SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Oxybutynin hydrochloride XL 10mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release tablet contains 10 mg of oxybutynin hydrochloride

Excipient(s) with known effect:

Each 10 mg prolonged release tablets contains 32.0 mg Lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablet.

Oxybutynin hydrochloride XL 10 mg prolonged release tablets Pink colored, round shaped, biconvex coated tablets imprinted with "EM2" on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

Oxybutynin hydrochloride XL is indicated in adults for the symptomatic treatment of urge incontinence and/or increased urinary frequency associated with urgency as may occur in patients with unstable bladder.

Paediatric population

Oxybutynin hydrochloride is indicated in children over 5 years of age for:

- Urinary incontinence, urgency and frequency in unstable bladder conditions due to idiopathic overactive bladder or neurogenic bladder disorders (detrusor over activity)

- Nocturnal enuresis associated with detrusor over activity, in conjunction with non-drug therapy, when other treatment has failed.

4.2 Posology and method of administration

Posology

Oxybutynin hydrochloride XL may be administered with or without food (see section 5.2).

Adults

Starting dose: the recommended starting dose is one 5 mg tablet once daily.

Maintenance dose/dose adjustment: In order to achieve a maintenance dose giving an optimal balance of efficacy and tolerability, after at least one week on 5 mg daily, the dose may be increased to 10 mg once daily, with subsequent incremental increases or decreases of 5 mg/day. There should be an interval of at least one week between dose changes.

Maximum dose: in patients requiring a higher dose, the total daily dose should not exceed 20 mg.

For patients currently taking oxybutynin immediate release, clinical judgement should be exercised in selecting the appropriate dose of Oxybutynin hydrochloride XL. The dosage should be adjusted to the minimum dose that achieves an optimal balance of efficacy and tolerability, taking into account the current immediate-release dose.

In case of a missed dose, the patient should wait and take the next dose at the regular time.

Elderly

No dosage adjustment is necessary in elderly patients.

Paediatric population

Children over the age of 5 years

Initial dose of 5 mg once a day increased in 5mg increments up to a maximum of 15 mg once a day.

Oxybutynin hydrochloride XL should not be used in children below age of 5 years, because safety and efficacy have not been established (see sections 5.1 and 5.2).

Method of administration

Oxybutynin hydrochloride XL must be swallowed whole with the aid of liquid, and must not be chewed, divided, or crushed because the tablet is formulated to provide prolonged release.

Patients should be advised that the tablet membrane may pass through the gastrointestinal tract unchanged. This has no bearing on the efficacy of the product.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the other excipients listed in section 6.1
- Myasthenia gravis
- Narrow-angle glaucoma or shallow anterior chamber
- Gastrointestinal obstructive disorders including paralytic ileus, intestinal atony
- Toxic megacolon
- Severe ulcerative colitis
- Bladder outflow obstruction where urinary frequency may be precipitated
- Porphyria.

4.4 Special warnings and precautions for use

Oxybutynin should be used with caution in patients with Parkinson's disease who are at greater risk of occurrence of adverse reactions to the product and in patients with autonomic neuropathy (such as those with Parkinson's disease), several gastro-intestinal motility disorders, hepatic or renal impairment.

Anticholinergic medicinal products may decrease gastrointestinal motility and should be used with caution in patients with gastrointestinal obstructive disorders, intestinal atony and ulcerative colitis.

Oxybutynin may aggravate cognitive disorders, symptoms of prostatic hypertrophy and tachycardia (thus be cautious in case of hyperthyroidism, congestive heart failure, cardiac arrhythmia, coronary heart disease, hypertension).

Anticholinergic CNS effects (such as hallucinations, agitation, confusion, somnolence) have been reported. Monitoring recommended, particularly in first few months after initiating therapy or increasing the dose. If anticholinergic CNS effects develop, termination of treatment or dose reduction may be considered.

Angioedema of the face, lips, tongue and/or larynx has been reported with oxybutynin. In some cases, angioedema occurred after the first dose. Angioedema associated with upper airway swelling has the potential to become life-threatening. If involvement of tongue, hypopharynx, or larynx occurs, oxybutynin should be promptly discontinued and appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided.

Since oxybutynin can cause narrow-angle glaucoma, patients should be advised to contact a physician immediately if they are aware of a sudden loss of visual acuity or ocular pain.

Oxybutynin may reduce salivary secretions, which could result in dental caries, parodontotsis, or oral candidiasis.

Anticholinergic medicinal products should be used with caution in patients who have hiatus hernia/gastro-oesophageal reflux and/or who are concurrently taking medicinal products (such as bisphosphonates) that can cause or exacerbate oesophagitis.

When oxybutynin is used in high environmental temperatures, this can cause heat prostration due to decreased sweating.

Elderly

Anticholinergic medicinal products should be used with caution in elderly patients, especially if frail, due to the risk of cognitive impairment. They also have a higher risk of occurrence of adverse reactions to the product.

Paediatric population

The use of oxybutynin hydrochloride in children under 5 years of age is not recommended. It has not been established whether oxybutynin hydrochloride can be used safely in this age group.

There is limited evidence supporting the use of Oxybutynin hydrochloride in children with mono symptomatic nocturnal enuresis (not related to detrusor over activity).

In children of 5 years of age or older, Oxybutynin hydrochloride should be used with caution as they may be more sensitive to the effects of the product, particularly the CNS and psychiatric adverse reactions.

Excipients

Oxybutynin hydrochloride tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Care should be taken if other anticholinergic agents are administered together with oxybutynin hydrochloride, as potentiation of anticholinergic effects could occur.

The anticholinergic activity of oxybutynin is increased by concurrent use of other anticholinergics or medicinal products with anticholinergic activity, such as amantadine and other anticholinergic antiparkinsonian medicinal products (e.g. levodopa), antihistamines, antipsychotics (e.g. phenothiazines, butyrophenones, clozapine), tricyclic antidepressants, atropine and related compounds like atropinic antispasmodics.

By reducing gastric motility, oxybutynin may affect the absorption of other drugs.

Oxybutynin is metabolised by cytochrome P450 isoenzyme CYP3A4. Concomitant administration with a CYP3A4 inhibitor can inhibit oxybutynin metabolism and increase oxybutynin exposure.

Oxybutynin, as an anticholinergic agent, may antagonize the effects of prokinetic therapies.

Sublingual nitrates may fail to dissolve under the tongue owing to dry mouth, resulting in reduced therapeutic effect.

Mean oxybutynin chloride concentrations were approximately 2 fold higher when Oxybutynin hydrochloride XL was administered with ketoconazole, a potent CYP3A4 inhibitor. Other inhibitors of cytochrome P450 3A4 enzyme system, such as antimycotic agents (e.g. itraconazole) or macrolide antibiotics, may increase oxybutynin exposure. The clinical relevance of such potential interaction is not known. Caution should be used when such drugs are co-administered.

Concomitant use with cholinesterase inhibitors may result in reduced cholinesterase inhibitor efficacy.

Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin (see section 4.7).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of oxybutynin in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition, or postnatal development (see section 5.3). The potential risk for humans is unknown. Oxybutynin hydrochloride XL should not be used during pregnancy unless clearly necessary.

Breastfeeding

When oxybutynin is used during breastfeeding, a small amount is excreted in the mother's milk. Use of Oxybutynin hydrochloride XL during breastfeeding is therefore not recommended.

Fertility

Reproduction studies with oral oxybutynin in the mouse, rat, hamster, and rabbit showed no evidence of impaired fertility.

4.7 Effects on ability to drive and use machines

Oxybutynin may cause drowsiness or blurred vision. Patients should be cautioned regarding activities requiring mental alertness such as driving, operating machinery or performing hazardous work while taking this medicine.

4.8 Undesirable effects

Like all medicines, oxybutynin can cause undesirable effects, although not everybody gets them. The frequency of possible undesirable effects listed below are currently defined as:

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), not known (cannot be estimated from the available data).

List of adverse reactions

The safety of Oxybutynin hydrochloride XL was evaluated in five double-blind, controlled (i.e., placebo or active comparator) clinical trials for the management of overactive bladder, in which 759 adult subjects received doses ranging from 5 to 20 mg/day. Additionally, safety was evaluated in one open-label (i.e., active comparator) clinical trial, in which 60 paediatric subjects received doses of 10 or 15 mg/day, Table 1 below reflects the adverse drug reactions reported with Oxybutynin hydrochloride XL in clinical trials in adults and from post marketing experience. Adverse drug reactions reported in the paediatric clinical trial are shown in Table 2.

Table 1: Adverse drug reactions reported in clinical trials in adults and from post marketing experience

	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)**	**Not known (cannot be estimated from the available data)**
Infections and infestations		Urinary tract infection			
Immune System Disorders			Hypersensitivity		Anaphylactic reaction
Psychiatric disorders		Confusional state, Insomnia	Hallucinations, Agitation, Memory impairment		Psychotic disorder, Anxiety, Cognitive disorders in the elderly Nightmares, and Paranoia, symptoms of depression, dependence to oxybutynin (in patients with history of drug or substance abuse)
Nervous system disorders	Dizziness, Headache, Somnolence	Dysgeusia	Convulsions		Cognitive Disorders, Drowsiness, Disorientation
Eye disorders	Vision blurred	Dry eyes	Angle closure glaucoma		Increased intraocular pressure, Mydriasis
Cardiac disorders		Palpitation, Tachycardia	Arrhythmia		
Vascular disorders		Flushing (which may be more marked in children)	Hypertension		
Respiratory, thoracic, and mediastinal disorders		Oropharyngeal pain, Cough, Nasal dryness, Dry throat	Dysphonia, Nasal congestion, Throat irritation		Epistaxis
Gastrointestinal disorders	Constipation, Dry mouth, Nausea	Gastroesophageal reflux, Abdominal pain,	Abdominal discomfort, Anorexia, decreased appetite,		Pseudo-obstruction in patients at risk (elderly or patients

		Dyspepsia, Diarrhoea, Vomiting, Flatulence	Dysphagia Frequent bowel movements		with constipation and treated with other drugs that decrease intestinal motility)
Skin and subcutaneous tissue disorders	Dry skin	Pruritus	Urticaria, Rash		Angioedema, Hypohidrosis, Photosensitivity
Musculoskeletal and connective tissue disorders					Muscle disorders manifested as muscle weakness, myalgia and/ or muscle spasms
Renal and urinary disorders		Urinary retention, Dysuria, Urinary hesitation	Residual urine		Impotence
General disorders and administration site conditions		Fatigue	Chest discomfort, Mucosal dryness, Thirst		
Investigations		Residual urine volume+			
Injury, poisoning and procedural complications			Fall		Heat stroke

+The bundled term residual urine volume consists of the preferred terms residual urine volume and residual urine volume increased.

Paediatric population

The safety of Oxybutynin hydrochloride XL was evaluated in 60 paediatric subjects (age range 5 to 15 years; dose range 10-15 mg/day) who participated in an open-label, active control, three-arm clinical trial. Adverse drug reactions reported by Oxybutynin hydrochloride XL -treated paediatric subjects in this clinical trial are shown in Table 2.

Table 2: Adverse drug reactions reported in clinical trials with paediatric subjects

	Very Common ≥1/10	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1000**
Metabolism and nutrition		Anorexia		

disorders				
Psychiatric disorders		Insomnia		
Nervous system disorders		Headache		
Vascular disorders		Flushing		
Gastrointestinal disorders	Constipation	Diarrhoea		
Skin and subcutaneous tissue disorders		Rash, Pruritus		

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of intoxication

The symptoms of overdosage with oxybutynin progress from an intensification of the usual side effects of CNS disturbances (from restlessness and excitement to psychotic behaviour), circulatory changes (flushing, fall in blood pressure, circulatory failure etc.), respiratory failure, paralysis and coma.

Management

Measures to be taken are:

1) immediate gastric lavage
2) physostigmine by slow intravenous injection
   - Adults: 0.5 to 2.0 mg of physostigmine by slow intravenous administration. Repeat after 5 minutes, if necessary up to a maximum total dose of 5 mg.
   - Paediatric population: 30 micrograms/kg of physostigmine by slow intravenous administration. Repeat after 5 minutes, if necessary up to a maximum total dose of 2 mg.

Fever should be treated symptomatically with tepid sponging or ice packs.

In pronounced restlessness or excitation, diazepam 10mg may be given by intravenous injection, tachycardia may be treated with intravenous propranolol and urinary retention managed by bladder catheterisation.

In the event of progression of the curare-like effect to the paralysis of the respiratory muscles, mechanical ventilation will be required.

The continuous release of oxybutynin from Oxybutynin hydrochloride XL should be considered in the treatment of overdose. Patients should be monitored for at least 24 hours.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: genito urinary system and sex hormones - urologicals – drugs for urinary frequency and incontinence. ATC code: G04B D04.

Mechanism of action

Oxybutynin acts as a competitive antagonist of acetylcholine at postganglionic muscarinic receptors, resulting in relaxation of bladder smooth muscle.

Pharmacodynamic effects

In patients with overactive bladder, characterised by detrusor muscle instability or hyperreflexia, cystometric studies have demonstrated that oxybutynin increases maximum urinary bladder capacity and increases the volume to first detrusor contraction. Oxybutynin thus decreases urinary urgency and frequency of both incontinence episodes and voluntary urination. Oxybutynin is a racemic (50:50) mixture of R- and S- isomers. Antimuscarinic activity resides predominantly in the R-isomer. The R-isomer of oxybutynin shows greater selectivity for the M1 and M3 muscarinic subtypes (predominant in bladder detrusor muscle and parotid gland) compared to the M2 subtype (predominant in cardiac tissue). The active metabolite, N-desethyloxybutynin, has pharmacological activity on the human detrusor muscle that is similar to that of oxybutynin in vitro studies, but has a greater binding affinity for parotid tissue than oxybutynin. The free base form of oxybutynin is pharmacologically equivalent to oxybutynin hydrochloride.

Paediatric population

An open-label study was conducted to evaluate the efficacy and safety of Oxybutynin hydrochloride XL in children aged 6-15 years with detrusor hyperreflexia due to neurogenic conditions, all used clean intermittent catheterisation, and all were current users of 10 or 15 mg oxybutynin hydrochloride administered as Ditropan syrup, Ditropan tablets or Ditropan XL extended-release tablets. The study results showed that there was an increase from baseline in mean urine volume per catheterisation, an increase from baseline in mean urine volume after morning awakening, from baseline in the mean percentage of catheterisations without a leaking episode, an increase from baseline in mean maximum cystometric capacity, a decrease from baseline in mean detrusor pressure at maximum cystometric pressure and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions as shown in the table below.

Change in Baseline to Week 24			
Parameter	n	Mean (SEM)	Range
Average volume per catheterisation (mL)	109	25.5 (5.9)	-292 to 245

Volume of 1st catheterisation after morning awakening (mL)	109	33.0 (8.3)	-223 to 450
Maximal bladder capacity (mL)*	105	75.4 (9.8)	-150 to 420
Detrusor pressure at maximal bladder capacity (cm H2O)*	105	-9.2 (2.3)	-102 to 64
Intravesical pressure at maximal bladder capacity (cm H2O)*	105	-7.5 (2.5)	-108 to 76
*Urodynamic studies			
At baseline, 66 of 116 (56.9%) patients had uninhibited detrusor contractions ≥ 15 cm H2O. At Week 24, 30 of 105 (28.6%) patients had uninhibited contractions ≥ 15 cm H2O. The percentage of catheterisations without a leaking accident increased from 36.0% at baseline to 55.5% at Week 24.			

5.2 Pharmacokinetic properties

Absorption

Following the first dose of Oxybutynin hydrochloride XL, oxybutynin plasma concentrations rise for 4 to 6 hours; thereafter, concentrations are maintained for up to 24 hours, thus reducing the fluctuations between peak and trough concentrations associated with oxybutynin immediate release formulations. Absolute bioavailability of immediate release oxybutynin has been estimated to be 2-11%. The relative bioavailabilities of R-oxybutynin and S-oxybutynin from Oxybutynin hydrochloride XL are 156% and 187% respectively, compared with oxybutynin immediate release. After a 10 mg single dose of Oxybutynin hydrochloride XL, the peak plasma concentrations of R-oxybutynin and S-oxybutynin, achieved after 12.7±5.4 and 11.8±5.3 hours respectively, are 1.0±0.6 and 1.8±1.0 ng/ml, and the plasma concentration time profiles of both enantiomers are similar in shape.

The pharmacokinetics of Oxybutynin hydrochloride XL are unaffected by food intake.

Distribution

Oxybutynin is widely distributed in body tissues following systemic absorption. The volume of distribution was estimated to be 193 L after intravenous administration of 5 mg oxybutynin hydrochloride. Both enantiomers of oxybutynin are highly bound (>99%) to plasma proteins. Both enantiomers of desethyloxybutynin are also highly bound (>97%) to plasma proteins. The major binding protein is alpha-1 acid glycoprotein.

Biotransformation and Excretion

Oxybutynin is extensively metabolised by the liver, primarily by the cytochrome P450 enzyme system, particularly CYP3A4 found mostly in the liver and gut wall. Its metabolic products include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and desethyloxybutynin, which is pharmacologically

active. Following Oxybutynin hydrochloride XL administration, area under the plasma concentration profiles of R- and S-desethyloxybutynin are 73% and 92%, respectively of those observed with oxybutynin immediate release formulations. Following intravenous administration of 5 mg oxybutynin, clearance was estimated to be 26 L/h. Less than 0.1% of the administered dose is excreted unchanged in the urine. The elimination half-life is 13.2±10.3 hours for R-oxybutynin and 12.4±6.1 hours for S-oxybutynin.

Special Populations

Paediatric population

The steady-state pharmacokinetics of Oxybutynin hydrochloride XL were evaluated in a limited number of children aged 6-15 years with detrusor overactivity associated with a neurological condition (e.g., spina bifida) receiving 10 or 15 mg total daily doses of Oxybutynin hydrochloride XL. The pharmacokinetics of Oxybutynin hydrochloride XL in these paediatric patients were consistent with those reported for adults. The table below summarizes maximum and average plasma concentrations for each of the four analytes, R- and S-Oxybutynin and R- and S-Desethyloxybutynin, by age group and total daily dose.

Mean (SD) Maximum and Average Concentrations (ng/mL) of R- and S-Oxybutynin and R- and S-Desethyloxybutynin in Children Following Administration of 10 and 15 mg Oxybutynin hydrochloride XL **Once Daily**

	Age <10 yrs[a]			**Age >10 yrs**[b]
Dose/Analyte	**C_{max}**	**C_{avg}**	**C_{max}**	**C_{avg}**
10 mg Dose				
R-Oxybutynin	1.39 (0.1)	0.91 (0.2)	1.37 (0.9)	1.06 (0.8)
S-Oxybutynin	2.46 (0.5)	1.58 (0.5)	2.45 (1.7)	2.00 (1.5)
R-Desethyloxybutynin	15.4 (2.2)	8.74 (2.8)	13.2 (9.7)	9.48 (6.8)
S-Desethyloxybutynin	6.81 (0.9)	4.38 (1.8)	8.05 (6.7)	6.70 (6.1)
15 mg Dose				
R-Oxybutynin	2.59 (1.4)	1.78 (0.8)	2.16 (2.0)	1.86 (2.0)
S-Oxybutynin	5.03 (3.2)	3.67 (2.1)	3.29 (2.7)	2.80 (2.7
R-Desethyloxybutynin	23.0 (11.0)	16.2 (6.0)	27.8 (22)	20.8 (22)
S-Desethyloxybutynin	13.3 (7.9)	10.3 (6.1)	12.2 (6.8)	9.13 (7.5)

a – 10 mg: n=3; 15 mg: n=6
b – 10 mg: n=5; 15 mg: n=2

Linearity/non-linearity

The pharmacokinetic parameters (Cmax and AUC) of oxybutynin and desethyloxybutynin are dose proportional following administration of 5-20 mg of Oxybutynin hydrochloride XL. Steady state oxybutynin plasma concentrations are achieved by Day 3 of repeated Oxybutynin hydrochloride XL dosing, with no observed change in oxybutynin and desethyloxybutynin pharmacokinetic parameters over time. These characteristics support linearity in the pharmacokinetics for oxybutynin.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of acute toxicity, repeat dose toxicity, genotoxicity, carcinogenic potential and local toxicity. In a fertility study of subcutaneous oxybutynin injections in rats, female fertility was impaired while no effect was noted in male animals. In a rabbit embryotoxicity study, organ anomalies were observed in the presence of maternal toxicity at a dose of 0.4 mg/kg/day subcutaneously. The relevance to human safety is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Oxybutynin hydrochloride XL 10 mg prolonged release tablets:

Core:

Lactose Monohydrate, Microcrystalline Cellulose, Hydroxypropylmethyl cellulose (K100 Premium LV CR), Hydroxypropylmethyl cellulose (K100 M), Iron Oxide Yellow, Iron Oxide Red, Purified Talc, Colloidal Anhydrous Silicon Dioxide, Magnesium Stearate.

Film coat:

Opadry OY-29020 Clear contains

HPMC 2910/Hypromellose

Macrogol/PEG

Enteric coat:

Acryl – EZE 93O540011 Pink contains

Methacrylic acid and Ethylacrylate Copolymer, Talc, Titanium Dioxide, Triethyl Citrate, Colloidal anhydrous Silica, Sodium bicarbonate, Sodium Lauryl Sulfate, Iron oxide red, Iron oxide yellow.

Printing Ink:

Opacode Black S-1-17823 Contains

Shellac Glaze~45% (20%Esterified) in Ethanol, IsopropyL alcohol, Ferrosoferric oxide (NF)/Black iron oxide, N-butyl alcohol, Propylene glycol, Ammonium hydroxide 28%

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

High density polyethylene bottles with child resistant closure and desiccant

Pack sizes: 28, 30, 56 or 84 tablets.

6.6 Special precautions for disposal

Do not remove or swallow the canister of granules. This contains desiccant which keeps the tablets dry.

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd

(Trading style: Accord)

Whiddon Valley

Barnstaple

Devon

EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 00142/1247

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/09/2021

10 DATE OF REVISION OF THE TEXT

30/10/2023