in which the medicine is being discontinued.

ZIABETA must be used with caution in patients with:

- Accompanying heart failure of any degree (see section 4.3).
- Diabetes mellitus showing large fluctuations in blood glucose values; symptoms of hypoglycaemia (e.g. tachycardia, palpitations or sweating) may be masked.
- Strict fasting.
- First degree AV block.
- Prinzmetal's angina; Cases of coronary vasospasm have been observed. Angina attacks cannot be excluded when bisoprolol is administered to patients with Prinzmetal's angina. Utmost caution must be exercised.
- Peripheral arterial occlusive disease. Aggravation of symptoms may occur (see section 4.5), especially when starting therapy in which case, ZIABETA should be discontinued.
- Hypovolaemia.
- Impaired liver function.
- Cholelithiasis acute cholecystitis has been reported.

ZIABETA may aggravate the symptoms of peripheral arterial occlusive disease (PAOD) or Raynaud's syndrome (due to unopposed arteriolar alpha-sympathetic activation).
Severe peripheral vascular disease and even peripheral gangrene may be precipitated.

Digitalisation of patients receiving long-term ZIABETA therapy may be necessary if congestive cardiac failure is likely to develop. This combination can be considered despite the potentiation of the negative chronotropic effect of the two medicines. Careful control of dosages, and of the individual patient's response (and notably pulse rate), is essential in this situation.

Hypersensitivity Reactions

ZIABETA may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. This also applies to desensitisation therapy. Epinephrine treatment may not always yield the expected therapeutic effect.

Psoriasis

Patients with psoriasis or with a history of psoriasis may have their conditions worsened by ZIABETA.

Hyperthyroidism

The symptoms of hyperthyroidism may be masked under treatment with bisoprolol.

Pheochromocytoma

In patients with pheochromocytoma bisoprolol must not be administered until after full alpha-receptor blockade.

General Anaesthesia

In patients undergoing general anaesthesia beta-blockade reduces the incidence of dysrhythmias and myocardial ischaemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The anaesthetist must be aware of beta-blockade because of the potential for interactions with other drugs, resulting in brady-dysrhythmias, attenuation of the reflex tachycardia and the decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

Asthma and Chronic Obstructive Pulmonary Disease

Although cardioselective ($beta_1$) beta-blockers may have less effect on lung function than nonselective beta-blockers, as with all beta-blockers, these should be avoided in patients with

obstructive airways diseases, unless there are compelling clinical reasons for their use. Where such reasons exist, ZIABETA may be used with caution. In bronchial asthma or other chronic obstructive pulmonary diseases, which may cause symptoms, concomitant bronchodilating therapy is recommended. An increase of the airway resistance may occur in patients with asthma, therefore, the dose of $beta_2$-stimulants may have to be increased.

Photosensitivity

Photosensitivity reactions may occur with hydrochlorothiazides. If photosensitivity reactions occur, it is recommended to protect exposed areas to the sun or to artificial UVA light. In severe cases it may be necessary to stop the treatment.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC (see section 4.8).

Fluid & Electrolyte Balance

Long-term, continuous administration of hydrochlorothiazide may lead to fluid and electrolyte disturbances, in particular to hypokalaemia and hyponatraemia, also to hypomagnesaemia and

hypochloraemia, and hypercalcaemia. Hypokalaemia facilitates the development of severe dysrhythmias, particularly torsade de pointes, which may be fatal.
During long term-therapy with ZIABETA, monitoring of serum electrolytes (especially potassium, sodium, calcium), creatinine and urea, the serum lipids (cholesterol and triglycerides), uric acid as well as blood glucose is recommended.

Metabolic alkalosis may worsen due to disturbance of fluid and electrolyte haemostasis.

Uric Acid

In patients with hyperuricaemia the risk for attacks of gout may be increased.

ZIABETA can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle closure glaucoma may include a history of sulphonamide or penicillin allergy.

4.5 Interaction with other medicines and other forms of interaction

Combinations not recommended

Lithium: ZIABETA may intensify the cardiotoxic and neurotoxic effect of lithium through a reduction of lithium excretion and should not be co-administered with ZIABETA.
The intravenous administration of calcium antagonists and antidysrhythmic medicines is not recommended during ZIABETA therapy.

Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type: Negative effect on contractility and atrio ventricular conduction. Intravenous administration of verapamil in patients on ZIABETA treatment may lead to profound hypotension and atrioventricular block.

Centrally acting antihypertensive medicines (e.g. clonidine, methyldopa, moxonodine): Concomitant use of centrally acting antihypertensive medicines may lead to a further reduction in heart rate and cardiac output and to vasodilation. Abrupt withdrawal may increase the risk of “rebound hypertension”.

Caution should be exercised when transferring a patient from clonidine. The withdrawal of clonidine may result in the release of large amounts of catecholamines, which may give rise to a hypertensive crisis. If beta-blockers are administered in these circumstances, the unopposed alpha receptor stimulation may potentiate this effect. If a beta-blocker and clonidine are given concurrently, the clonidine should not be discontinued until several days after the withdrawal of the beta-blocker, as severe rebound hypertension may occur.

Combinations to be used with caution

Calcium antagonists of the dihydropyridine type (e.g. nifedipine, amlodipine): Concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

Concomitant use with other antihypertensive medicines or with other medicines with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines) may increase the risk of hypotension.

ACE inhibitors (e.g. captopril, enalapril), Angiotensin II antagonists: There is a risk of a significant fall in blood pressure and/or acute renal failure during the initiation of ACE inhibitor therapy in patients with pre-existing sodium depletion (particularly in patients with renal artery stenosis).

If prior diuretic therapy has produced sodium depletion, either stop the diuretic 3 days before starting ACE inhibitor therapy, or initiate ACE inhibitor therapy at a low dose.

Caution should be taken in prescribing bisoprolol with Class 1 antidysrhythmic medicines such as quinidine, disopyramide, myocardial depressants, and inhibitors of AV conduction such as calcium antagonists. Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

Class-III antidysrhythmic medicines (e.g. amiodarone): Effect on atrio-ventricular conduction time may be potentiated.

Antidysrhythmic medicines that may induce torsade de pointes (Class IA e.g. quinidine, hydroquinidine, disopyramide, and Class III e.g. amiodarone, sotalol, dofetilide, ibutilide): Hypokalaemia may facilitate the occurrence of torsades de pointes.

Non-antidysrhythmic medicines that may induce torsade de pointes (e.g. astemizole, i.v. erythromycin, halofantrine, pentamidine, sparfloxacin, vincamine): Hypokalaemia may facilitate the occurrence of torsades de pointes.

Parasympathomimetic medicines: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.

Topical beta-blockers (e.g. eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.

Insulin and oral antidiabetic medicines: Increase of blood sugar lowering effect. Blockade of beta-adrenoceptors may mask symptoms of hypoglycaemia (see section 4.4).

Anaesthesia: Attenuation of the reflex tachycardia and increase of the risk of hypotension.

Digoxin: Increase of atrio-ventricular conduction time, reduction in heart rate. If hypokalaemia and/or hypomagnesaemia develop during treatment with ZIABETA, the myocardium may show increased sensitivity to digoxin, leading to an enhanced effect and adverse effects of the digoxin.

Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect. In patients developing hypovolaemia, the concomitant administration of NSAIDs can trigger acute renal failure.

Beta-sympathomimetics (e.g. dobumamine): Combination with bisoprolol may reduce the effect of both medicines.

Sympathomimetics that activate both beta- and alpha-adrenoceptors [e.g. norepinephrine (noradrenaline), epinephrine (adrenaline)]: Combination with bisoprolol may unmask the alpha-adrenoceptor-mediated vasoconstrictor effect of these medicines leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with nonselective beta-blockers.

Potassium-wasting medicines (e.g. corticosteroids, ACTH, carbenoxolone, amphotericin B, furosemide, or laxatives): Concomitant use may result in increased potassium losses.

Methyldopa: haemolysis due to the formation of antibodies to hydrochlorothiazide has been described.

The effect of uric-acid-lowering agents may be attenuated in concomitant administration of ZIABETA.

Cholestyramine, colestipol: reduces the absorption of the hydrochlorothiazide component of ZIABETA.

Combinations to be considered

Mefloquine: increased risk of bradycardia.

Monoamine oxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of the beta-blockers but also risk of hypertensive crisis.

Corticosteroids: Reduced antihypertensive effect (corticosteroid-induced water and sodium retention).

Rifampicin: Slight reduction of the half-life of bisoprolol possible due to the induction of hepatic drug-metabolising enzymes. Normally no dosage adjustment is necessary.

Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.
In high-dose salicylate administration the toxic effect of salicylates on the central nervous system may be enhanced.

4.6 Fertility, pregnancy and lactation

Pregnancy

ZIABETA is not recommended during pregnancy

ZIABETA reduces placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Administration to pregnant mothers shortly before giving birth or during labour may result in the newborn infants being born hypotonic, collapsed and hypoglycaemic.

Lactation

ZIABETA is not recommended in breastfeeding women. Hydrochlorothiazide (contained in ZIABETA) can inhibit milk production.

Fertility

No human data on fertility are known for the combination product.

4.7 Effects on ability to drive and use machines

ZIABETA can cause dizziness and hypotension. The individual patient's response to treatment may impair their ability to drive a vehicle or to use machines. This needs to be considered particularly at the start of treatment, upon change of medication, or in conjunction with alcohol.

4.8 Undesirable effects

Tabulated summary of adverse reactions

Common (≥ 1 % and < 10 %), uncommon (≥ 0,1 % and < 1 %), rare (≥ 0,01 % and < 0,1 %), Very rare (< 0,01 %) including isolated cases.

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Not known: non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma) (see section 4.4)

Blood and lymphatic system disorders

Rare: leucopenia, thrombocytopenia

Very rare: agranulocytosis

Metabolism and nutrition disorders

Uncommon: loss of appetite

Very rare: metabolic alkalosis

Uncommon: hyperglycaemia, hyperuricaemia, disturbances of fluid and electrolyte balance (in hypokalaemia and hyponatraemia, also hypomagnesaemia and hypochloraemia as well as hypercalcaemia)

Psychiatric disorders

Uncommon: depression, sleep disorders

Rare: nightmares, hallucinations

Nervous system disorders

Common: dizziness, headache

Eye disorders

Rare: reduced tear flow, visual disturbances

Very rare: conjunctivitis

Not known: acute myopia, acute angle-closure glaucoma

Ear and labyrinth disorders

Rare: hearing disorders

Cardiac disorders

Uncommon: bradycardia, AV-conduction disturbances, worsening of heart failure

Vascular disorders

Common: feeling of coldness or numbness in extremities

Uncommon: orthostatic hypotension

Rare: syncope

Respiratory, thoracic and mediastinal disorders

Uncommon: bronchospasm in patients with bronchial asthma or history of obstructive airways disease

Rare: allergic rhinitis

Gastrointestinal disorders

Common: gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation

Uncommon: abdominal complaints

Very rare: pancreatitis

Hepato-biliary disorders

Rare: hepatitis, jaundice

Skin and subcutaneous tissue disorders

Rare: hypersensitivity reactions such as itching, flush, rash, photodermatitis, purpura, urticaria

Very rare: anaphylactic reactions, alopecia, cutaneous lupus erythematosus. ZIABETA may provoke or worsen psoriasis or induce psoriasis-like rash.

Musculoskeletal and connective tissue disorders

Uncommon: muscle weakness, muscle cramps

Reproductive system and breast disorders

Rare: erectile dysfunction

General disorders

Common: fatigue

Uncommon: asthenia

Very rare: chest pain

Investigations

Uncommon: increase in amylase, increase of serum creatinine and urea, increased triglyceride and cholesterol levels, glucosuria

Rare: increase in liver enzymes (AST, ALT)

Description of selected adverse reactions

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and NMSC has been observed (see also sections 4.4 and 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

The most common signs expected with overdose of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. There is a wide inter-individual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive.

The clinical picture in acute or chronic overdose of hydrochlorothiazide is characterised by the extent of fluid and electrolyte loss. Most common signs are dizziness, nausea, somnolence, hypovolaemia, hypotension, hypokalaemia.

Cases of mild overdose should be observed for at least four hours, as apnoea and cardiovascular collapse may appear suddenly.

Management

In general, if overdose occurs, discontinuation of ZIABETA and supportive and symptomatic treatment is recommended.

Repeated activated charcoal is necessary in severe overdose.

Atropine may be used to treat severe bradycardia. If the response is inadequate, glucagon may be given intravenously. Alternatively, dobutamine or isoprenaline, may be required to reverse beta-blockade. Intravenous cardiac pacing may be required for severe bradycardia. Bronchospasm should be treated with IV aminophylline or inhaled, or IV beta-agonist, e.g. salbutamol.

Limited data suggest that bisoprolol is hardly dialyzable. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 7.1.3 Other hypotensives

ZIABETA is a combination of two antihypertensive agents, bisoprolol and hydrochlorothiazide.

Bisoprolol

Bisoprolol is a $ß_1$-selective beta-adrenoceptor antagonist with low $ß_2$-receptor affinity.

It has no intrinsic sympathomimetic activity nor membrane-stabilising properties. It reduces blood pressure, and by blockade of the cardiac ß$_1$-receptors, reduces heart rate and depresses plasma renin levels.

Hydrochlorothiazide

Hydrochlorothiazide is a benzothiadiazine diuretic. Thiazides inhibit sodium and chloride reabsorption in the kidney tubules and produce a corresponding increase in potassium excretion.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and Non-Melanoma Skin Cancer (NMSC) has been observed. One study included a population comprised of 71,533 cases of Basal cell carcinoma (BCC) and of 8,629 cases of Squamous cell carcinoma (SCC) matched to 1,430,833 and 172,462 population controls, respectively. High hydrochlorothiazide use (≥ 50,000 mg cumulative) was associated with an adjusted odds ratio (OR) of 1,29 (95 % CI: 1,23 - 1,35) for BCC and 3,98 (95 % CI: 3,68 - 4,31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to hydrochlorothiazide: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2,1 (95 % CI: 1,7 - 2,6) increasing to OR 3,9 (3,0 - 4,9) for high use (~25,000 mg) and OR 7,7 (5,7 - 10,5) for the highest cumulative dose (~100,000 mg) (see section 4.4).

5.2 Pharmacokinetic properties

Bisoprolol

Absorption

Because of its moderate hepatic metabolism, it is subject only to a small hepatic first pass metabolism. Therefore, bisoprolol displays a high bioavailability of 90 % after an oral dose and absorption is not affected by food. Tmax varies from 1 – 4 hours.

Distribution

The plasma protein binding of bisoprolol is about 30 %. The distribution volume is 3,5 l/kg. Total clearance is approximately 15 l/h.

Biotransformation

40 % of a bisoprolol dose is metabolised in the liver. Bisoprolol metabolites are inactive.

Elimination:

Bisoprolol is absorbed after oral administration in man and excreted predominantly via the urine as unaltered substance and metabolites. The plasma elimination half-life is 10-12 hours, resulting in a duration of action of 24 hours.

Hydrochlorothiazide

Absorption

Hydrochlorothiazide is well absorbed from the gastro-intestinal tract. It is reported to have a bioavailability of about 60 to 80 %. Tmax varies from 1,5 – 5 hours (mean ~4 hours).

Distribution

Plasma protein binding is 40 %.

Elimination

The plasma half-life is about 5 hours with a subsequent longer terminal phase; its biological half-life is up to about 15 hours. It is excreted unchanged in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ZIABETA 2,5 mg/6,25 mg, film-coated tablet

Tablet core: Calcium hydrogen phosphate, magnesium stearate, maize starch, microcrystalline cellulose, crospovidone.

Film coating: Polysorbate, hypromellose, iron oxide, macrogol, titanium dioxide.

ZIABETA 5 mg/6,25 mg, film-coated tablet

Tablet core: Calcium hydrogen phosphate, magnesium stearate, maize starch, microcrystalline cellulose, silica, colloidal.

Film coating: Polysorbate, hypromellose, iron oxide, macrogol, titanium dioxide.

ZIABETA 10 mg/6,25 mg, film-coated tablet

Tablet core: Calcium hydrogen phosphate, magnesium stearate, maize starch, microcrystalline cellulose, silica, colloidal.

Film coating: Polysorbate, hypromellose, macrogol, titanium dioxide.

6.2 Incompatibilities

None

6.3 Shelf life

ZIABETA 2,5 mg/6,25 mg: 24 months

ZIABETA 5 mg/6,25 mg: 36 months

ZIABETA 10 mg/6,25 mg: 36 months

6.4 Special precautions for storage

Store at or below 30 °C. Store in the original package in order to protect from light.

6.5 Nature and contents of container

30 Tablets in blisters of 10 tablets each.

6.6 Special precautions for disposal and other handling

Any unused (including expired) product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Merck (Pty) Ltd

1 Friesland Drive

Longmeadow Business Estate South,

Modderfontein, 1645

South Africa

Name and address of the manufacturer

Merck Healthcare KGaA

250 Frankfurterstrasse

64293 Darmstadt

Germany

8. REGISTRATION NUMBERS

ZIABETA 2,5 mg/6,25 mg:	37/7.1.3/0564
ZIABETA 5 mg/6,25 mg:	37/7.1.3/0610
ZIABETA10 mg/6,25 mg:	37/7.1.3/0611

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 April 1988

10. DATE OF REVISION OF THE TEXT

17/03/2022