# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

ZYGOSİS 40 mg Lyophilised Powder for Solution for I.V. Injection
Sterile

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Active Substance:**
45.1 mg pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

**Excipients:**

| | |
|---|---|
| Disodium edetate dehydrate | 1 mg |
| Sodium hydroxide | q.s. |

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for solution for injection.
White to almost white powder, clear reconstituted solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

- Gastroesophageal reflux,
- Gastric and duodenal ulcer,
- Short-term maintenance of hemostasis and prevention of re-bleeding in patients with acute bleeding gastric or duodenal ulcers,
- Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions.

### 4.2 Posology and method of administration

**Posology/frequency and duration of administration**
This medicine should be administered by a healthcare professional and under appropriate medical supervision.

Intravenous administration is recommended only if oral administration is not appropriate. Data are available on intravenous use for up to 7 days. Therefore, as soon as oral therapy is possible, treatment with ZYGOSİS i.v. should be discontinued and 40 mg pantoprazole p.o. should be administered instead.

<u>For the treatment of duodenal ulcer, gastric ulcer, moderate to severe gastroesophageal reflux:</u>
The recommended intravenous dose is one vial (40 mg pantoprazole) per day.

Short-term maintenance of hemostasis and prevention of re-bleeding in patients with acute bleeding gastric or duodenal ulcers:
In patients with acute hemorrhagic gastric or duodenal ulcers, 80 mg should be administered as a bolus infusion over 2-15 minutes, followed by a continuous intravenous infusion of 8 mg/h given over 3 days (72 hours).

Long-term treatment of Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions:
Treatment should start with a daily dose of 80 mg. Thereafter, the dose can be titrated up or down as needed based on the measurements of gastric acid secretion. With doses above 80 mg daily, the dose should be divided and given twice daily. A temporary increase of the dose above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control.

In case a rapid acid control is required, a starting dose of 2 x 80 mg Pantoprazole i.v. is sufficient to manage a decrease of acid output into the target range (< 10 mEq/h) within one hour in the majority of patients.

Oral treatment should be started as soon as clinically confirmed.

**Method of administration:**
ZYGOSİS is administered by i.v. injection.

The solution is prepared by adding 10 ml of saline to the vial containing the powder for injection. The prepared solution may be administered directly or after mixing it with 100 ml sodium chloride 9 mg/ml (0.9%) saline or 5% glucose (55 mg/ml) solution.

ZYGOSİS should not be mixed with other substances other than specified solvents.

Intravenous injection should be performed over 2-15 minutes.

After preparation the solution must be used within 12 hours.

**Additional information on special populations:**
**Renal failure:**
No dose adjustment is necessary in patients with impaired renal function.

**Hepatic failure:**
A daily dose of 20 mg pantoprazole (half a vial of 40 mg pantoprazole) should not be exceeded in patients with severe liver impairment. Liver enzymes should also be monitored during treatment. ZYGOSİS should be discontinued when liver enzymes are elevated.
**Pediatric population:**
There is not enough clinical experience of treatment in children. Therefore, ZYGOSİS vial containing powder for i.v injection should not be used in children under 18 years of age unless

the necessary data are provided.

**Geriatric population:**
No dose adjustment is necessary in elderly patients.

**4.3 Contraindications**
ZYGOSİS should not be used in patients with known hypersensitivity to the active substance, substituted benzimidazoles or to any of the excipients.

**4.4 Special warnings and precautions for use**

Hepatic impairment:
In patients with severe liver impairment, the liver enzymes should be monitored during therapy. In the case of a rise of the liver enzymes, ZYGOSİS should be discontinued (see section 4.2).

Gastric malignancy:
In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded. Because symptomatic response to pantoprazole may mask the symptoms of gastric malignancy and may delay diagnosis.

Further investigation is to be considered if symptoms persist despite adequate treatment.

Co-administration with HIV protease inhibitors
Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, due to significant reduction in their bioavailability (see section 4.5).

Bone fracture:
Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10-40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Hypomagnesemia:
Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular

arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

Interactions with Diagnostic Investigations for Neuroendocrine Tumors
Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop PPI treatment before assessing CgA levels and consider repeating the test if initial CgA levels are high. Tests should be carried out in the same laboratory as the reference intervals between the tests may vary if serial tests are being carried out (e.g. for monitoring).

Subacute cutaneous lupus erythematosus:
Proton pump inhibitors are associated with very infrequent cases of subacute cutaneous lupus erythematosus. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping ZYGOSİS. Subacute cutaneous lupus erythematosus after previous treatment with a proton pump inhibitor may increase the risk of the same condition with other proton pump inhibitors.

Laboratory tests:
Elevated serum chromogramin A (CgA) levels have been reported to be associated with PPI use. Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, ZYGOSİS treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Gastrointestinal infections caused by bacteria:
Pantoprazole, like all proton pump inhibitors (PPIs), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with ZYGOSİS may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter* or *C. difficile* (see Section 5.1).

Long-term treatment:
Patients should be observed regularly, especially in long-term treatments over a 1-year period.
This medicinal product contains less than 1 mmol (23 mg) of sodium in each vial; in fact, “it does not contain sodium”.

## 4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products with pH dependent absorption pharmacokinetics
Because of profound and long-lasting inhibition of gastric acid secretion, ZYGOSİS may interfere with the absorption of other medicinal products with pH-dependent oral bioavailability (e.g. some azole antifungals such as ketoconazole, itraconazole, posaconazole and other medicine such as erlotinib).

HIV drugs (atazanavir):
Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, due to significant reduction in their bioavailability (see section 4.4).

If the combination of HIV protease inhibtiors with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended. A pantoprazole dose of 20 mg per day should not be exceeded. Dosage of the HIV protease inhibitor may need to be adjusted.

Coumarin anticoagulants (phenprocoumon or warfarin):
Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenoprocoumon or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenoprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Patients treated with pantoprazole and warfarin or phenprocoumon may need to be monitored for increase in INR and prothrombin time.

Methotrexate:
Concomitant use of high dose methotrexate (e.g. 300 mg) and proton-pump inhibitors has been reported to increase methotrexate levels in some patients. Therefore, in settings where high-dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of pantoprazole may need to be considered.

Other interactions studies:
Pantoprazole is extensively metabolized in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4.

Interaction studies with medicinal products also metabolized with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, and an oral contraceptive containing levonorgestrel and ethinyl oestradiol did not reveal clinically significant interactions.
An interaction of pantoprazole with other medicinal products or compounds, which are metabolized using the same enzyme system, cannot be excluded.

Results from a range of interaction studies demonstrate that pantoprazole does not affect the metabolism of active substances metabolized by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol) or does not interfere with p-glycoprotein related absorption of digoxin.

There were no interactions with concomitantly administered antacids.

Interaction studies have also been performed by concomitantly administering pantoprazole with the respective antibiotics such as clarithromycin, metronidazole, amoxicillin. No clinically relevant interactions were found.

Medicinal products that inhibit or induce CYP2C19:
Inhibitors of CYP2C19 such as fluvoxamine could increase the systemic exposure of pantoprazole. In patients treated with inhibitors of CYP2C19 such as fluvoxamine or those with hepatic impairment, a dose reduction may be considered for patients treated long-term with high doses of pantoprazole.

Enzyme inducers affecting CYP2C19 and CYP3A4 such as rifampicin and St John´s wort (Hypericum perforatum) may reduce the plasma concentrations of PPIs that are metabolized through these enzyme systems.

**Additional information on special populations:**
No interaction study has been performed in special populations.

**4.6 Pregnancy and lactation**

**General recommendation**
Pregnancy category: B

**Women with childbearing potential/Contraception**
Specific tests with an oral contraceptive containing levonorgestrel and ethinyl estradiol showed no clinically significant interaction (see Section 4.5).

**Pregnancy**
Limited data on pregnant women (between 300-1000 pregnancy outcomes) indicate no adverse effects of pantoprazole on the pregnancy or the health of the fetus/newborn (malformative or feto/neonatal toxicity).

No significant epidemiological data have been obtained so far. Animal studies have shown reproductive toxicity (see section 5.3). Potential risk for human is unknown.
Care should be taken when using in pregnant women.

**Lactation**
Animal studies have shown excretion of pantoprazole in breast milk. There is insufficient

information on the excretion of pantoprazole in human milk but excretion into human milk has been reported. A risk to the newborns/infants cannot be excluded. Therefore, a decision on whether to discontinue breast-feeding or to discontinue/abstain from ZYGOSİS therapy should take into account the benefit of breast-feeding for the child, and the benefit of ZYGOSİS therapy for the breastfeeding mother.

**Reproduction ability/Fertility**
There was no evidence of impaired fertility following the administration of pantoprazole in animal studies (see section 5.3).

In animal reproduction studies, signs of slight foetotoxicity were observed at doses above 5 mg/kg. There is no evidence of impaired fertility or teratogenic effects (see section 5.3).

**4.7 Effects on ability to drive and use machines**
Pantoprazole has no or negligible influence on the ability to drive and use machines.

Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machines.

**4.8 Undesirable effects**
Approximately 5% of patients can be expected to experience adverse drug reactions. The most commonly reported adverse drug reactions are diarrhea and headache, occurred in approximately 1% of patients.

Undesirable effects listed according to the system organ class are ranked under the following frequency classification:

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)

| Frequency / System Organ Class | Common (≥1/100 <1/10) | Uncommon: (≥1/1,000 <1/100) | Rare (≥1/10,000 <1/1,000) | Very rare (<1/10,000, including isolated reports) | Unknown |
|---|---|---|---|---|---|
| Blood and lymphatic system disorders | | | Agranulocytosis | Thrombocytopenia Leukopenia, Pancytopenia | |
| Immune system disorders | | | Hypersensitivity (including anaphylactic reactions and anaphylactic shock) | | |

| Frequency / System Organ Class | Common (≥1/100 <1/10) | Uncommon: (≥1/1,000 <1/100) | Rare (≥1/10,000 <1/1,000) | Very rare (<1/10,000, including isolated reports) | Unknown |
|---|---|---|---|---|---|
| Metabolism and nutrition disorders | | | Hyperlipidemias and lipid increases (triglycerides, cholesterol); Weight changes | | Hyponatremia, Hypomagnesaemia (see section 4.4) Hypocalcaemia[(1)]; Hypokalemia |
| Psychiatric disorders | | Sleep disorders | Depression (and all aggravations) | Disorientation (and all aggravations) | Hallucination; Confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence) |
| Nervous system disorders | | Dizziness Headache | Taste disturbance | | |
| Eye disorders | | | Disturbances in vision (blurred vision) | | |
| Gastrointestinal disorders | Fundic gland polyps (benign) | Nausea/ vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort Diarrhea | | | |
| Hepatobiliary disorders: | | Increased liver enzymes (transaminases, γ-GT) | Increased bilirubin | | Hepatocellular injury; Jaundice; Hepatocellular failure |
| Skin and subcutaneous tissue disorders | | Allergic reactions such as itching, exanthema and eruption; Pruritus | Urticaria, angioedema; | | Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity; Subacute cutaneous lupus |

| Frequency / System Organ Class | Common (≥1/100 <1/10) | Uncommon: (≥1/1,000 <1/100) | Rare (≥1/10,000 <1/1,000) | Very rare (<1/10,000, including isolated reports) | Unknown |
|---|---|---|---|---|---|
| | | | | | erythematosus (see section 4.4). |
| Musculoskeletal and connective tissue disorders | | Fracture of the hip, wrist or spine (see section 4.4). | Arthralgia; myalgia | | Muscle spasm [(2)] |
| Renal and urinary disorders | | | | | Interstitial nephritis (with possible progression to renal failure) |
| Reproductive system and breast disorders | | | Gynecomastia | | |
| General disorders and administration site conditions | Injection site thrombophlebitis | Asthenia, fatigue and malaise | Body temperature increased; Peripheral edema | | |

[(1)] Hypocalcaemia in association with hypomagnesemia

[(2)] Muscle spasm as a consequence of electrolyte disturbances

### 4.9 Overdose and therapy

There are no known symptoms of overdose in man.
Systemic exposure with up to 240 mg i.v. administered over 2 minutes were well tolerated.
As pantoprazole is extensively protein bound, it is not readily dialyzable.
In the case of an overdose with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

**Pharmacotherapeutic Group:** Proton pump inhibitors
**ATC Code:** A02BC02

Mechanism of Action
Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific blockade of the proton pumps of the parietal cells.
Pantoprazole is converted to its active form in the acidic environment in the parietal cells where it inhibits the H+, K+-ATPase enzyme, the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid

secretion. In most patients, freedom from symptoms is achieved within two weeks. As with other proton pump inhibitors and $H_2$ receptor inhibitors, treatment with pantoprazole reduces acidity in the stomach and thereby increases gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, it can inhibit hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the product is given orally or intravenously.

Pharmacodynamic Effects
The fasting gastrin values increase under pantoprazole. On short-term use, in most cases they do not exceed the upper limit of normal. During long-term treatment, gastrin levels double in most cases. An excessive increase, however, occurs only in isolated cases. As a result, a mild to moderate increase in the number of specific endocrine (ECL) cells in the stomach is observed in a minority of cases during long-term treatment (simple to adenomatoid hyperplasia). However, according to the studies conducted so far, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids as were found in animal experiments (see section 5.3) have not been observed in humans.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract.

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalized patients, possibly also *Clostridium difficile*.

An influence of a long-term treatment with pantoprazole exceeding one year cannot be completely ruled out on endocrine parameters of the thyroid according to results in animal studies.

## 5.2 Pharmacokinetic properties

**General properties:**
Pharmacokinetics of ZYGOSİS do not vary after single or repeated administration. Concomitant food intake does not affect AUC, maximum concentration and bioavailability. In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole are linear after both oral and intravenous administration.

Absorption
Information on absorption is not valid since it is directly administered to the bloodstream.

Distribution
Pantoprazole's serum protein binding is about 98%. Volume of distribution is about 0.15 L/kg

Biotransformation
Pantoprazole is almost exclusively metabolized in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation, other metabolic pathways include oxidation by CYP3A4.

Elimination:
Terminal half-life is about 1 hour and clearance is about 0.1 L/h/kg. There were a few cases of subjects with delayed elimination. Because of the specific binding of pantoprazole to the proton pumps of the parietal cell the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).
Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole, the rest is excreted with the faces. The main metabolite in both the serum and urine is desmethylpantoprazole which is conjugated with sulphate. The half-life of the main metabolite (about 1.5 hours) is not much longer than that of pantoprazole.

Linearity/Non-linearity
In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole are linear after both oral and intravenous administration.

**Special Populations**

Polymorphic metabolism:
Approximately 3% of the European population lack a functional CYP2C19 enzyme and are called poor metabolizers. In these individuals the metabolism of pantoprazole is probably mainly catalyzed by CYP3A4. After a single-dose administration of 40 mg pantoprazole, the mean area under the plasma concentration-time curve was approximately 6 times higher in poor metabolizers than in subjects having a functional CYP2C19 enzyme (extensive metabolizers). Mean peak plasma concentrations were increased by about 60%. These findings have no implications for the posology of pantoprazole.

Renal impairment:
No dose reduction is recommended in patients with impaired renal function (incl. dialysis patients). As with healthy subjects, pantoprazole's half-life is short and only very small amounts of pantoprazole are dialyzed. Although the main metabolite has a moderately delayed half-life (2-3 h), excretion is still rapid and thus accumulation does not occur.
Hepatic impairment:
Although for patients with liver cirrhosis (classes A and B according to Child) the half-life values increased to between 7 and 9 h and the AUC values increased by a factor of 5-7, the maximum serum concentration only increased slightly by a factor of 1.5 compared with healthy subjects.

Pediatric population:
Following administration of single intravenous doses of 0.8 or 1.6 mg/kg pantoprazole to children aged 2-16 years there was no significant association between pantoprazole clearance

and age or weight. AUC and volume of distribution were in accordance with data from adults.

Geriatric population:
A slight increase in AUC and $C_{max}$ in elderly volunteers compared with younger counterparts is also not clinically relevant.

### 5.3 Preclinical safety data
Preclinical data from conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity reveal no special hazard to humans.

In the two-year carcinogenicity studies in rats neuroendocrine neoplasms were found. In addition, squamous cell papilloma was found in the forestomach of rats. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and allows the conclusion that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during chronic high-dose treatment. In the two-year rodent studies an increased number of liver tumors was observed in rats and in female mice and was interpreted as being due to pantoprazole's high metabolic rate in the liver.

A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose (200 mg/kg). The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no harmful effects on the thyroid glands are expected.

In animal reproduction studies, signs of slight fetotoxicity were observed at doses above 5 mg/kg.

Investigations revealed no evidence of impaired fertility or teratogenic effects.

Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentration of pantoprazole in the fetus is increased shortly before birth.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of Excipients
Disodium edetate dihydrate
Sodium hydroxide
Water for injection

### 6.2 Incompatibilities
This medicinal product should not be prepared or mixed with substances other than those stated in section 6.6.

## 6.3 Shelf Life

Shelf life is 24 months.
From a microbiological point of view, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of the user.

## 6.4 Special precautions for storage

Store at room temperature below 25°C.
Keep container in the outer carton in order to protect from light.
For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

## 6.5 Nature and contents of container

Colorless (type I) glass vial containing 40 mg powder for solution for injection.

## 6.6 Special precautions for disposal and other handling

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

A ready-to-use solution is prepared by injecting 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection into the vial containing the powder. The appearance of the product after reconstitution is a clear solution. This solution may be administered directly or may be administered after mixing it with 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection or glucose monohydrate 55 mg/ml (5%) solution for injection. Glass or plastic containers should be used for dilution.
After reconstitution, or reconstitution and dilution, chemical and physical in use stability has been demonstrated for 12 hours at 25°C.

From a microbiological point of view, the product should be used immediately.

ZYGOSİS should not be prepared or mixed with solvents other than those stated.

Intravenous injection should be performed over 2-15 minutes.
The contents of the vial are for single use only. Any product that has remained in the container or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed) should be disposed of in accordance with local requirements.

# 7. MARKETING AUTHORISATION HOLDER

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## 8. MARKETING AUTHORISATION NUMBER

2018/386

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 20.07.2018
Date of renewal of the authorization: -

## 10. DATE OF REVISION OF THE TEXT

30.12.2019