SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Chordyna 2 mg, tabletten
Chordyna 4 mg, tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Chordyna 2-4 mg, tabletten 2 mg tablets
Each tablet contains 2 mg tizanidine (as 2.29 mg tizanidine hydrochloride).

Excipients with known effect:
Each tablet contains 106.79 mg lactose monohydrate and 11.76 mg sucrose.

Chordyna 2-4 mg, tabletten 4 mg tablets
Each tablet contains 4 mg tizanidine (as 4.57 mg tizanidine hydrochloride).

Excipients with known effect:
Each tablet contains 104.51 mg lactose monohydrate and 11.76 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Chordyna 2-4 mg, tabletten 2 mg tablets
White to yellowish coloured, round and biconvex tablet, with a break score on one side and with a diameter of about 8 mm.
The tablet can be divided into equal doses.

Chordyna 2-4 mg, tabletten 4 mg tablets
White to yellowish coloured, round and biconvex tablet, with a cross break score on one side and with a diameter of about 8 mm.
The tablet can be divided into equal doses, either halves or quarts.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Spasms of the skeletal muscles
- associated with static and functional disorders of the spine (cervical and lumbar syndromes)
- after surgical interventions on the musculoskeletal system, e.g. herniated disc or joint disorders of the hip.

Spasticity due to neurological disorders, such as
- multiple sclerosis, chronic myelopathy, degenerative spinal cord disease, cerebrovascular accidents and cerebral palsy.

4.2 Posology and method of administration

Chordyna 2-4 mg, tabletten has a narrow therapeutic index and a high inter-patient variability in tizanidine plasma concentrations. Therefore, it is important to adjust the dose individually.
A low starting dose of 2 mg three times daily can reduce the risk of side effects. The dose should be increased gradually and with caution according to the individual patient's need and the therapeutic response.

Posology

Spasms of the skeletal muscles
The recommended dose is 2-4 mg 3 times daily.
In severe cases, an extra dose of 2-4 mg may be given, preferably late in the evening to reduce the sedative effect.

Spasticity due to neurological disorders
The initial daily dose should not exceed 6 mg in 3 divided doses. This dose may be increased in steps by 2-4 mg at intervals of half or full week.
The optimum therapeutic response is usually achieved with a daily dose of between 12 and 24 mg, divided into 3-4 equal doses throughout the day.
The total daily dose should not exceed 36 mg.

Special populations

Paediatric population
The safety and efficacy of tizanidine in children and adolescents under 18 years have not been established. Limited data are available. Tizanidine cannot be recommended for the use in children and adolescents (see section 4.8).

Elderly
Experience with tizanidine in the elderly is limited.
In this patient group the starting dose should be as low as possible and it should be increased in small increments, according to tolerability and efficacy.

Renal impairment
In patients with renal impairment (CL_{CR} < 25 mL/min) treatment should be started with 2 mg once daily with slow titration to achieve the effective dose. Dosage increases should be in increments of no more than 2 mg according to tolerability and effectiveness. If efficacy has to be improved, it is advisable to slowly increase the once-daily dose before increasing the frequency of administration. Renal function should be monitored as appropriate in these patients (see sections 4.4 and 5.2).

Hepatic impairment
Tizanidine is contraindicated in patients with severe hepatic impairment (see section 4.3).
Only limited data are available in this patient group. Tizanidine is mainly metabolised in the liver (see section 5.2). Its use is associated with reversible abnormalities in liver function (see sections 4.4 and 4.8). Tizanidine should be used with caution in patients with mild and moderate hepatic impairment. The starting dose should be as low as possible and it should be increased in small increments, according to tolerability and efficacy.

Discontinuing therapy
If therapy needs to be discontinued, particularly in patients who have been receiving high doses for long periods, the dose should be decreased slowly. This is to prevent or reduce the risk of rebound hypertension and tachycardia (see section 4.4).

Method of administration
Oral use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Severe hepatic impairment
- Concomitant use of tizanidine with potent CYP1A2 inhibitors such as fluvoxamine or ciprofloxacin (see section 4.5)

4.4 Special warnings and precautions for use

CYP1A2 inhibitors
Because of potential drug interactions, tizanidine is contraindicated in patients taking potent CYP1A2 inhibitors, such as fluvoxamine or ciprofloxacin (see section 4.3).
Adverse reactions such as hypotension, bradycardia, or excessive drowsiness can occur when tizanidine is taken with other CYP1A2 inhibitors (see section 4.5). Concomitant use should be avoided unless the necessity for tizanidine therapy is clinically evident. In such a case, tizanidine should be used with caution.

Hypotension
Tizanidine is an α_2-adrenergic agonist that can produce hypotension. Syncope has been reported in the post marketing setting. The chance of significant hypotension may possibly be minimised by titration of the dose and by focusing attention on signs and symptoms of hypotension prior to dose advancement. In addition, patients moving from a supine to fixed upright position may be at increased risk for hypotension and orthostatic effects (see section 4.5).

Withdrawal syndrome
Withdrawal adverse reactions include rebound hypertension, tachycardia, and hypertonia. To minimise the risk of these reactions, particularly in patients who have been receiving high doses (20 to 28 mg daily) for long periods (9 weeks or more) or who may be on concomitant treatment with narcotics, the dose should be decreased slowly (2 to 4 mg per day).

Hepatic impairment
Since hepatic dysfunction has been reported in association with tizanidine, but rarely at daily doses up to 12 mg, it is recommended that liver function tests should be monitored monthly for the first four months in patients receiving doses of 12 mg and higher and in patients who develop clinical symptoms suggestive of hepatic dysfunction, such as unexplained nausea, anorexia or tiredness. Treatment with tizanidine should be discontinued if serum levels of SGPT (serum glutamic-pyruvic transaminase) and/or SGOT (serum glutamic-oxaloacetic transaminase) are persistently above three times the upper limit of the normal range. Tizanidine should be discontinued in patients with symptoms compatible with hepatitis or where jaundice occurs.

Cardiovascular, hepatic or renal disorders
Caution is required in patients with cardiovascular disorders, coronary artery disease, or renal or hepatic disorders. Regular clinical laboratory and ECG monitoring is recommended during treatment with tizanidine.

Renal impairment
Tizanidine should be used with caution in patients with renal insufficiency (creatinine clearance < 25 mL/min), as clearance is reduced by more than 50%. In these patients, during titration, the individual doses should be reduced. If higher doses are required, individual doses rather than dosing frequency should be increased. These patients should be monitored closely for the onset or increase in severity of the common adverse events (dry mouth, somnolence, asthenia, and dizziness) as indicators of potential overdose (see section 4.2).

Sedation
Tizanidine can cause sedation, which may interfere with everyday activity. In multiple dose studies, the prevalence of patients with sedation peaked following the first week of titration and then remained stable for the duration of the maintenance phase of the study.

Hallucinosis/Psychotic-like symptoms
Tizanidine use has been associated with hallucinations. Formed, visual hallucinations or delusions have been reported in 5 of 170 patients (3%) in two North American controlled clinical studies. Most of the patients were aware that the events were unreal. One patient developed psychosis in association with the hallucinations. One patient among these 5 continued to have problems for at least 2 weeks following discontinuation of tizanidine. Discontinuing should be considered in patients who develop hallucinations.

Hypersensitivity reactions
Tizanidine can cause anaphylaxis. Signs and symptoms including respiratory compromise, urticaria, and angioedema of the throat and tongue have been reported. Patients should be informed of the signs and symptoms of severe allergic reactions and instructed to discontinue tizanidine and seek immediate medical care if they occur.

Chordyna 2-4 mg, tabletten contains lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Chordyna 2-4 mg, tabletten 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

CYP1A2 inhibitors
The concomitant use of tizanidine with potent CYP1A2 inhibitors such as fluvoxamine or ciprofloxacin is contraindicated (see section 4.3). Fluvoxamine or ciprofloxacin increases the exposure to tizanidine by a mean of 10- to 33-fold, respectively. The hypotensive and sedative effects of tizanidine can increase markedly.
The concomitant use of tizanidine with other CYP1A2 inhibitors may lead to a marked increase in tizanidine serum levels (see sections 4.4 and 5.2). Therefore, the concomitant use of tizanidine with other CYP1A2 inhibitors such as some antiarrythmics (amiodarone, mexiletine, propafenone, and verapamil), cimetidine, famotidine, some fluoroquinolones (enoxacin, pefloxacin, norfloxacin), rofecoxib, acyclovir, and ticlopidine should be avoided. If their use is clinically necessary, the patients should be closely monitored. If adverse reactions such as hypotension, bradycardia, or excessive drowsiness occur, tizanidine therapy should be reduced or discontinued.

Oral contraceptives
Combined hormonal contraceptives moderately increase tizanidine levels and might increase its adverse effects. If concomitant use is clinically necessary, and if adverse reactions such as hypotension, bradycardia, or excessive drowsiness occur, tizanidine therapy should be reduced or discontinued.

CYP1A2 inducers
In the contrary to CYP1A2 inhibitors, CYP1A2 inducers may lead to a decrease in tizanidine serum levels.

Rifampicin
Rifampicin appears to be only a weak to moderate inducer of CYP1A2. The clinical relevance is unclear. A small increase in dose might be required if rifampicin is given to those taking

established doses of tizanidine.

Drugs that prolong the QT interval
The concurrent use of more than one drug that prolongs the QT interval increases the risk of torsade de pointes. Therefore, caution is advised when tizanidine is used concurrently.

Antihypertensives
As tizanidine may induce hypotension it may potentiate the effect of antihypertensive products, including diuretics, and caution should therefore be exercised in patients receiving blood pressure lowering products.
Caution should also be exercised when tizanidine is used concurrently with ß-adrenoceptor blocking substances or digoxin as the combination may potentiate hypotension or bradycardia (see section 4.4).

Other CNS depressants
The sedative effects of tizanidine with CNS depressants (e.g. benzodiazepines, opioids, tricyclic antidepressants) may be additive. Monitor patients who take tizanidine with another CNS depressant for symptoms of excess sedation.

Alcohol
Alcohol increases the overall amount of drug in the bloodstream after a dose of tizanidine. This was associated with an increase in adverse reactions of tizanidine. The CNS depressant effects of tizanidine and alcohol are additive.

Smoking
Smoking decreases the plasma levels of tizanidine.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of tizanidine in pregnancy has not been established.
Therefore, tizanidine should not be used in pregnant women unless the benefit clearly outweighs the risk.

Breast-feeding
The safety of tizanidine in breast-fed infants of mothers receiving tizanidine is not known. Tizanidine and/or its metabolites have been found in the milk of rodents (see section 5.3). Therefore, tizanidine should not be used in nursing mothers unless the benefit clearly outweighs the risk.

Fertility
Reproductive studies in rats and rabbits indicate that tizanidine does not have embryonic or teratogenic potential but at maternally toxic doses of 10-100 mg/kg per day tizanidine can retard foetal development due to its pharmacodynamic effects.

4.7 Effects on ability to drive and use machines

Tizanidine has minor or moderate influence on the ability to drive and use machines. Patients experiencing drowsiness or dizziness should be advised against activities requiring a high degree of alertness.

4.8 Undesirable effects

a. Summary of the safety profile

Many adverse effects have been found to be dose related and slow titration of doses appears

to reduce the frequency of occurrence.

With low doses, such as those recommended for the relief of painful muscle spasms, somnolence, fatigue, dizziness, dry mouth, decreased blood pressure, nausea, gastrointestinal disturbances, and increased hepatic enzymes have been reported, usually as mild and transient adverse reactions.

With the higher doses recommended for the treatment of spasticity, the adverse reactions reported with low doses are more frequent and more pronounced, but seldom severe enough to require discontinuation of treatment.

b. Tabulated list of adverse reactions

The table below shows the frequencies of adverse reactions which have been reported in clinical trials and post-marketing experience. The frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (frequency cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Not known
Infections and infestations				Infections Rhinitis Pharyngitis
Immune system disorders				Hypersensitivity reactions including anaphylaxis, angioedema and urticaria(1)
Psychiatric disorders	Sleep disorders Insomnia			Confusion(1) Nervousness Hallucinations(1)
Nervous system disorders		Somnolence Drowsiness(2) Dizziness(2) Fatigue(2)		Headache Ataxia Dyskinesia Dysarthria Syncope(1) Vertigo(1)
Eye disorders				Accommodation disorder Blurred vision(1)
Cardiac disorders		Bradycardia Tachycardia		QT prolongation(1)
Vascular disorders		Hypotension(2)		
Gastrointestinal disorders	Dry mouth(2) Gastrointestinal disturbances(2)	Nausea(2)		Vomiting Abdominal pain Constipation
Hepatobiliary disorders				Hepatitis(1) Hepatic failure(1)
Skin and subcutaneous tissue disorders				Pruritus(1) Rash(1) Dermatitis(1)
Musculoskeletal and connective tissue disorders	Muscular weakness			

System organ class	Very common	Common	Uncommon	Not known
Renal and urinary disorders				Pollakiuria Urinary tract infection
General disorders and administration site conditions				Anorexia Asthenia(1) Withdrawal syndrome(1) Flu-like illness
Investigations		Blood pressure decreased	Hepatic enzymes increased	
(1) Adverse reactions reported in post marketing experience (2) With slow upward titration of the dose of tizanidine, these effects are usually not severe enough to require discontinuation of treatment.				

c. Description of selected adverse reactions

Hallucinations
The hallucinations are self-limiting, without evidence of psychosis, and have invariably occurred in patients concurrently taking potentially hallucinogenic substances, e.g. antidepressants.

Withdrawal syndrome
Rebound hypertension and tachycardia have been observed after sudden withdrawal of tizanidine, when it had been used chronically, and/or in high daily dosages, and/or concomitantly with antihypertensive drugs. In extreme cases, rebound hypertension might lead to cerebrovascular accident (see sections 4.4 and 4.5).

d. Paediatric population

Spontaneous adverse event reports were compared in a clinical adverse event database for children (≤ 16 years; n = 99) and adults (> 16 years; n = 1,153). The overall safety of tizanidine in the paediatric group appeared good; however, the adverse event profile differed from that in adults. The most common adverse event classes in children were psychiatric disorders (52.5%) followed by nervous system disorders (29.3%), and gastrointestinal disorders (16.2%), whereas the most common adverse event classes in adults were nervous system disorders (42.4%), general disorders and administration site conditions (28.6%), and gastrointestinal disorders (21.3%). Serious adverse events were substantially less frequent in children than adults (19.2% vs 45.9%).

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

[according to Appendix V – to be completed nationally]

4.9 Overdose

Clinical experience is limited. In one case, where an adult patient ingested 400 mg tizanidine, recovery was uneventful.

Symptoms
Nausea, vomiting, hypotension, bradycardia, QT prolongation, dizziness, miosis, respiratory distress, coma, restlessness, and somnolence may occur.

Management
General supportive measures are indicated and an attempt should be made to remove ingested substance from the gastro-intestinal tract using gastric lavage or by repeated administration of high doses of activated charcoal. The patient should be well hydrated as forced diuresis is expected to accelerate the elimination of tizanidine. Further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: musculo-skeletal system; muscle relaxants; centrally acting agents; other centrally acting agents
ATC code: M03BX02

The exact mechanism of action of tizanidine has not been fully clarified. It is believed that the pharmacodynamic effects of tizanidine are primarily linked to its α_2-adrenergic agonist properties, although its imidazoline receptor binding may play a role. The predominant effect of tizanidine appears to occur presynaptically in the spinal cord by reducing release of the excitatory amino acids glutamate and aspartate from the presynaptic terminal of spinal interneurons. There is some evidence of postsynaptic action on excitatory amino acid receptors.

In humans, tizanidine reduces pathologically increased muscle tone, including resistance to passive movements and alleviates painful spasms and clonus.

5.2 Pharmacokinetic properties

Absorption
Tizanidine is rapidly and almost completely absorbed. The maximum plasma concentration is reached approximately 1 hour after administration. The mean absolute bioavailability is approximately 34% because of the strong first-pass metabolism. The average maximum plasma concentration (C_{max}) of tizanidine is 12.3 ng/mL after a single administration and 15.6 ng/mL after repeated administration of 4 mg tizanidine. Concomitant use of food has no relevant influence on the pharmacokinetic profile of tizanidine. Food increases C_{max} by about one third, but has no effect on the extent of absorption (AUC). The increase in C_{max} is not considered clinically relevant.

Distribution
Mean steady-state volume of distribution (VSS) following i.v. administration is 2.6 L/kg. Tizanidine is 30% bound to plasma proteins. Tizanidine has linear pharmacokinetics in the dose range of 1-20 mg.

Biotransformation
Tizanidine undergoes rapid and extensive metabolism in the liver (about 95%). Tizanidine is mainly metabolised *in vitro* by CYP1A2. The metabolites appear to be inactive.

Elimination
The elimination half-life of tizanidine from plasma is 2 to 4 hours. The metabolites are primarily excreted via the renal route (approx. 70% of the dose). Only a small part of the active substance is excreted unchanged via the urine (approx. 4.5%).

Special patient groups

Renal impairment

In patients with renal insufficiency (creatinine clearance < 25 mL/min), maximum mean plasma levels were found to be two times higher than in healthy volunteers. Also the terminal half-life was extended to approximately 14 hours, resulting in a significant (mean approximately 6-fold) increase in bioavailability (AUC).

Hepatic impairment
No specific studies have been conducted with this population. Because tizanidine is metabolised mainly in the liver by CYP1A2, hepatic impairment can lead to increased systemic exposure. Tizanidine is contraindicated in patients with significant hepatic impairment (see section 4.3).

The influence of hepatic impairment on the pharmacokinetics of tizanidine has not been evaluated. Because tizanidine is extensively metabolised in the liver, hepatic impairment would be expected to have significant effects on pharmacokinetics of tizanidine.

Paediatric population
Tizanidine has not been evaluated in the paediatric population.

Elderly (over 65 years of age)
No specific pharmacokinetic study was conducted to investigate age effects. Cross study comparison of pharmacokinetic data following single dose administration of 6 mg tizanidine showed that younger subjects cleared the drug 4-times faster than the elderly subjects.

5.3 Preclinical safety data

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

Tizanidine has been found to pass into the milk of nursing rats with a milk to blood concentration ratio of 1.8:1.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Starch, pregelatinised (maize)
Macrogol 4000
Stearic acid (E 570)
Sucrose
Magnesium stearate (E 470b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

No special storage conditions.

6.5 Nature and contents of container

Opaque PVC/PVdC/PVC-aluminium blister packs with 10, 30, 60, 90, 100 or 120 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Bausch Health Ireland Limited
3013 Lake Drive, Citywest Business Campus
Dublin 24, D24PPT3
Ierland

8. MARKETING AUTHORISATION NUMBERS

Chordyna 2 mg, tabletten: RVG 131476
Chordyna 4 mg, tabletten: RVG 131477

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 4 februari 2026

10. DATE OF REVISION OF THE TEXT