SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

Forvent® 18 microgram Capsules for inhalation

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule for inhalation contains 18 μg tiotropium equivalent to 22,5 μg tiotropium bromide monohydrate (INN = tiotropium bromide).
The powder is contained in hard gelatine capsules.
Contains sugar (5,5 mg lactose monohydrate per capsule).
For full list of excipients, please see section 6.1.

3 PHARMACEUTICAL FORM

Capsules for inhalation

Light green, opaque, hard gelatine capsules, containing a white powder, with "TI 01" and the Boehringer Ingelheim company logo printed in black on the capsule.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

FORVENT is indicated for the long term maintenance treatment of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and chronic bronchitis associated with emphysema.

4.2 Posology and method of administration

Posology

Recommended dosage: Inhale the contents of one capsule once daily, at the same time each day, using the HandiHaler® device (see **HandiHaler® INSTRUCTIONS FOR USE** in the Patient Information Leaflet (PIL)).
FORVENT capsules must not be swallowed.

Optimum efficacy can only be expected within a few days of usage.

Special Populations

Elderly patients can use the recommended dose of FORVENT capsules for inhalation.

Renally impaired patients can use tiotropium at the recommended dose. However, FORVENT use should be monitored closely in patients with moderate to severe renal impairment (see section 4.4 and section 5.2 *c) Characteristics in patients*).

Hepatically impaired patients can use FORVENT at the recommended dose (see section 5.2 *c) Characteristics in patients*).

Paediatric population
There is no relevant use in the paediatric population (below 18 years).

Method of administration
Please refer to the **HandiHaler® INSTRUCTIONS FOR USE** in the PIL.

4.3 Contraindications
FORVENT capsules for inhalation are contraindicated in patients with a history of hypersensitivity to atropine or its derivatives e.g. ipratropium, oxitropium, tiotropium or to any other component of this product (see section 6.1 and section 4.4).

4.4 Special warnings and precautions for use
FORVENT, as a once daily maintenance bronchodilator, should not be used for the initial treatment of acute episodes of bronchospasm, i.e. rescue therapy.
Immediate hypersensitivity reactions may occur after administration of FORVENT inhalation powder.

FORVENT should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction.

Inhaled FORVENT may cause inhalation-induced bronchospasm.

The use of FORVENT should be monitored closely in patients with moderate to severe renal impairment (creatinine clearance of $\leq$ 50 mL/min) (see section 5.2).

Patients must be instructed in the correct administration of FORVENT capsules for inhalation. Care must be taken not to allow the powder to enter into their eyes. Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema may be signs of acute narrow-angle glaucoma. Should any combination of these symptoms develop, specialist advice should be sought immediately. Miotic eye drops are not considered to be effective treatment for eye symptoms following the use of FORVENT.
FORVENT should not be used more frequently than once daily.
FORVENT capsules are to be used only with the HandiHaler® device (see **HandiHaler® INSTRUCTIONS FOR USE** in the PIL).
FORVENT contains 5,5 mg of lactose monohydrate per capsule.
Patients with rare hereditary conditions of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction
Although no formal medicine interaction studies have been performed, tiotropium bromide has been used concomitantly with other medicines, commonly used in the

treatment of COPD, including sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids without clinical evidence of medicine interactions.
Common concomitant medications (LABA (long-acting $beta_2$ agonist), ICS (inhaled corticosteroids) and their combinations) used by patients with COPD were not found to alter the exposure to FORVENT.

Limited information about co-administration of other anticholinergic medicines with FORVENT is available from two clinical trials: Acute single dose administration of ipratropium bromide with chronically administered FORVENT in COPD patients (n = 64) and healthy volunteers (n = 35) was not associated with an increase in adverse events, changes in vital signs or electrocardiographic findings. However, chronic co-administration of other anticholinergic medicines with FORVENT has not been studied and is, therefore, not recommended.

4.6 Fertility, pregnancy and lactation
Safety in pregnancy and lactation have not been established.

Pregnancy
There is a limited amount of data from the use of tiotropium in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant doses.
The use of FORVENT during pregnancy is not recommended.

Breastfeeding
It is unknown whether tiotropium bromide is excreted in human breast milk. Studies in rodents have demonstrated that excretion of tiotropium bromide in breast milk occurs in small amounts.
Tiotropium bromide is a long-acting compound.
Use of FORVENT during breastfeeding is not recommended.

Fertility
Clinical data on fertility are not available for tiotropium. A non-clinical study performed with tiotropium showed no indication of any adverse effect on fertility (see section 5.3).

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. FORVENT may cause dizziness or blurred vision, which may influence the ability to drive and use machinery.

4.8 Undesirable effects
Many of the listed effects can be assigned to the anticholinergic properties of FORVENT. Adverse drug reactions were identified from data obtained in clinical trials.
The frequencies given below are based on crude incidence rates of adverse drug reactions observed in the tiotropium group, 9 647 patients, pooled from a database comprising of 28 placebo-controlled clinical trials with treatment periods ranging between four weeks and four years, contributing 12 469 person years of exposure to tiotropium.

Frequency classes: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥ 1/10 000, < 1/1000); very rare (< 1/10 000); not known (frequency not known if no adverse drug reaction was observed in the pooled clinical trial database).

Frequency	MedDRA Preferred Term
Metabolism and nutrition disorders:	
Not known:	dehydration
Nervous system disorders:	
Uncommon:	dizziness, headache, dysgeusia
Rare:	insomnia
Eye disorders:	
Uncommon:	blurred vision
Rare:	glaucoma, increased intraocular pressure
Cardiac disorders:	
Uncommon:	atrial fibrillation
Rare:	tachycardia, palpitations, supraventricular tachycardia
Respiratory, thoracic and mediastinal disorders:	
Uncommon:	pharyngitis, dysphonia, cough
Rare:	bronchospasm, epistaxis, laryngitis, sinusitis
Gastrointestinal disorders:	
Common:	dry mouth
Uncommon:	gastro-oesophageal reflux disease, constipation, oropharyngeal candidiasis
Rare:	intestinal obstruction, ileus paralytic, gingivitis, glossitis, dysphagia, stomatitis, nausea
Not known:	dental caries
Skin and subcutaneous tissue disorders:	
Uncommon:	rash
Rare:	Hypersensitivity, urticaria, pruritus, angioedema
Not known:	anaphylactic reaction, skin infection, skin ulcer, dry skin
Musculoskeletal and connective tissue disorders:	
Not known:	joint swelling
Renal and urinary disorders:	
Uncommon:	urinary retention, dysuria
Rare:	urinary tract infection

Post-marketing experience

Adverse reactions have been identified during worldwide post-approval use of FORVENT. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions are: application site irritation (glossitis, mouth ulceration, and pharyngolaryngeal pain), dizziness, dysphagia, hoarseness, intestinal obstruction including ileus paralytic, intraocular pressure

increased, oral candidiasis, palpitations, pruritus, tachycardia, throat irritation, and urticaria.

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. Healthcare providers are asked to report any suspected adverse reactions to the South African Health Products Regulatory Authority (SAHPRA) via the Med Safety App (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website. Suspected adverse reactions can also be reported directly to the holder of the certificate of registration using the email address pv_local_south_africa@boehringer-ingelheim.com.

4.9 Overdose
In theory, high doses of tiotropium may lead to anticholinergic signs and symptoms. Acute intoxication by inadvertent oral ingestion of FORVENT capsules for inhalation is unlikely due to low oral bioavailability.
Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Category and class: A 10.2.1 Bronchodilators-inhalants

Mechanism of action
Tiotropium is a long-acting, antimuscarinic agent. In vitro, it has similar affinity to the subtypes of muscarinic receptors, M_1 to M_5. In the airways, isolated muscle inhibition of M_3 receptors in the smooth muscle results in relaxation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations.
In non-clinical in-vitro as well as in-vivo studies bronchoprotective effects were dose-dependent and lasted longer than 24 hours. The long duration of effect may be related to its slow dissociation from M3 receptors.

Pharmacodynamic effects
Dissociation from M_2-receptors is faster than from M1 or especially M_3, which in functional in vitro studies, appeared as kinetic receptor subtype selectivity of M_3 and M_1 over M_2.

5.2 Pharmacokinetic properties
a) General introduction
Tiotropium is a non-chiral quaternary ammonium compound and is sparingly soluble in water. Tiotropium is not readily absorbed into the systemic circulation of rats and dogs after oral administration of aqueous solutions. Many of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy.

b) General characteristics of the active substance after administration of the medicine

Absorption: Following dry powder inhalation in young healthy volunteers, the absolute bioavailability is 19,5 %. Oral solutions of tiotropium have an absolute bioavailability of 2 - 3 %.
Distribution: Tiotropium has a plasma protein binding of 72 % and shows a volume of distribution (V_{SS}) of 32 L/kg after intravenous administration in young healthy volunteers.

Studies in rats have shown that tiotropium penetrates the blood-brain barrier poorly.
Biotransformation: The extent of biotransformation is small. This is evident from a urinary excretion of 74 % of unchanged substance after an intravenous dose to young healthy volunteers. The major metabolic pathway is non-enzymatic ester cleavage to the alcohol N-methylscopine and dithienylglycolic acid, which do not bind to muscarinic receptors. Some faecal excretion is seen in the rat and dog.

In-vitro experiments with human liver microsomes and human hepatocytes suggest that some further drug (< 20 % of dose after intravenous administration) is metabolised by cytochrome P450 dependent oxidation and subsequent glutathione conjugation to a variety of Phase II-metabolites. This enzymatic pathway can be inhibited by the CYP450 2D6 (and 3A4) inhibitors, quinidine, ketoconazole and gestodene. Thus CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a smaller part of the dose. Tiotropium even in supra-therapeutic concentrations does not inhibit cytochrome P450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A in human liver microsomes.

Elimination: The effective half-life of tiotropium ranges between 27-45 h in healthy volunteers and COPD patients. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers. Urinary excretion of unchanged substance in young healthy volunteers is 74 % of an intravenous dose. Following dry powder inhalation to COPD patients to steady-state, urinary excretion is 7 % (1,3 microgram) of the unchanged dose over 24 hours, the remainder being mainly non-absorbed medicine in the gut that is eliminated by the faeces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine. After chronic once daily inhalation by chronic obstructive pulmonary disease (COPD) patients, pharmacokinetic steady state was reached by day 7 with no accumulation thereafter.

Linearity/nonlinearity: Tiotropium demonstrates linear pharmacokinetics in the therapeutic range independent of the formulation.

c) Characteristics in patients
Elderly Patients: Advancing age was associated with a decrease of tiotropium renal clearance (365 mL/min in COPD patients < 65 years to 271 mL/min in COPD patients > 65 years). This did not result in a corresponding increase in $AUC_{0-6,ss}$ or $C_{max,ss}$ values.

Renally Impaired Patients: Following once daily inhaled administrations of tiotropium to steady-state in COPD patients, with mild renal impairment (CL_{CR} 50-80 mL/min) resulted in slightly higher $AUC_{0-6,ss}$ (between 1,8 – 30 % higher) and similar $C_{max,ss}$ values compared to patients with normal renal function (Cl_{CR} > 80 mL/min).

In COPD patients with moderate to severe renal impairment (CL_{CR} < 50 mL/min) the intravenous administration of tiotropium resulted in doubling of the plasma concentrations (82 % increase in AUC_{0-4h}), and 52 % higher C_{max} compared to COPD patients with normal renal function, which was confirmed by plasma concentrations after dry powder inhalation.

Hepatically Impaired Patients: Although formal studies in patients with impaired liver function have not been done, liver insufficiency is not expected to have any relevant influence on tiotropium pharmacokinetics. Tiotropium is predominantly cleared by renal elimination (74 % in young healthy volunteers) and by simple non-enzymatic ester cleavage to products that do not bind to muscarinic receptors.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate (which contains milk protein).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years
The in-use stability for each blister strip half containing 5 capsules is 4 to 5 days.

6.4 Special precautions for storage

Store at or below 25 °C.
Do not freeze. Keep out of reach of children.

6.5 Nature and contents of container

Cartons containing 30 capsules for inhalation.
Cartons containing a HandiHaler® device and 30 capsules for inhalation.
The capsules are packaged in aluminium blister strips containing 10 capsules per strip.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER(S)

36/10.2.1/0045

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 November 2002

10 DATE OF REVISION OF THE TEXT

05 May 2026

NAMIBIA Reg. No.	NS2
10/10.2.1/0351	