Aclipak
Paclitaxel

1. NAME OF THE MEDICINAL PRODUCT

Aclipak 6mg/ ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One millilitre of concentrate for solution for infusion contains 6 mg of paclitaxel.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
A clear, colourless to slightly yellow, viscous solution.
It is multiple use product.

4. CLINICAL DATA

4.1. Therapeutic indications

Ovarian carcinoma

- First line therapy in combination with a platinum compound for the treatment of advanced metastatic carcinoma of the ovary.
- Second line therapy for the treatment of advanced metastatic carcinoma of the ovary.

Breast cancer

Initial treatment of advanced or metastatic breast cancer in combination with trastuzumab, in patients who over-express HER-2 at a 3+level as determined by immunohistochemistry and for whom an antracycline is not suitable.

- Second-line therapy for treatment of metastatic carcinoma of the breast, after failure of standard therapy.

Non-small cell lung carcinoma

- First-line therapy in combination with a platinum compound or as a single agent for the treatment of non-small cell carcinoma of the lung in patients who are not candicates for potentially curative surgery and/or radiation therapy.

4.2. Posology and method of administration

Before the initiation of *Aclipak* therapy, all patients should receive premedication with glucocorticoids (20 mg dexamethasone, given orally at 12 and 6 hours before of *Aclipak* administration), antihistamines anti-H_1 (50 mg diphenhydramine or 10 mg chlopheniramine intravenously) and antihistamines anti-H_2 (cimetidine 300 mg or ranitidine 50 mg intravenously, 30 - 60 minutes before *Aclipak* therapy).
The *Aclipak* solution should be administered through an in-line filter included in the infusion line, with a microporous membrane with a mesh diameter of less than 0.22 µm.

Ovarian cancer
First line treatment
Although other therapeutic regimens are still under investigation, a combination of *Aclipak* and cisplatin is recommended. Depending on the duration of infusion, the recommended posology is:
Aclipak 175 mg/m², given as intravenous infusion over 3 hours; followed by cisplatin 75 mg/m² every three weeks, or *Aclipak* 135 mg/m² in a 24-hour infusion followed by cisplatin 75 mg/m², with a pause of 3 weeks between cures.
Second line treatment
The recommended *Aclipak* dose is 175 mg/m² given as a 3-hour intravenous infusion, with a pause of 3 weeks between the cycles.

Breast cancer
First line treatment
If associated with trastuzumab, the recommended *Aclipak* posology is 175 mg/m², given as intravenous infusion over 3 hours, with a pause of 3 weeks between cures. *Aclipak* infusion can be started in the day following the administration of the first dose of trastuzumab or immediately after the second trastuzumab dose, if the first dose was well tolerated.
Second line treatment
The recommended *Aclipak* dose is 175 mg/m² given as a 3-hour intravenous infusion, with a pause of 3 weeks between cures.

Treatment of advanced non-small cell lung carcinoma
The recommended *Aclipak* posology is of 175 mg/m², given as intravenous infusion over 3 hours; followed by the administration of cisplatin 80 mg/m², with a pause of 3 weeks between cures.
The following *Aclipak* doses will be administered depending on the individual tolerance of patients. *Aclipak* administration should not be repeated unless neutrophil count is ≥ 1.500/mm³ and thrombocyte count ≥ 100.000/mm³. Patients with severe neutropenia (less than 500/mm³ for 7 days or longer) or severe peripheral neuropathy should receive doses reduced with 20% at the next cures (section Special warnings and precautions for use).

Children and adolescents
Safety and efficacy were not established for this group of patients.

First-line therapy in combination with a platinum compound or as a single agent for the treatment of non-small cell carcinoma of the lung in patients who are not candidates for potentially curative surgery and/or radiation therapy.

Patients with hepatic impairment:
Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments (see section Special warnings and precautions for use and Pharmacokinetic properties).
Paclitaxel is not recommended in patients with severely impaired hepatic function.

4.3. Contraindications

- Hypersensitivity to paclitaxel or any of the excipients in the product, particularly macroglolglycerol ricinoleate (Cremophor EL®).
- Pregnancy and lactation (Section Pregnancy and lactation).
- Neutropenia below 1500/mm³.

4.4. Special warnings and precautions for use

Aclipak must be administered under the supervision of a specialist physician, experienced in the use of antineoplastic chemotherapeutic agents. Because severe hypersensitivity reaction can occur, proper medication and life support equipment must be available. Patients must be treated with corticosteroids and antihistamines, antagonists of H_1 and H_2, as premedication. *Aclipak* must be administered before cisplatin, when used in combination (see section Interaction with other medicinal products and other forms of interaction).
Significant hypersensitivity reactions (dyspnoea, arterial hypotension requiring treatment, angioedema and generalised urticaria) have been observed in less than 1% of the patients treated with paclitaxel, after the administration of adequate premedication. These reactions are probably histamine-mediated. In case of severe hypersensitivity reactions, *Aclipak* administration should be discontinued immediately, symptomatic therapy should be initiated and *Aclipak* administration will not be restarted.
Bone marrow suppression (primarily neutropenia) is the main dose-limiting factor. Therefore, during *Aclipak* therapy complete blood count must be frequently monitored. *Aclipak* therapy should not be administered again until neutrophil count is ≥ 1500 cells/mm³ and thrombocyte count ≥ 100 000/mm³.
Rarely, severe conduction disturbances were reported when used as single agent. Should they occur, they should be treated accordingly, and during subsequent *Aclipak* cures, continuous cardiac monitoring must be initiated. During administration, arterial hypotension, arterial hypertension and bradycardia were observed; the patients are usually asymptomatic and generally do not require treatment. Monitoring of the vital signs is recommended, especially during the first hour of *Aclipak* infusion. Serious cardiovascular events were observed more frequently in patients with non-small cell lung carcinoma than in those with ovarian or breast cancer.
When *Aclipak* - trastuzumab association is used as initial treatment for metastatic breast cancer, cardiac function should be carefully monitored. Patients treated with this combination should undergo baseline cardiac assessment, including history, physical examination, ECG, echocardiogram and/or MUGA scan. Cardiac function should be further monitored (e.g. every 3 months). This monitoring allows the identification of patients who develop cardiac dysfunction. Patients who develop cardiac dysfunction may benefit from more frequent monitoring (e.g. every 6-8 weeks). If patients have a continued decrease in left ventricular ejection fraction, but remain asymptomatic, the physician should carefully evaluate the risk benefit ratio.
Although peripheral neuropathy occurs frequently, the development of severe symptoms is unusual. In case severe symptoms occur, *Aclipak* dosage should be reduced by 20% in all subsequent courses. In patients with NSCLC and in ovarian cancer patients, *Aclipak* administration as a 3-hour infusion, in combination with cisplatin as first-line therapy resulted in a greater incidence of severe neurotoxic effects than in those treated with *Aclipak* as monotherapy or cyclophosphamide followed by cisplatin.
There is no evidence of increased *Aclipak* toxicity when administered in a 3 hour infusion in patients with mild hepatic dysfunction. There are no data available for patients with severe baseline cholestasis. When *Aclipak* long-term infusion is administered in patients with moderate-severe hepatic insufficiency, bone marrow suppression can occur with a higher frequency. *Aclipak* is not recommended in patients with severely impaired hepatic function.
Special care should be taken to avoid intra-arterial administration of *Aclipak*. In animal studies investigating local tolerance of *Aclipak*, severe tissue reactions occurred following intra-arterial administration of paclitaxel.
Pseudomembranous colitis has been rarely reported, including cases in patients that have not been treated concomitantly with antibiotics. This reaction must be considered in the differential diagnosis of cases of severe or persistent of diarrhoea occurring during or short time after paclitaxel therapy.
Aclipak in combination with radiotherapy of the lung may contribute to the development of interstitial pneumonitis, regardless of their chronological order.
Excipients
Because *Aclipak* contains ethanol (385 mg/ml), the CNS effects, as well as other effects must be considered. It may be harmful for the patients with alcoholism. Caution is advised when used in patients with hepatic diseases or epilepsy.
Aclipak contains also macroglolglycerol ricinoleate, which might cause serious adverse reactions.

4.5. Interactions with other medicinal products and other forms of interaction

Paclitaxel clearance is not influenced by the administration of cimetidine as premedication. As first line therapy in ovarian carcinoma, it is recommended that *Aclipak* should be administered before cisplatin. In this case, the safety profile of *Aclipak* was similar to that observed in monotherapy. *Aclipak* administration after cisplatin causes more profound bone marrow suppression and a 20% decrease in paclitaxel clearance.
The metabolism of paclitaxel is catalyzed by the isoenzymes CYP2C8 and CYP3A4, which belong to the cytochrome P450 complex. Clinical studies have demonstrated that CYP2C8-mediated metabolism of paclitaxel to 6α-hydroxypaclitaxel is the main metabolic pathway in humans. Based on the current knowledge, clinically relevant interactions between paclitaxel and other products metabolized by CYP2C8 are not to be expected.
Concomitant administration of ketoconazole, a potent inhibitor of CYP3A4 isoenzyme does not inhibit paclitaxel elimination; the products can be administered concomitantly without requiring dose adjustment.
Supplementary data about the possibility of interactions between paclitaxel and other products that are substrates/inhibitors of CYP3A4 are limited. Therefore, caution is recommended when paclitaxel is administered concomitantly with products known as substrate or inhibitor of CYP3A4.

4.6. Pregnancy and lactation

It has been demonstrated that *Aclipak* has an embryotoxic and foetotoxic effect in rabbits, and decreases fertility in rats.
There is no information on *Aclipak* use during pregnancy. Like other cytotoxic medicines, *Aclipak* can cause foetal abnormalities if administered in pregnant women; therefore, *Aclipak* is contraindicated during pregnancy. Women will be advised to avoid pregnancy during *Aclipak* therapy and to immediately inform their treating physician if they become pregnant.
It is not known whether *Aclipak* is excreted in maternal milk. *Aclipak* is contraindicated during lactation. During the therapy with *Aclipak*, lactation should be discontinued.

4.7. Effects on ability to drive and use machines

It has not been demonstrated that *Aclipak* interferes with the ability of car driving or using machines. However, patients should be warned that the product contains alcohol.

4.8. Adverse reactions

The frequency and severity of the adverse reactions are generally similar in all patients receiving *Aclipak* for the treatment of ovarian cancer, breast cancer or non-small cell lung carcinoma; none of the toxic effects is clearly influenced by age.
When *Aclipak* is administered as first line treatment for ovarian cancer as a 3-hour infusion, neurotoxicity, arthralgia/myalgia and hypersensitivity can occur more frequently and may be more severe in patients treated with *Aclipak* followed by cisplatin than in those receiving cyclophosphamide followed by cisplatin.

Myelosuppression
Myelosuppression is less frequent and less severe if *Aclipak* is administered as a 3-hour infusion followed by cisplatin, as compared with the administration of cyclophosphamide followed by cisplatin.
If used as the first line treatment for metastatic breast cancer and when paclitaxel is administered in a three- hour infusion, in association with trastuzumab, the following events are reported with a higher frequency than in the case of monotherapy with paclitaxel: heart failure (8% vs. 1%), infections (46% vs. 27%), chills (42% vs. 4%), fever (47% vs. 23%), cough (42% vs. 27%), rash (39% vs. 18%) arthralgias (37% vs. 21%), tachycardia (12% vs. 4%), diarrhoea (45% vs. 30%), hypertonia (11% vs. 3%), epistaxis (18% vs. 4%), acne (11% vs. 3%), herpes simples (12% vs. 3%), insomnia (25% vs. 13%), rhinitis (22% vs. 5%), sinusitis (21% vs. 7%) and reactions at the injection site (7% vs. 1%). Part of this frequency differences may be due to the increased number and duration of the treatment with the association paclitaxel/trastuzumab as compared with paclitaxel as monotherapy.
The most frequent and significant adverse reaction of paclitaxel was bone marrow suppression. Severe neutropenia (< 500/mm³) has been reported in 28% of patients, but was not associated with febrile episoces in patients treated with paclitaxel. Only 1% of patients had severe neutropenia lasting for 7 days or more. Thrombocytopenia has been reported in 11% of the patients. In 9% of the patients thrombocyte count declined to a value of 50,000/mm³ at least once during the study.
Anaemia was observed in 64% of the patients treated with paclitaxel, but was severe (Hb < 8 g/dl) in only 6% of the patients. The incidence and severity of anaemia is correlated with the baseline haemoglobin level.
Acute myeloid leukaemia and myelodysplastic syndrome have been reported outside of phase III clinical trials.

Myelosupression is less frequent and less severe with a 3-hour infusion than with a 24-hour infusion schedule. The posology recommended for the combination paclitaxel/cisplatin for the first line chemotherapy of ovarian cancer appeared to cause a more severe myelosuppression than paclitaxel in monotherapy or paclitaxel followed by cisplatin using the recommended schedule of 175 mg/m² over 3-hour infusion.

Hypersensitivity reactions
Significant hypersensitivity reactions with possible fatal outcome (defined as arterial hypotension requiring therapy, angioedema, respiratory distress requiring bronchodilator therapy and generalised urticaria) occurred in 2 (<1%) of patients treated with paclitaxel.
34% of patients (1,7% of all courses) experienced minor hypersensitivity reactions (mainly flushing and rash), which did not require therapeutic intervention nor did they prevent continuation of paclitaxel therapy.

Cardiac and vascular disorders
Arterial hypotension and bradycardia were observed in 22% and 5% of patients, respectively; most cases were mild and did not require treatment.
During clinical trials, ECG abnormalities were recorded in 17% of patients. In most cases, no clear relationship between paclitaxel administration and ECG changes could be defined and these alterations were of little clinical relevance.
One patient (< 1 %) experienced arterial hypertension during paclitaxel therapy. In addition, 2 patients (< 1%) presented severe thrombotic events (thrombosis of the upper extremity and thrombophlebitis). One patient each (<1%) experienced the following significant cardiovascular adverse reactions: arterial hypotension associated with septic shock, cardiomyopathy and tachycardia associated with fever. In early clinical studies, conducted with varying dosages and infusion schedules, 2% of the patients treated with paclitaxel experienced severe cardiovascular adverse reactions, possibly related to paclitaxel: asymptomatic ventricular tachycardia, tachycardia with bigeminy, atrioventricular block and syncope. These cases occurred more frequently in patients with non-small cell lung carcinoma.
Cases of myocardial infarction have been rarely reported.
Administration of trastuzumab in combination with paclitaxel in patients previously treated with anthracyclines was accompanied by an increased frequency and severity of cardiac dysfunction in comparison with patients treated with paclitaxel as monotherapy, and very rarely lead to death.

Nervous system disorders
Neurotoxicity, mainly peripheral neuropathy, appeared to be more frequent and severe in patients treated with 175 mg/m² 3-hour infusion (85% neurotoxicity, 15% severe) than in patients treated with paclitaxel 135 mg/m² 24-hour infusion, in association with cisplatin (25% peripheral neuropathy, 3% severe).
Peripheral neuropathy can occur after the first treatment course and the frequency can increase with exposure to paclitaxel.
Sensory symptoms have usually improved or resolved within several months after paclitaxel discontinuation. Pre-existing neuropathies, resulting from prior therapy are not a contraindication for paclitaxel therapy.
Other neurologic manifestations have been reported outside the randomized trials: grand mal seizures, encephalopathy, motor neuropathy, autonomic neuropathy with paralytic ileus and orthostatic hypotension.
Also, optic nerve and/or visual disturbances (scotoma) have been reported, particularly in patients receiving high doses. These effects were generally reversible.
Ototoxicity (hearing loss, tinnitus) has been very rarely reported and it may be related to paclitaxel-related neuropathy, underlying disease or pre-existing conditions.

Musculoskeletal, connective tissue and bone disorders
Arthralgia or myalgias affected 60% of patients and was severe in 13% of patients treated with paclitaxel.

Skin and subcutaneous tissue disorders:
Alopecia was observed in almost all patients. Mild and transient changes of the nails and skin have been reported.
Rarely, cutaneous lesions occurring following radiotherapy were reported outside phase III trials.
Stevens-Johnson syndrome, epidermal necrolysis and erythema multiforma were very rarely reported; concomitant factors may contribute to the development of these effects. Exfoliative dermatitis was very rarely reported.

Gastrointestinal disorders
Gastrointestinal adverse reactions were mild to moderate: nausea/ vomiting, diarrhoea and stomatitis were reported by 43%, 28% and 18% of patients, respectively. Outside randomized clinical trials, other adverse effects have been reported: bowel obstruction / perforation, mesenteric thrombosis, ischaemic colitis. Pseudomembranous colitis has been rarely reported.
Rarely, there has been reported a severe elevation (> 5 times the normal value) of AST (SGOT), alkaline phosphatase or bilirubin, in 5%, 4% and 1% of patients, respectively. Hepatic necrosis and encephalopathy have been reported in patients treated with paclitaxel outside phase III clinical trials.

General disorders and administration site conditions
Injection site reactions during intravenous administration can lead to local oedema, pain, erythema and induration; occasionally, extravasation can cause cellulitis. Skin discoloration can occur. Currently, no specific therapy is known in case of extravasation.
Radiation pneumonitis has been described in some patients receiving associated radiation therapy.

4.9. Overdosage

An antidote for paclitaxel overdosage is unknown. The possible complications of paclitaxel overdosage are myelosuppression, peripheral neurotoxicity and stomatitis.

5. PHARMACOLOGIC PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastics, alkaloids from plants and other natural products, taxanes. ATC code: L01C D01.
Paclitaxel is a novel chemotherapeutic agent that promotes the assembly of microtubules from tubuline dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of microtubule network that is essential for the vital cell functions during interphase and mitosis. More, paclitaxel induces the formation of abnormal microtubule 'groups' or "arrays" throughout the cell cycle and multiple microtubule asters during mitosis.

5.2. Pharmacokinetic properties

Following intravenous administration of *Aclipak*, paclitaxel exhibits a biphasic decline in plasma concentrations.
Pharmacokinetic parameters of paclitaxel have been determined after infusions of 3 or 24 hours, using doses of 135 and 175 mg/m². Mean terminal plasma half-life estimates following elimination ranged from 3 to 52.7 hours and the mean, non-compartmentally derived, values for total body clearance ranged from 11.6 to 24.0 l/hour/m²; the total body clearance appears to diminish with increased plasma paclitaxel concentrations. The mean apparent distribution volume at steady-state was between 198 and 686 l/m², indicating extensive extravascular distribution and/or tissue binding. In the case of 3-hour infusion with increasing doses, paclitaxel pharmacokinetics is non-linear. For a 36% increase of the dose, from 135 mg/m² to 175 mg/m², the values of the maximum plasma concentrations (C_{max}) and area under the curve depending on time ($AUC0_\infty$) increased with 75%, respectively 81%.
The intrapatient variability to systemic paclitaxel exposure was minimal.
Paclitaxel accumulation was not observed after multiple therapeutic courses. In vitro studies indicated an 89 - 98% binding of the drug to serum proteins. The presence of cimetidine, ranitidine, dexamethasone or diphenhydramine does not affect protein binding of paclitaxel.
Paclitaxel distribution in the body has not been fully elucidated in humans.
The mean values for cumulative urinary recovery of unchanged drug ranged from 1.3 to 12.6% of the administered dose, indicating a significant extrarenal clearance. Hepatic metabolism and biliary clearance appear to be the main mechanism of paclitaxel disposition. Paclitaxel is metabolized mainly by cytochrome P450 enzymes. The main metabolites are hydroxylated derivatives. The formation of 6-α-hydroxypaclitaxel, 3'-p-dhydroxypaclitaxel and 6-α-,3'-p-dihydroxipaclitaxel is catalyzed by the CYP2C8-, 3A4, by both 2C8 and 3A4, respectively. The effect of renal or hepatic dysfunction upon paclitaxel disposition following the administration as a 3-hour infusion has not been investigated formally.
The pharmacokinetic parameters obtained from a patient undergoing hemodialysis and treated with *Aclipak* infusions at a dose of 135 mg/m² for 3 hours have been within the limits of those obtained from non-dialysed patients.

6. PHARMACEUTICAL PROPERTIES

6.1. List of excipients

Anhydrous citric acid
Macroglolglycerol ricinoleate (Cremophor® EL)
Ethanol

6.2. Incompatibilities

Infusion sets containing PVC components should not be used, because they can leach DEHP (di-(2-ethylhexyl)-phtalate) in contact with macroglolglycerol ricinoleate (Cremophor® EL). Therefore, the diluted solution must be stored in glass vials or plastic bags for infusion (polypropylene, polyolefin) and is administered using polyethylene infusion kits.

6.3. Shelf life

The expiry date is indicated on the packaging
28 days after first vial opening
27 hours after dilution

6.4. Special precautions for storage

Store in original package to protect from light.
Do not store above 30°C.
The diluted solution (0.3 - 1.2 mg paclitaxel/ml) is stable 27 hours at 25°C.
The product is stable 28 days at 25°C after first vial opening.
It is multiple use product.

6.5. Nature and contents of packaging

Carton box with one vial of 5 ml concentrate for solution for infusion
Carton box with one vial of 16.67 ml concentrate for solution for infusion
Carton box with one vial of 25 ml concentrate for solution for infusion
Carton box with one vial of 43.33 ml concentrate for solution for infusion
Carton box with one vial of 50 ml concentrate for solution for infusion

6.6. Instructions concerning the preparation and handling of the medicinal product for administration

Generally, as for other antineoplastic agents, *Aclipak* requires special precautions for handling.
The preparation of the solution must be performed in an aseptic designated area, by trained personnel. The use of gloves is recommended. In case *Aclipak* solution comes into contact with the skin or mucous membranes, wash immediately and abundantly with soap and water. After accidental contact with the skin, tingling, burning and redness have been observed. Upon inhalation, dyspnoea, chest pain, sore throat can occur.
If unopened vials are refrigerated, a precipitate may form that redissolves with little or no agitation after reaching room temperature. Product quality is not affected. If the solution remains cloudy or if an insoluble precipitate is observed, the vial should not be used.

Preparation of the solution for intravenous infusion
Aclipak must be aseptically diluted in one of the following solutions for infusion:
0.9 % NaCl; 5% glucose; 5% glucose in Ringer solution. The final concentration of the solution must range from 0.3 to 1.2 mg/ml. These solutions are stable physically and chemically for up to 27 hours at room temperature (about 25°C) and normal light. Following multiple needle entries and product withdrawals, *Aclipak* vials maintain their sterility, physical and chemical stability for up to 28 days at 25°C. Other conditions and storage times are the responsibility of the user. Diluted solutions should not be refrigerated. Due to the diluting agent, after preparation the solution can be slightly cloudy. The *Aclipak* solution should be administered through an in-line filter included in the infusion line, with a microporous membrane with a mesh diameter of maximum 0.22 µ. No changes of medicinal product potency have been noted when this kind of filter was used.
There have been rare reports of precipitation during infusion, usually towards the end of a 24-hour infusion period. Although the cause of this precipitation has not been elucidated, it is probably linked to the supersaturation of the diluted solution. To reduce the precipitation risk, *Aclipak* should be used as soon as possible after dilution, and excessive agitation, vibration or shaking should be avoided. The infusion sets should be flushed thoroughly before use. During infusion the appearance of the solution should be inspected regularly and the infusion should be stopped if precipitation is present.
To minimize patient exposure to DEHP, which may be leached from PVC infusion bags, sets, or other medical instruments, *Aclipak* diluted solution should be stored in glass or polypropylene vials or plastic bags (polypropylene, polyolefin) and administered through polyethylene lined administration sets. All the items used for preparation, infusion administration or otherwise coming into contact with *Aclipak* should undergo disposal according to local guidelines for the handling of cytotoxic products.

7. Registration Number

MAL10012446AZ

8. MANUFACTURER NAME AND ADDRESS:

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9. DATE OF TEXT REVIEW

February 2024

Actavis

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1794 PL 03

ARTWORK						
Description			Aclipak Leaflet- Malaesia			
Pharmacode			1794			
Printed packaging material code			1794 PL 03			
Previous printed packaging material code						
EAN code (Product code)						
Dimensions			130 x 600 mm / folded size 130 x 400 mm			
Colors	Pantone ☒ CMYK ☐		1. Black			
Fonts						
Overprinted data	—		—			
DTP Artwork	Regulatory Affairs	Production	Quality Control	Quality Assurance	Extern proof reading	
Please place your electronic signature in the designated area						
LEAFLETS ONLY - SECTION FOR THE EXTERN CO-OPERATION PARTNER: Does the SHELF-LIFE of the product appear in the leaflet? YES (please mention it here*):					NO: ☐	

*Toggle or sticky note in Adobe Reader / write it with the typewriter in Adobe Acrobat / Handwrite