Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

OxyContin 160 mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 144 mg of oxycodone as 160 mg of oxycodone hydrochloride.

Excipient: Each tablet contains 157.0 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablets.
Each 160 mg tabletis blue, capsule-shaped, of approximately 16 mm in length by 6 mm in diameter marked OC on one side and 160 on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of severe pain. ***OxyContin*** is indicated in adults 20 years of age and over.

4.2 Posology and method of administration

Posology
Prescribers should consider concomitant treatment with antiemetics and laxatives for the prevention of nausea, vomiting and constipation.

Adults:
OxyContin tablets should be taken at 12-hourly intervals. The dosage is dependent on the severity of the pain, the patient's previous history of analgesic requirements, the patient's body weight, and sex (higher plasma concentrations are produced in females).

The usual starting dose for debilitated elderly patients, opioid naïve patients or patients presenting with severe pain uncontrolled with weaker opioids is 10 mg 12-hourly. Some patients may benefit from a starting dose of 5 mg to minimise the incidence of side effects. The dose should then be carefully titrated, every day if necessary, to achieve pain relief. Given the time to reach steady state, patients' doses should only be titrated up after 24 hours and increases should be made, where possible, in 25% - 50% increments. The correct dosage for any individual patient is that which controls the pain and is well tolerated, for a full 12 hours. The need for escape medication more than twice a day indicates that the dosage of ***OxyContin*** tablets should be increased.

Conversion from oral morphine:
Patients receiving oral morphine before oxycodone therapy should have their daily dose based on the following ratio: 10 mg of oral oxycodone is equivalent to 20 mg of oral morphine. It must be emphasised that this is a guide to the dose of ***OxyContin*** tablets required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Elderly patients:
A dose adjustment is not usually necessary in elderly patients.
Controlled pharmacokinetic studies in elderly patients (aged over 65 years) have shown that compared with younger adults the clearance of oxycodone is only slightly reduced. No untoward adverse drug reactions were seen based on age, therefore adult doses and dosage intervals are appropriate.

Non-malignant pain:
Treatment with oxycodone should be short and intermittent to minimise the risk of dependence. The need for continued treatment should be assessed at regular intervals. Patients should not usually require more than 160 mg per day.

Cancer-related pain:
Patients should be titrated up to a dose which achieves pain relief unless unmanageable adverse drug reactions prevent this.

Patients with renal or hepatic impairment:
Unlike morphine preparations, the administration of oxycodone does not result in significant levels of active metabolites. However, the plasma concentration of oxycodone in this patient population may be increased compared with patients having normal renal or hepatic function. The dose initiation should follow a conservative approach in these patients The recommended adult starting dose should be reduced by 50% (for example a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control according to their clinical situation.

Paediatric population and adults under 20 years of age:
Not recommended. Experience in children is limited. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration
OxyContin tablets are for oral use.

***OxyContin* tablets must be swallowed whole and are not to be broken, chewed or crushed. Taking broken, chewed or crushed *OxyContin* tablets may lead to a rapid release and absorption of a potentially fatal dose of oxycodone.**

Missed dose:
If a patient forgets to take a dose but remembers within 4 hours of the time the dose was due to be taken, the tablets can be taken straight away. The next dose should be taken at the normal time. Beyond 4 hours the prescriber may need to consider alternative rescue medicine until the next dose is due.

Duration of treatment
Oxycodone should not be used for longer than necessary.

Discontinuation of treatment:
When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

4.3 Contraindications

Hypersensitivity to oxycodone or to any of the excipients listed in section 6.1.
Oxycodone must not be used in any situation where opioids are contraindicated: severe respiratory depression with hypoxia, elevated carbon dioxide levels in the blood, head injury, paralytic ileus, acute abdomen, delayed gastric emptying, severe chronic obstructive lung disease, severe bronchial asthma, cor pulmonale, known sensitivity to morphine or other opioids.

4.4 Special warnings and precautions for use

The major risk of opioid excess is respiratory depression.

Caution must be exercised when administering oxycodone to the debilitated elderly; patients with severely impaired pulmonary function, impaired hepatic or renal function; patients with myxoedema, hypothyroidism, Addison's disease, toxic psychosis, adrenocortical insufficiency, prostate hypertrophy, head injury (due to the risk of raised intracranial pressure), convulsive disorders, delirium tremens, disorders of consciousness, hypotension, hypovolaemia. Use with caution in opioid dependent patients, diseases of the biliary tract, biliary or ureteric colic, pancreatitis, obstructive and inflammatory bowel disorders, chronic obstructive airways disease, reduced respiratory reserve, alcoholism or patients taking benzodiazepines, other CNS depressants (including alcohol) or MAO inhibitors. In patients in whom caution is required, a reduction in dosage may be advisable.

Doses of ***OxyContin*** tablets in excess of 60 mg may cause fatal respiratory depression when administered to patients not previously exposed to opioids and should only be used in opioid-tolerant patients. Care should be taken in the prescription of daily oxycodone dosages of 120 mg or more.

OxyContin tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, ***OxyContin*** tablets should be discontinued immediately (see section 4.3). As with all opioid preparations, patients about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive oxycodone for 12 hours prior to the intervention. If further treatment with ***OxyContin*** tablets is indicated then the dosage should be adjusted to the new post-operative requirement.

As with all opioid preparations, oxycodone products should be used with caution following abdominal surgery as opioids are known to impair intestinal motility and should not be used until the physician is assured of normal bowel function.

OxyContin is not recommended for pre-operative use or within the first 12-24 hours post-operatively.

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. There may also be cross-tolerance with other opioids. Prolonged use of this product may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. Withdrawal symptoms may include yawning, mydriasis, lacrimation, rhinorrhoea, tremor, hyperhidrosis, anxiety, agitation, irritability, chills, hot flushes, piloerection, joint pain, diaphoresis, abdominal cramps, diarrhoea, convulsions and insomnia.

Hyperalgesia that will not respond to a further dose increase of oxycodone may occur, particularly in high doses. An oxycodone dose reduction or change to an alternative opioid may be required.

Oxycodone has an abuse profile similar to other strong agonist opioids. Oxycodone may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence (addiction) to opioid analgesics, including oxycodone. ***OxyContin*** tablets should be used with particular care in patients with a history of alcohol and drug abuse.

The prolonged release tablets must be swallowed whole and not be broken, chewed or crushed. The administration of broken, chewed or crushed prolonged release oxycodone tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone (see section 4.9).

Concomitant use of alcohol and ***OxyContin*** may increase the undesirable effects of ***OxyContin***; concomitant use should be avoided.

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, such as local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis and valvular heart injury, which may be fatal.

It should be emphasised that patients, once titrated to an effective dose of a certain opioid, should not be changed to other analgesic preparations without clinical assessment and careful retitration as necessary. Otherwise, a continuous analgesic action is not ensured.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Empty matrix (tablets) may be seen in the stool.

Opioids, such as oxycodone hydrochloride, may influence the hypothalamic-pituitary-adrenal or – gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical symptoms may manifest from these hormonal changes.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

There can be an enhanced CNS depressant effect which can result in profound sedation, respiratory depression, coma and death during concomitant therapy with benzodiazepines or other drugs which affect the CNS such as alcohol, phenothiazines, antidepressants, anaesthetics, hypnotics, non-benzodiazepine sedatives, muscle relaxants, other opioids, neuroleptic drugs, antihypertensives and SSRIs. Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

Concomitant administration of oxycodone with anticholinergics or medicines with anticholinergic activity (e.g. tricyclic anti-depressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects. Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

Monoamine oxidase inhibitors are known to interact with narcotic analgesics, producing CNS excitation or depression associated with hypertensive or hypotensive crisis (see section 4.4). Oxycodone should be used with caution in patients administered MAO-inhibitors or who have received MAO-inhibitors during the last two weeks (see section 4.4).

Alcohol may enhance the pharmacodynamic effects of ***OxyContin***; concomitant use should be avoided.

Oxycodone is metabolised mainly by CYP3A4, with a contribution from CYP2D6. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azole-antifungals (e.g. ketoconazole, voriconazole, itraconazole, and posaconazole), protease inhibitors (e.g. boceprevir, ritonavir, indinavir, nelfinavir and saquinavir), cimetidine and grapefruit juice may cause a reduced clearance of oxycodone that could cause an increase of the plasma concentrations of oxycodone. Therefore the oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- Itraconazole, a potent CYP3A4 inhibitor, administered 200 mg orally for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 2.4 times higher (range 1.5 - 3.4).

- Voriconazole, a CYP3A4 inhibitor, administered 200 mg twice-daily for four days (400 mg given as first two doses), increased the AUC of oral oxycodone. On average, the AUC was approximately 3.6 times higher (range 2.7 - 5.6).

- Telithromycin, a CYP3A4 inhibitor, administered 800 mg orally for four days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.8 times higher (range 1.3 – 2.3).

- Grapefruit Juice, a CYP3A4 inhibitor, administered as 200 ml three times a day for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.7 times higher (range 1.1 – 2.1).

CYP3A4 inducers, such as rifampicin, carbamazepine, phenytoin and St John´s Wort may induce the metabolism of oxycodone and cause an increased clearance of oxycodone that could cause a reduction of the plasma concentrations of oxycodone. The oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- St Johns Wort, a CYP3A4 inducer, administered as 300 mg three times a day for fifteen days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 50% lower (range 37-57%).

- Rifampicin, a CYP3A4 inducer, administered as 600 mg once-daily for seven days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 86% lower

Drugs that inhibit CYP2D6 activity, such as paroxetine, fluoxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations.

4.6 Fertility, pregnancy and lactation

Use of this medicinal product should be avoided to the extent possible in patients who are pregnant or lactating.

Pregnancy
There are limited data from the use of oxycodone in pregnant women. Infants born to mothers who have received opioids during the last 3 to 4 weeks before giving birth should be monitored for respiratory depression. Withdrawal symptoms may be observed in the newborn of mothers undergoing treatment with oxycodone.

Oxycodone penetrates the placenta. Oxycodone should not be used during pregnancy and labour due to impaired uterine contractility and the risk of neonatal respiratory depression.

For animal studies see section 5.3.

Breastfeeding
Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. Oxycodone should, therefore, not be used in breastfeeding mothers

Fertility
Non-clinical toxicology studies in rats have not shown any effects upon fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Oxycodone may impair the ability to drive and use machines. Oxycodone may modify patients' reactions to a varying extent depending on the dosage and individual susceptibility. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

The most commonly reported adverse reactions are nausea and constipation, both occurring in approximately 25 to 30 % of patients. If nausea or vomiting are troublesome, oxycodone may be combined with an antiemetic. Constipation should be anticipated as with any strong opioid, and treated appropriately with laxatives. Should opioid related adverse events persist, they should be investigated for an alternative cause.

Adverse drug reactions are typical of full opioid agonists, and tend to reduce with time, with the exception of constipation. Anticipation of adverse drug reactions and appropriate patient management can improve acceptability.

The most serious adverse reaction, as with other opioids, is respiratory depression (see section 4.9). This is most likely to occur in elderly, debilitated or opioid-intolerant patients.

The following frequency categories form the basis for classification of the undesirable effects:

Term	Frequency
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

	Very Common	Common	Uncommon	Rare	Not known
Immune system disorders			hypersensitivity		anaphylactic responses
Endocrine disorders			syndrome of inappropriate antidiuretic hormone secretion (SIADH)		
Metabolism and nutrition disorders		decreased appetite	dehydration, weight fluctuation		
Psychiatric disorders		abnormal dreams, anxiety, confusional state, depression, insomnia, nervousness, abnormal thinking	agitation, depersonalisation, affect lability, euphoric mood, hallucinations, decreased libido, drug dependence (see section 4.4.)		aggression
Nervous system disorders	somnolence, dizziness, headache	tremor, lethargy	amnesia, convulsion, hyperkinesia, hypertonia, hypoaesthesia, hypotonia, involuntary muscle contractions, speech disorder, stupor, paraesthesia, , dysgeusia, syncope		hyperalgesia
Eye disorders			visual impairment, lacrimation disorder, miosis		
Ear and labyrinth disorders			tinnitus, vertigo		

Cardiac disorders			palpitations (in the context of withdrawal syndrome)		
Vascular disorders			vasodilatation	orthostatic hypotension, hypotension	
Respiratory, thoracic and mediastinal disorders		dyspnoea, bronchospasm	rhinitis, epistaxis, hiccup, voice alteration, respiratory depression,		
Gastrointestinal disorders	constipation, nausea, vomiting	abdominal pain, diarrhoea, dry mouth, dyspepsia	dysphagia, flatulence, gastritis, mouth ulceration, eructation, ileus, stomatitis		dental caries
Hepatobiliary disorders			increased hepatic enzyme		biliary colic, cholestasis
Skin and subcutaneous tissue disorders	pruritus	rash, hyperhidrosis	dry skin	urticaria	
Renal and urinary disorders		urinary disorders	urinary retention		
Reproductive system and breast disorders			erectile dysfunction, hypogonadism		amenorrhoea
General disorders and administration site conditions		asthenia, fever, fatigue	chills, chest pain, drug withdrawal syndrome (see sections 4.2 and 4.4), gait disturbance, malaise, oedema, peripheral oedema, drug tolerance, thirst		drug withdrawal syndrome neonatal

Tolerance may occur in patients treated with oxycodone, although this has not been a significant problem in the clinical trial programme. Patients requiring marked dose escalation should have their pain control regimen carefully reviewed.

Paediatric population and adults under 20 years of age:
The frequency, type and severity of adverse reactions in children and adults under 20 years of age are expected not to be different from adults 20 years and over.

For infants born to mothers receiving oxycodone see section 4.6.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Acute overdose with oxycodone can be manifested by respiratory depression, somnolence, progressing to stupor or coma, hypotonia, miosis, bradycardia, hypotension, pulmonary oedema and death.

Treatment of oxycodone overdose: A patent airway must be maintained. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed.

In the case of massive overdose, administer naloxone 0.8 mg intravenously. Repeat at 2-3 minute intervals as necessary, or by an infusion of 2 mg in 500 ml of normal saline or 5% dextrose (0.004 mg/ml).

The infusion should be run at a rate related to the previous bolus doses administered and should be in accordance with the patient's response. However, because the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. ***OxyContin*** tablets will continue to release and add to the oxycodone load for up to 12 hours after administration and the management of oxycodone overdose should be modified accordingly.

For less severe overdose, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. Naloxone should be administered cautiously to persons who are known, or suspected, to be physically dependent on oxycodone. In such cases, an abrupt or complete reversal of opioid effects may precipitate pain and an acute withdrawal syndrome.

Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug, particularly when a prolonged release formulation has been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids, opioids, analgesics;
ATC code: N02AA05

Oxycodone is a full opioid agonist with no antagonist properties and has an affinity for kappa, mu and delta opiate receptors in the brain and spinal cord. The therapeutic effect is mainly analgesic, anxiolytic, antitussive and sedative. The mechanism of action involves CNS opioid receptors for endogenous compounds with opioid-like activity.

Gastrointestinal system
Opioids may induce spasm of the sphincter of Oddi.

Endocrine system
See section 4.4.

Other pharmacological effects
In vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown. Whether oxycodone, a semi-synthetic opioid, has immunological effects similar to morphine is unknown.

Paediatric population
Overall the safety data obtained with oral oxycodone in 9 clinical, pharmacodynamic and pharmacokinetic studies including a total of 629 infants and children (aged 2 months to 17 years) demonstrate that oral oxycodone is tolerated well in paediatric patients with only minor adverse events affecting mainly the gastrointestinal and nervous system.

The positive safety data obtained with oral oxycodone are confirmed by 9 studies performed with bucally, intramuscularly and intravenously administered oxycodone in a total of 1860 infants and children who also experienced only mild adverse events comparable to those observed with the use of oral oxycodone.

The dose of oxycodone administered parenterally to infants and children in clinical trials was in the range of 0.025 mg/kg to 0.1 mg/kg, with 0.1 mg/kg being the most frequently used dosage followed by 0.05 mg/kg. The dose of i.v. oxycodone was in the range of 0.025 mg/kg to 0.1 mg/kg, with 0.1 mg/kg being the most frequently used dosage followed by 0.05 mg/kg. The dose of i.m. oxycodone was in the range of 0.02 mg/kg to 0.1 mg/kg. The dose of orally administered oxycodone was in the range of 0.1 mg/kg (starting dose) to 1.24 mg/kg/day. Buccally administered dose of oxycodone was 0.1 mg/kg.

Overall, the adverse events in these studies of oxycodone in infants and children appear consistent with the known safety profile of oxycodone elaborated in the numerous clinical trials performed in adults and described in the SmPC. No new or unexpected safety signals were identified in these studies. All of the adverse events reported were consistent with the known safety profile of oxycodone as well as of other comparable strong opioids. However ***OxyContin*** is not recommended in children and adults below 20 years of age due to insufficient data on safety and efficacy.

5.2 Pharmacokinetic properties

Oxycodone has a high absolute bioavailability of up to 87% following oral administration. It has an elimination half-life of approximately 3 hours and is metabolised principally to noroxycodone via CYP 3A4 and oxymorphone via CYP2D6. Oxymorphone has some analgesic activity but is present in plasma in low concentrations and is not considered to contribute to oxycodone's pharmacological effect.

The release of oxycodone from ***OxyContin*** tablets is biphasic, with an initial relatively fast release providing an early onset of analgesia, followed by a more controlled release which determines the 12 hour duration of action. The mean apparent elimination half-life of ***OxyContin*** tablets is 4.5 hours which leads to steady-state being achieved in about one day.

Release of oxycodone from ***OxyContin*** tablets is independent of pH.

OxyContin tablets have an oral bioavailability comparable with conventional oral oxycodone, but the former achieve maximal plasma concentrations at about 3 hours rather than about 1 to 1.5 hours. Peak and trough concentrations of oxycodone from ***OxyContin*** tablets 10 mg administered 12-hourly are equivalent to those achieved from conventional oxycodone 5 mg administered 6-hourly.

All strengths of ***OxyContin*** tablets are bioequivalent in terms of both rate and extent of absorption. Ingestion of a standard high-fat meal does not alter the peak oxycodone concentration or the extent of oxycodone absorption from ***OxyContin*** tablets.

Paediatric population

The pharmacokinetic properties of oral oxycodone in infants and children were examined in 3 studies including a total of 63 infants and children aged 0.5 to 7.6 years. In addition pharmacokinetics of buccal and sublingual oxycodone was studied in 30 children aged 0.5-7.5 years. These studies did not reveal significant different results in comparison to adults. Oral oxycodone was tolerated well in these pharmacokinetic studies with only minor adverse events.

5.3 Preclinical safety data

Teratogenicity
Oxycodone has shown no effect on fertility or foetal development in rats and rabbits except at doses leading to toxic effects in the dams.

Carcinogenicity
No animal tests have been performed to examine the carcinogenic effects of oxycodone.

Mutagenicity
Oxycodone was not mutagenic in bacterial mutation tests or in in-vivo micronucleus assay(s) in mice. As is the case with other opioids, oxycodone was shown to be genotoxic in some in-vitro assays (e.g. mouse lymphoma assay).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Polyvidone
Ammoniomethacrylate polymer dispersion
Sorbic acid
Triacetin
Stearyl alcohol
Talc
Magnesium stearate

Film coat
Hypromellose (E464)
Indigo carmine (E132)
Titanium dioxide (E171)
Macrogol 400
Polysorbate 80 (E433)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Three years

6.4 Special precautions for storage

Do not store above 25^{o}C

6.5 Nature and contents of container

PVC blister packs with aluminium foil backing.
Pack sizes: 28, 56 and 112 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Mundipharma Pharmaceuticals Limited
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8 MARKETING AUTHORISATION NUMBER

PA1688/005/010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th July 2010

Date of last renewal: 16th July 2015

10 DATE OF REVISION OF THE TEXT

November 2017