Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pramipexole Mylan 0.18 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.25 mg pramipexole dihydrochloride monohydrate equivalent to 0.18 mg pramipexole.

Please note:
Pramipexole doses as published in the literature refer to the salt form.
Therefore, doses will be expressed in terms of both pramipexole base and pramipexole salt (in brackets).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

A white to off white, 9.0mm x 4.5mm, biconvex oval shaped tablet debossed with ‘PX2’ on one side of the tablet and ‘M’ on one side of the breakline on the other side.

The tablets can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Pramipexole Mylan is indicated in adults for treatment of the signs and symptoms of idiopathic Parkinson’s disease, alone (without levodopa) or in combination with levodopa, i.e. over the course of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or “on off” fluctuations).

4.2 Posology and method of administration

Posology

Parkinson’s disease
The daily dose is administered in equally divided doses 3 times a day.

Initial treatment
Doses should be increased gradually from a starting-dose of 0.264 mg of base (0.375 mg of salt) per day and then increased every 5 - 7 days. Providing patients do not experience intolerable undesirable effects, the dose should be titrated to achieve a maximal therapeutic effect.

Ascending – Dose Schedule of Pramipexole Mylan				
Week	Dosage (mg of base)	Total Daily Dose (mg of base)	Dosage (mg of salt)	Total Daily Dose (mg of salt)
1	3 x 0.088	0.264	3 x 0.125	0.375
2	3 x 0.18	0.54	3 x 0.25	0.75

3	3 x 0.35	1.1	3 x 0.5	1.50

If a further dose increase is necessary the daily dose should be increased by 0.54 mg of base (0.75 mg of salt) at weekly intervals up to a maximum dose of 3.3 mg of base (4.5 mg of salt) per day.
However, it should be noted that the incidence of somnolence is increased at doses higher than 1.5 mg (of salt) per day (see section 4.8).

Maintenance treatment
The individual dose of pramipexole should be in the range of 0.264 mg of base (0.375 mg of salt) to a maximum of 3.3 mg of base (4.5 mg of salt) per day. During dose escalation in pivotal studies, efficacy was observed starting at a daily dose of 1.1 mg of base (1.5 mg of salt). Further dose adjustments should be done based on the clinical response and the occurrence of adverse reactions. In clinical trials approximately 5% of patients were treated at doses below 1.1 mg of base (1.5 mg of salt). In advanced Parkinson's disease, pramipexole doses higher than 1.1 mg of base (1.5 mg of salt) per day can be useful in patients where a reduction of the levodopa therapy is intended. It is recommended that the dose of levodopa is reduced during both the dose escalation and the maintenance treatment with Pramipexole Mylan, depending on reactions in individual patients (see section 4.5).

Treatment discontinuation
Abrupt discontinuation of dopaminergic therapy can lead to the development of a neuroleptic malignant syndrome. Pramipexole should be tapered off at a rate of 0.54 mg of base (0.75 mg of salt) per day until the daily dose has been reduced to 0.54 mg of base (0.75 mg of salt).
Thereafter the dose should be reduced by 0.264 mg of base (0.375 mg of salt) per day (see section 4.4).

Patients with renal impairment
The elimination of pramipexole is dependent on renal function. The following dose schedule is suggested for initiation of therapy:

Patients with a creatinine clearance above 50 ml/min require no reduction in daily dose or dosing frequency.

In patients with a creatinine clearance between 20 and 50 ml/min, the initial daily dose of Pramipexole Mylan should be administered in two divided doses, starting at 0.088 mg of base (0.125 mg of salt) twice a day (0.176 mg of base/0.25 mg of salt daily). A maximum daily dose of 1.57 mg pramipexole base (2.25 mg of salt) should not be exceeded.

In patients with a creatinine clearance less than 20 ml/min, the daily dose of Pramipexole Mylan should be administered in a single dose, starting at 0.088 mg of base (0.125 mg of salt) daily. A maximum daily dose of 1.1 mg pramipexole base (1.5 mg of salt) should not be exceeded.

If renal function declines during maintenance therapy, the Pramipexole Mylan daily dose should be reduced by the same percentage as the decline in creatinine clearance, i.e. if creatinine clearance declines by 30%, then the Pramipexole Mylan daily dose should be reduced by 30%. The daily dose can be administered in two divided doses if creatinine clearance is between 20 and 50 ml/min, and as a single daily dose if creatinine clearance is less than 20 ml/min.

Patients with hepatic impairment
Dose adjustment in patients with hepatic failure is probably not necessary, as approx. 90% of absorbed active substance is excreted through the kidneys. However, the potential influence of hepatic insufficiency on Pramipexol Mylan pharmacokinetics has not been investigated.

Paediatric population
The safety and efficacy of pramipexole in children below 18 years have not been established. There is no relevant use of Pramipexole Mylan in the paediatric population in Parkinson's disease.

Method of administration
For oral use.

The tablets should be taken orally, swallowed with water, and can be taken either with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

When prescribing Pramipexole Mylan in a patient with Parkinson's disease with renal impairment a reduced dose is suggested in line with section 4.2.

Hallucinations
Hallucinations are known as a side-effect of treatment with dopamine agonists and levodopa. Patients should be informed that (mostly visual) hallucinations can occur.

Dyskinesia
In advanced Parkinson's disease, in combination treatment with levodopa, dyskinesia can occur during the initial titration of Pramipexole Mylan. If they occur, the dose of levodopa should be decreased.

Sudden onset of sleep and somnolence
Pramipexole has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported uncommonly. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with Pramipexole Mylan.

Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of dose or termination of therapy may be considered. Because of possible additive effects, caution should be advised when patients are taking other sedating medicinal products or alcohol in combination with pramipexole (see sections 4.5, 4.7 and section 4.8).

Impulse control disorders
Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including Pramipexole Mylan. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Mania and delirium
Patients should be regularly monitored for the development of mania and delirium. Patients and carers should be made aware that mania and delirium can occur in patients treated with pramipexole. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Patients with psychotic disorders
Patients with psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks.

Co-administration of antipsychotic medicinal products with pramipexole should be avoided (see section 4.5).

Ophthalmologic monitoring
Ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities occur.

Severe cardiovascular disease
In case of severe cardiovascular disease, care should be taken. It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of postural hypotension associated with dopaminergic therapy.

Neuroleptic malignant syndrome

Symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Plasma protein binding
Pramipexole is bound to plasma proteins to a very low (< 20%) extent, and little biotransformation is seen in man. Therefore, interactions with other medicinal products affecting plasma protein binding or elimination by biotransformation are unlikely. As anticholinergics are mainly eliminated by biotransformation, the potential for an interaction is limited, although an interaction with anticholinergics has not been investigated. There is no pharmacokinetic interaction with selegiline and levodopa.

Inhibitors/competitors of active renal elimination pathway
Cimetidine reduced the renal clearance of pramipexole by approximately 34%, presumably by inhibition of the cationic secretory transport system of the renal tubules. Therefore, medicinal products that are inhibitors of this active renal elimination pathway or are eliminated by this pathway, such as cimetidine, amantadine, mexiletine, zidovudine, cisplatin, quinine and procainamide, may interact with pramipexole resulting in reduced clearance of pramipexole. Reduction of the pramipexole dose should be considered when these medicinal products are administered concomitantly with Pramipexole Mylan.

Combination with levodopa
When Pramipexole Mylan is given in combination with levodopa, it is recommended that the dose of levodopa is reduced and the dose of other anti-parkinsonian medicinal products is kept constant while increasing the dose of Pramipexole Mylan.

Because of possible additive effects, caution should be advised when patients are taking other sedating medicinal products or alcohol in combination with pramipexole (see section 4.4, 4.7 and 4.8).

Antipsychotic medicinal products
Co-administration of antipsychotic medicinal products with pramipexole should be avoided (see section 4.4), e.g. if antagonistic effects can be expected.

4.6 Fertility, pregnancy and lactation

Pregnancy
The effect on pregnancy and lactation has not been investigated in humans. Pramipexole was not teratogenic in rats and rabbits, but was embryotoxic in the rat at maternotoxic doses (see section 5.3).
Pramipexole Mylan should not be used during pregnancy unless clearly necessary, i.e. if the potential benefit justifies the potential risk to the foetus.

Breast-feeding
As pramipexole treatment inhibits secretion of prolactin in humans, inhibition of lactation is expected. The excretion of pramipexole into breast milk has not been studied in women. In rats, the concentration of active substance-related radioactivity was higher in breast milk than in plasma.
In the absence of human data, Pramipexole Mylan should not be used during breast-feeding. However, if its use is unavoidable, breast-feeding should be discontinued.

Fertility
No studies on the effect on human fertility have been conducted. In animal studies, pramipexole affected oestrous cycles and reduced female fertility as expected for a dopamine agonist. However, these studies did not indicate direct or indirect harmful effects with respect to male fertility.

4.7 Effects on ability to drive and use machines

Pramipexole Mylan can have a major influence on the ability to drive and use machines.

Hallucinations or somnolence can occur.

Patients being treated with Pramipexole Mylan and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also sections 4.4, 4.5 and 4.8).

4.8 Undesirable effects

Expected adverse reactions
The following adverse reactions are expected under the use of Pramipexole Mylan: abnormal dreams, amnesia, behavioural symptoms of impulse control disorders and compulsions such as binge eating, compulsive shopping, hypersexuality and pathological gambling; cardiac failure, confusion, constipation, delirium, delusion, dizziness, dyskinesia, dyspnoea, fatigue, hallucinations, headache, hiccups, hyperkinesia, hyperphagia, hypotension, inappropriate antidiuretic hormone secretion, insomnia, libido disorders, mania, nausea, paranoia, peripheral oedema, pneumonia, pruritus, rash and other hypersensitivity; restlessness, somnolence, sudden onset of sleep, syncope, visual impairment including diplopia, vision blurred and visual acuity reduced, vomiting, weight decrease including decreased appetite, weight increase.

Based on the analysis of pooled placebo-controlled trials, comprising a total of 1,923 patients on pramipexole and 1,354 patients on placebo, adverse drug reactions were frequently reported for both groups. 63% of patients on pramipexole and 52% of patients on placebo reported at least one adverse drug reaction.

Tables 1 and 2 display the frequency of adverse drug reactions from placebo-controlled clinical trials in Parkinson's disease and other indication. The adverse drug reactions reported in these tables are those events that occurred in 0.1% or more of patients treated with pramipexole and were reported significantly more often in patients taking pramipexole than placebo, or where the event was considered clinically relevant. The majority of adverse drug reactions were mild to moderate, they usually start early in therapy, and most tended to disappear even as therapy was continued.

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: 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).

Parkinson's disease, most common adverse reactions
The most commonly (≥ 5%) reported adverse drug reactions in patients with Parkinson's disease more frequent with pramipexole treatment than with placebo were nausea, dyskinesia, hypotension, dizziness, somnolence, insomnia, constipation, hallucination, headache and fatigue. The incidence of somnolence is increased at doses higher than 1.5 mg pramipexole salt per day (see section 4.2). A more frequent adverse drug reaction in combination with levodopa was dyskinesia. Hypotension may occur at the beginning of treatment, especially if pramipexole is titrated too fast.

Table 1: Parkinson's disease

System Organ Class	Adverse Drug Reaction
Infections and infestations	
Uncommon	pneumonia
Endocrine disorders	
Uncommon	inappropriate antidiuretic hormone secretion[1]
Psychiatric disorders	
Common	abnormal dreams, behavioural symptoms of impulse control disorders and compulsions; confusion, hallucinations, insomnia
Uncommon	binge eating[1], compulsive shopping, delusion, hyperphagia[1], hypersexuality, libido disorder, paranoia, pathological gambling, restlessness,

	delirium
Rare	mania
Nervous system disorders	
Very common	dizziness, dyskinesia, somnolence
Common	headache
Uncommon	amnesia, hyperkinesia, sudden onset of sleep, syncope
Eye disorders	
Common	visual disturbance including diplopia, vision blurred and visual acuity reduced.
Cardiac disorders	
Uncommon	cardiac failure[1]
Vascular disorders	
Common	hypotension
Respiratory, thoracic and mediastinal disorders	
Uncommon	dyspnoea, hiccups
Gastrointestinal disorders	
Very common	nausea
Common	constipation, vomiting
Skin and subcutaneous tissue disorders	
Uncommon	hypersensitivity, pruritus, rash
General disorders and administration site conditions	
Common	fatigue, peripheral oedema
Investigations	
Common	weight decrease including decreased appetite
Uncommon	weight increase

[1] This side effect has been observed in post-marketing experience. With 95% certainty, the frequency category is not greater than uncommon, but might be lower. A precise frequency estimation is not possible as the side effect did not occur in a clinical trial database of 2,762 patients with Parkinson's Disease treated with pramipexole.

Other indication, most common adverse reactions

The most commonly (≥ 5%) reported adverse drug reactions in patients with other indication treated with pramipexole were nausea, headache, dizziness and fatigue. Nausea and fatigue were more often reported in female patients treated with pramipexole (20.8% and 10.5%, respectively) compared to males (6.7% and 7.3%, respectively).

Table 2: Other Indication

System Organ Class	**Adverse Drug Reaction**
Infections and infestations	
Uncommon	pneumonia
Endocrine disorders	
Uncommon	inappropriate antidiuretic hormone secretion[1]
Psychiatric disorders	
Common	abnormal dreams, insomnia
Uncommon	behavioural symptoms of impulse control disorders and compulsions such as, binge eating, compulsive shopping, hypersexuality, and pathological gambling[1]; delusion[1], hyperphagia[1], paranoia[1], confusion, hallucination, libido disorder, restlessness, mania[1], delirium[1]
Nervous system disorders	

Common	dizziness, headache, somnolence
Uncommon	amnesia[1], dyskinesia, hyperkinesia[1], sudden onset of sleep, syncope
Eye disorders	
Uncommon	visual disturbance including diplopia, vision blurred and visual acuity reduced.
Cardiac disorders	
Uncommon	cardiac failure[1]
Vascular disorders	
Uncommon	hypotension
Respiratory, thoracic and mediastinal disorders	
Uncommon	dyspnoea, hiccups
Gastrointestinal disorders	
Very common	nausea
Common	constipation, vomiting
Skin and subcutaneous tissue disorders	
Uncommon	hypersensitivity, pruritus, rash
General disorders and administration site conditions	
Common	fatigue
Uncommon	peripheral oedema
Investigations	
Uncommon	weight decrease including decreased appetite, weight increase

[1]This side effect has been observed in post-marketing experience. With 95% certainty, the frequency category is not greater than uncommon, but might be lower. A precise frequency estimation is not possible as the side effect did not occur in a clinical trial database of 1,395 patients with other indication treated with pramipexole.

Somnolence
Pramipexole is commonly associated with somnolence and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes (see also section 4.4).

Libido disorders
Pramipexole may uncommonly be associated with libido disorders (increased or decreased).

Impulse control disorders
Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including Pramipexole Mylan (see section 4.4).

In a cross-sectional, retrospective screening and case-control study including 3,090 Parkinson's disease patients, 13.6% of all patients receiving dopaminergic or non-dopaminergic treatment had symptoms of an impulse control disorder during the past six months. Manifestations observed include pathological gambling, compulsive shopping, binge eating, and compulsive sexual behaviour (hypersexuality). Possible independent risk factors for impulse control disorders included dopaminergic treatments and higher doses of dopaminergic treatment, younger age ($\leq$ 65 years), not being married and self-reported family history of gambling behaviours.

Cardiac failure
In clinical studies and post-marketing experience cardiac failure has been reported in patients with pramipexole. In a pharmaco-epidemiological study pramipexole use was associated with an increased risk of cardiac failure compared with non-use of pramipexole (observed risk ratio 1.86; 95% CI, 1.21-2.85).

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

There is no clinical experience with massive overdosage. The expected adverse events would be those related to the pharmacodynamic profile of a dopamine agonist, including nausea, vomiting, hyperkinesia, hallucinations, agitation and hypotension. There is no established antidote for overdosage of a dopamine agonist. If signs of central nervous system stimulation are present, a neuroleptic agent may be indicated. Management of the overdose may require general supportive measures, along with gastric lavage, intravenous fluids, administration of activated charcoal and electrocardiogram monitoring.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-Parkinson drugs, dopamine agonists, ATC code: N04BC05

Mechanism of action
Pramipexole is a dopamine agonist that binds with high selectivity and specificity to the D_2 subfamily of dopamine receptors of which it has a preferential affinity to D_3 receptors, and has full intrinsic activity.

Pramipexole alleviates Parkinsonian motor deficits by stimulation of dopamine receptors in the striatum. Animal studies have shown that pramipexole inhibits dopamine synthesis, release, and turnover.

Pharmacodynamic effects
In human volunteers, a dose-dependent decrease in prolactin was observed. In a clinical trial with healthy volunteers, where pramipexole prolonged-release tablets were titrated faster (every 3 days) than recommended up to 3.15 mg pramipexole base (4.5 mg of salt) per day, an increase in blood pressure and heart rate was observed. Such effect was not observed in patient studies.

Clinical efficacy and safety in Parkinson's disease
In patients pramipexole alleviates signs and symptoms of idiopathic Parkinson's disease.
Placebo-controlled clinical trials included approximately 1,800 patients of Hoehn and Yahr stages I – V treated with pramipexole. Out of these, approximately 1,000 were in more advanced stages, received concomitant levodopa therapy, and suffered from motor complications.

In early and advanced Parkinson's disease, efficacy of pramipexole in controlled clinical trials was maintained for approximately six months. In open continuation trials lasting for more than three years there were no signs of decreasing efficacy. In a controlled double blind clinical trial of 2 year duration**,** initial treatment with pramipexole significantly delayed the onset of motor complications, and reduced their occurrence compared to initial treatment with levodopa. This delay in motor complications with pramipexole should be balanced against a greater improvement in motor function with levodopa (as measured by the mean change in UPDRS-score). The overall incidence of hallucinations and somnolence was generally higher in the escalation phase with the pramipexole group. However there was no significant difference during the maintenance phase. These points should be considered when initiating pramipexole treatment in patients with Parkinson's disease.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing pramipexole in all subsets of the paediatric population in Parkinson's disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Pramipexole is rapidly and completely absorbed following oral administration. The absolute bioavailability is greater than 90% and the maximum plasma concentrations occur between 1 and 3 hours. Concomitant administration with food did not reduce the extent of pramipexole absorption, but the rate of absorption was reduced. Pramipexole shows linear kinetics and a small inter-patient variation of plasma levels.

Distribution
In humans, the protein binding of pramipexole is very low (< 20%) and the volume of distribution is large (400 l). High brain tissue concentrations were observed in the rat (approx. 8-fold compared to plasma).

Biotransformation
Pramipexole is metabolised in man only to a small extent.

Elimination
Renal excretion of unchanged pramipexole is the major route of elimination. Approximately 90% of ^{14}C-labelled dose is excreted through the kidneys while less than 2% is found in the faeces. The total clearance of pramipexole is approximately 500 ml/min and the renal clearance is approximately 400 ml/min. The elimination half-life (t½) varies from 8 hours in the young to 12 hours in the elderly.

5.3 Preclinical safety data

Repeated dose toxicity studies showed that pramipexole exerted functional effects, mainly involving the CNS and female reproductive system, and probably resulting from an exaggerated pharmacodynamic effect of pramipexole.

Decreases in diastolic and systolic pressure and heart rate were noted in the minipig, and a tendency to a hypotensive effect was discerned in the monkey.

The potential effects of pramipexole on reproductive function have been investigated in rats and rabbits. Pramipexole was not teratogenic in rats and rabbits but was embryotoxic in the rat at maternally toxic doses. Due to the selection of animal species and the limited parameters investigated, the adverse effects of pramipexole on pregnancy and male fertility have not been fully elucidated.

A delay in sexual development (i.e., preputial separation and vaginal opening) was observed in rats. The relevance for humans is unknown.

Pramipexole was not genotoxic. In a carcinogenicity study, male rats developed Leydig cell hyperplasia and adenomas, explained by the prolactin-inhibiting effect of pramipexole. This finding is not clinically relevant to man. The same study also showed that, at doses of 2 mg/kg (of salt) and higher, pramipexole was associated with retinal degeneration in albino rats. The latter finding was not observed in pigmented rats, nor in a 2-year albino mouse carcinogenicity study or in any other species investigated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Maize starch pregelatinised
Sodium citrate anhydrous
Silica, colloidal anydrous
Magnesium stearate
Hydroxypropylcellulose
Crospovidone type A

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25ºC.
Blister: Store in the original package in order to protect from light.
Bottle: Keep the bottle tightly closed in order to protect from light.

6.5 Nature and contents of container

Aluminium/Aluminium foil blisters containing 10, 20, 30, 60, 80, 90,100 or 200 tablets.
High-density polyethylene bottles containing 30, 90, 100, 200 or 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd
T/A Gerard Laboratories
35-36 Baldoyle Industrial Estate
Grange Road
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0577/138/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 1st July 2014

10 DATE OF REVISION OF THE TEXT

August 2015