MERZ THERAPEUTICS

I AM HELMUT

I HAVE GOALS
I HAVE ASPIRATIONS
HELP ME ACHIEVE THEM

The First and Only* UK approved Botulinum neurotoxin type A in Sialorrhea

The first and only botulinum neurotoxin type A approved for the treatment of chronic sialorrhea due to neurological disorders in adults.[1]

* As of May 2019

Prescribing information can be found on page 8

XEOMIN®
Botulinum neurotoxin type A
HELPING PATIENTS ACHIEVE THEIR GOALS

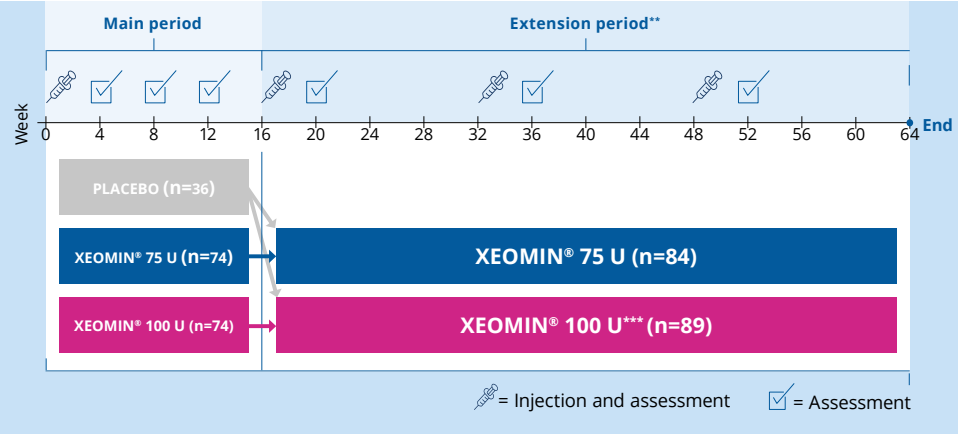
SIALORRHEA CAN NEGATIVELY IMPACT PATIENTS' QUALITY OF LIFE AND CONTRIBUTE TO SOCIAL ISOLATION.[2,3]

Left untreated, sialorrhea is associated with perioral skin breakdown, aspiration pneumonia, choking and dehydration, which can lead to increased morbidity and mortality.[2-5]

> **The worst symptom of all is sialorrhea. Experiencing disability is already a burden, but feeling saliva running uncontrollably from your mouth is socially unbearable… You feel disgusting, hate yourself – depression is a constant companion.**
>
> – Helmut, patient with Parkinson's disease

SIAXI – THE LARGEST CONTROLLED BoNT-A SIALORRHEA STUDY TO DATE[6,7]

The SIAXI trial was a prospective, placebo-controlled, randomised, double-blind, parallel-group phase III study with 184 patients*, exploring treatment of sialorrhea in patients with Parkinson's disease and/or other neurological disorders.[6]



Primary endpoint: The co-primary endpoints were the change in unstimulated salivary flow rate (uSFR) from study baseline to week 4, and the patients' Global Impression of Change Scale (GICS) score at week 4.[6]

* 184 patients were treated in the main phase of the study. 173 patients entered the extension period.

** Extension period includes patients from the placebo group: n=15 in XEOMIN 75 U and n=17 in XEOMIN 100 U.

*** XEOMIN® is approved for the treatment of sialorrhea at the recommended dosage of 100 U. All data presented here will focus on this dosage group. Reduction in unstimulated salivary flow was statistically significant compared to placebo after 8 weeks in both the 75 U and 100 U dosage groups.

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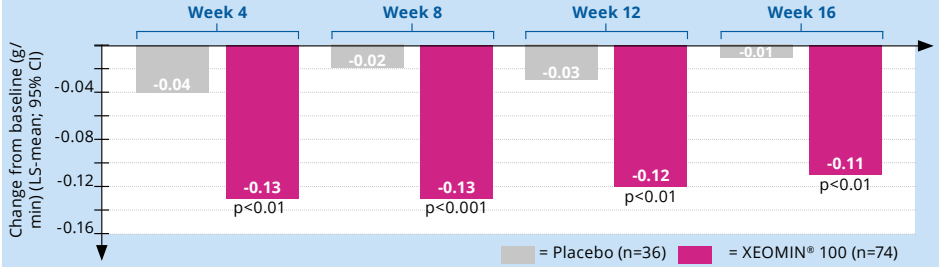
XEOMIN®: HELPING PATIENTS WITH SIALORRHEA

SIGNIFICANT REDUCTION IN UNSTIMULATED SALIVARY FLOW RATE FROM BASELINE VS. PLACEBO[6]

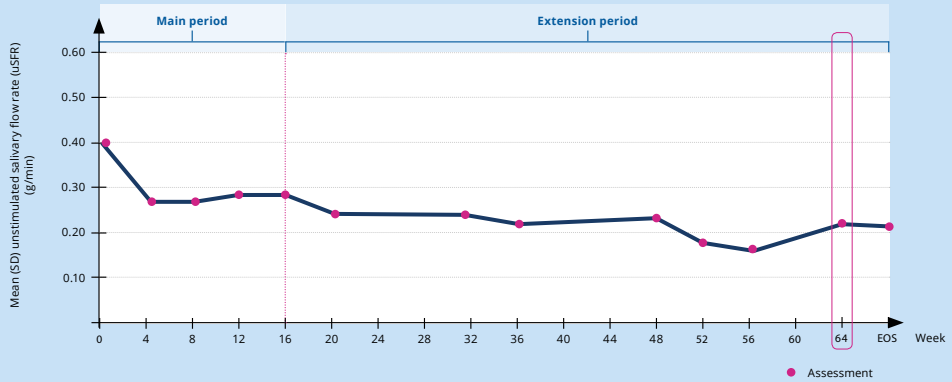
CHANGE FROM BASELINE IN uSFR



- 100 units of XEOMIN® showed a significant reduction in **unstimulated salivary flow rate (uSFR)** vs. placebo from 4 to 16 weeks (p<0.01).[6]
- 75 units of XEOMIN® showed a reduction in uSFR vs. placebo, however did not achieve statistical significance at week 4.[6]

SUSTAINED REDUCTION OF SIALORRHEA SYMPTOMS WITH REPEATED TREATMENTS OVER 64 WEEKS[8]

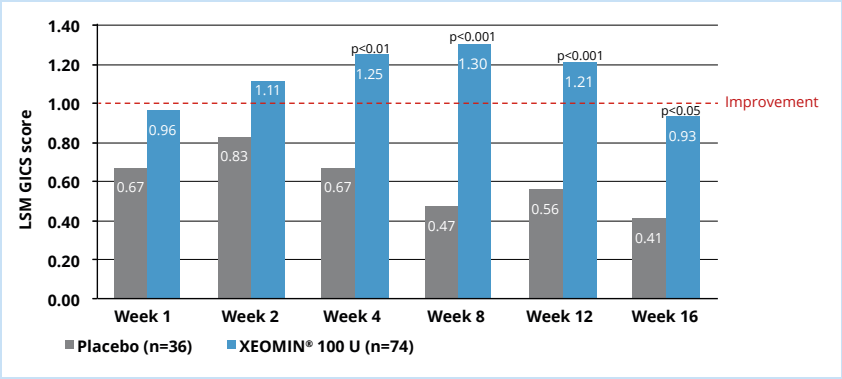
CHANGE FROM BASELINE IN uSFR



Data from patients who received four cycles of active treatment (100 U XEOMIN®) (main period n = 74; extension period n = 89).

PATIENTS REPORTED SIGNIFICANT IMPROVEMENTS IN THEIR FUNCTIONING VS. PLACEBO[6†]

PATIENTS' GLOBAL IMPRESSION OF CHANGE SCORE (WEEK 1 TO 16)



† According to the Global Impression of Change Scale

- Patients reported significant improvements in their functioning vs. placebo.[6†]
- 75 units of XEOMIN® showed a reduction in uSFR vs. placebo, however did not achieve statistical significance at week 4.[6]

XEOMIN® HAS AN ESTABLISHED TOLERABILITY AND SAFETY PROFILE[6]

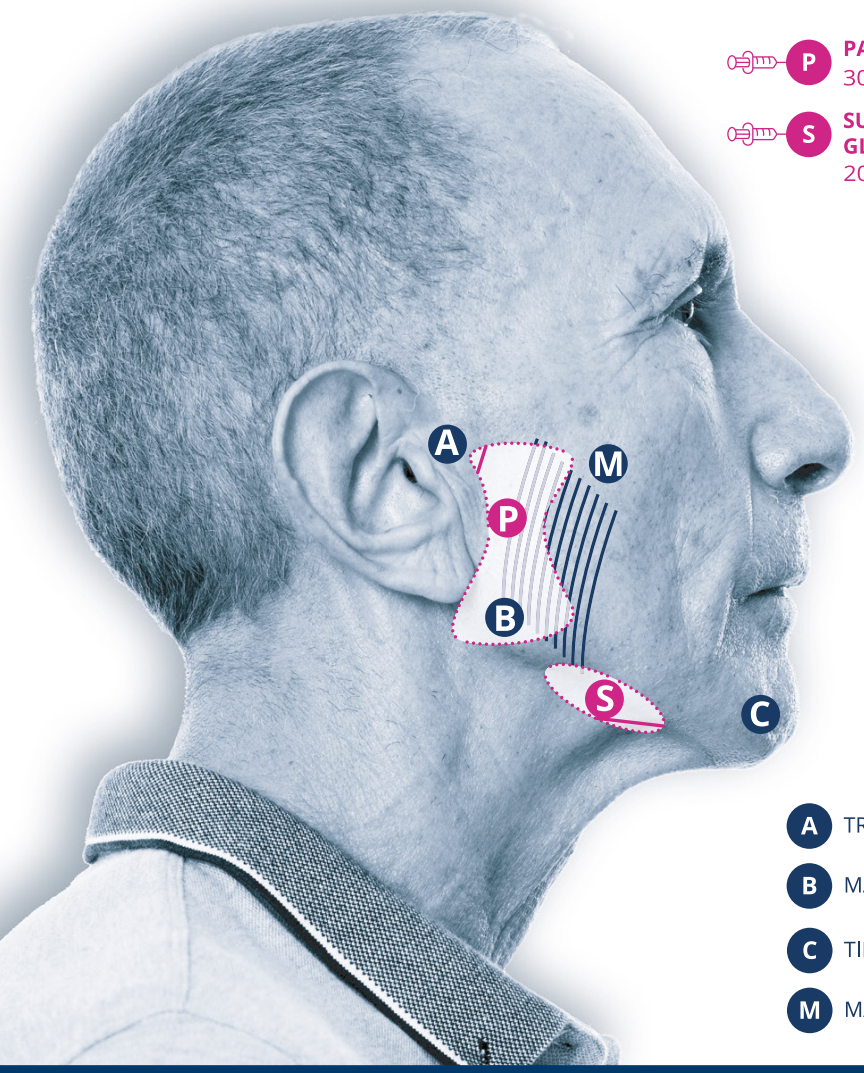
Generally well-tolerated in main study phase up to 16 weeks[9]

MOST COMMON ADVERSE EVENTS (AEs)[††]

	Placebo (n=36)	XEOMIN® 75 U (n=74)	XEOMIN® 100 U (n=74)
	Percentage of patients		
Fall	0	8.1 (6)	2.7 (2)
Dry mouth	0	5.4 (4)	4.1 (3)
Hypertension	2.8 (1)	2.7 (2)	4.1 (3)
Contusion	0	5.4 (4)	0
Tooth extraction	0	0	5.4 (4)
Diarrhoea	2.8 (1)	1.4 (1)	4.1 (3)
Dysphagia	0	4.1 (3)	0
Urinary tract infection	0	4.1 (3)	0

†† Reported by > 3% of patients in any treatment group; data are number of patients by % in Phase III study. During the injection cycle, patients received 4 injections: 1 in the parotid gland on each side and 1 in the submandibular gland on each side.

The percentage of patients with AEs and treatment-related AEs in the XEOMIN® group was similar to those observed with placebo. There were no unexpected AEs with XEOMIN®.



P **PAROTID GLAND(S)**
30 U Injection

S **SUBMANDIBULAR GLAND(S)**
20 U Injection

A TRAGUS

B MANDIBLE ANGLE

C TIP OF CHIN

M MASSETER

XEOMIN®: INJECTION GUIDANCE

XEOMIN® IS INJECTED DIRECTLY INTO THE SALIVARY GLANDS[1] PROVIDING TARGETED TREATMENT OF SIALORRHEA[6,10]

RECOMMENDED TOTAL DOSE[6*]

GLAND(S)	UNITS PER SIDE	TOTAL
Parotid gland(s)	30 Units	**60 Units**
Submandibular gland(s)	20 Units	**40 Units**
Total	50 Units	**100 Units**

* The timing for repeat treatment should be determined based on the actual clinical need of the individual patient, and no sooner than every 16 weeks.

XEOMIN®
Botulinum neurotoxin type A
HELPING PATIENTS ACHIEVE THEIR GOALS

Xeomin® (Clostridium Botulinum neurotoxin type A (150 kD), free from complexing proteins) 50/100/200 unit vials. Prescribing Information: M-XEO-UK-0246. Please refer to the Summary of Product Characteristics (SmPC) before prescribing. **Presentation:** 50/100/200 units (U) of Clostridium Botulinum Neurotoxin type A as a powder for solution for injection. **Indications:** Treatment of blepharospasm and hemifacial spasm, cervical dystonia of a predominantly rotational form (spasmodic torticollis), spasticity of the upper limb, and chronic sialorrhea due to neurological disorders in adults. Symptomatic treatment in children and adolescents aged 2 to 17 years and weighing ≥ 12 kg of chronic sialorrhea due to neurological / neurodevelopmental disorders **Dosage and Administration:** For intramuscular and intraglandular injection. Due to unit differences in the potency assay, unit doses for Xeomin are not interchangeable with those for other preparations of Botulinum toxin type A. Reconstitute with 0.9% sodium chloride. Xeomin may only be administered by appropriately qualified healthcare practitioners with expertise in the treatment of the relevant indication and the use of the required equipment, in accordance with national guidelines. ***Blepharospasm and hemifacial spasm:*** The initial recommended dose is 1.25-2.5 U per injection site, injected into the medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. The initial dose should not exceed 25 U per eye but this can be subsequently increased. The total dose should not exceed 100 U every 12 weeks. Treatment intervals should be determined based on the actual clinical need of the individual patient. Additional sites in the brow area, the lateral orbicularis oculi muscle and in the upper facial area may also be injected if spasms here interfere with vision. Patients with hemifacial spasm should be treated as for unilateral blepharospasm. ***Spasmodic torticollis:*** Xeomin is usually injected into the sternocleidomastoid, levator scapulae, scalenus, splenius capitis and/or the trapezius muscle(s) or any of the muscles responsible for controlling head position that may be involved. No more than 200 U should be injected for the first course of therapy. Adjustments can be made in subsequent courses depending on the response, but not exceeding a total dose of 300 U at any one treatment session. No more than 50 U should be administered at any one injection site. Treatment intervals of less than 10 weeks are not recommended. Treatment intervals should be determined based on the actual clinical need of the individual patient. ***Spasticity of the upper limb:*** The dose and number of injection sites should be tailored to the individual patient based on the size, number and location of muscles involved, the severity of spasticity, and the presence of local muscle weakness. The maximum total dose for the treatment of upper limb spasticity should not exceed 500 U per treatment session, and no more than 250 U should be administered to the shoulder muscles. Repeated treatment should generally be no more frequent than every 12 weeks. Treatment intervals should be determined based on the actual clinical need of the individual patient. ***Chronic sialorrhea (adults):*** A reconstituted solution at a concentration of 5 units/0.1 ml should be used. Inject into the parotid and submandibular glands on both sides (per treatment four injections in total). The dose is divided with a ratio of 3:2 between the parotid and submandibular glands as follows: Parotid glands 30 U per side, Submandibular glands 20 U per side. Inject close to the centre of the gland. The recommended dose per treatment session is 100 U. Do not exceed this maximum dose. Treatment intervals should be determined based on the actual clinical need of the individual patient. Repeat treatment more frequent than every 16 weeks is not recommended. ***Chronic sialorrhea (children/adolescents):*** A reconstituted solution at a concentration of 2.5 units/0.1 ml should be used. Inject into the parotid and submandibular glands on both sides (per treatment four injections in total). The body-weight dose is divided with a ratio of 3:2 between the parotid and submandibular glands. No recommendations can be made for children weighing less than 12 kg. The injection site should be close to the centre of the gland. Treatment intervals should be determined based on the actual clinical need of the individual patient. Repeat treatment should be no more frequent than every 16 weeks. Please see the SmPC for full prescribing recommendation. **Contraindications:** Known hypersensitivity to Botulinum neurotoxin type A or to any of the excipients, generalised disorders of muscle activity (e.g. myasthenia gravis, Lambert-Eaton syndrome) and presence of infection or inflammation at the proposed injection site. **Special warnings and precautions:** Care should be taken not to inject into blood vessels. Use with caution in patients with any bleeding disorder or receiving anticoagulant therapy or other substances that could have an anticoagulant effect. Caution in patients with pre-existing neuromuscular disorders such as patients suffering from amyotrophic lateral sclerosis, other diseases which result in peripheral neuromuscular dysfunction or where the targeted muscles display pronounced weakness or atrophy. Generally, patients with a history of aspiration or dysphagia should be treated with caution. Extreme caution should be exercised when treating these patients for cervical dystonia. Spread of Botulinum toxin type A to sites distant from the injection site has been reported. Some of these can be life threatening and there have been reports of death, some associated with dysphagia, pneumonia and/or significant debility. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise. If serious (e.g. anaphylactic reactions) and/or immediate hypersensitivity reactions occur, appropriate medical therapy should be instituted. Too frequent doses may increase the risk of antibody formation, and possible treatment failure. Should not be used during pregnancy unless clearly necessary and the potential benefit justifies the risk. Should not be used during breast-feeding. ***Blepharospasm and hemifacial spasm:*** Injections near the levator palpebrae superioris should be avoided to reduce the occurrence of ptosis. In order to prevent ectropion, injections into the lower lid area should be avoided, and vigorous treatment of any epithelial defect is necessary. Careful testing of corneal sensation should be performed in patients with previous eye operations. Due to its anticholinergic effects, it should be used with caution in patients at risk of developing narrow angle glaucoma. ***Spasmodic torticollis:*** Xeomin should be injected carefully when injecting at sites close to sensitive structures such as the carotid artery lung apices and oesophagus. Patients should be informed that injections of Xeomin for the management of spasmodic torticollis may cause mild to severe dysphagia with the risk of aspiration and dyspnoea. Limiting the dose injected into the sternocleidomastoid muscle to less than 100 U may decrease the occurrence of dysphagia. Patients with smaller neck muscle mass, or patients who require bilateral injections into the sternocleidomastoid muscles are at greater risk. ***Spasticity of the upper limb:*** Xeomin should be injected carefully when injecting at sites close to sensitive structures such as the carotid artery, lung apices and oesophagus. Xeomin is not likely to be effective in improving range of motion at a joint affected by a fixed contracture. New onset or recurrent seizures have been reported, typically in patients who are predisposed to experiencing these events. ***Chronic sialorrhea (adults/children/adolescents):*** In cases of medication-induced sialorrhea, the possibility of replacement, reduction, or even termination of the inducing medication should be considered before using Xeomin. Efficacy and safety of Xeomin in patients with medication-induced sialorrhea were not investigated. If "dry mouth" develops in association with the administration of Xeomin consider reducing the dose. A dental visit at the beginning of treatment is recommended. The dentist should be informed about sialorrhea treatment with Xeomin to be able to decide about appropriate measures for caries prophylaxis. **Interactions:** No interaction studies have been performed. Concomitant use with aminoglycosides or spectinomycin requires special care. Peripheral muscle relaxants should be used with caution. 4-Aminoquinolines may reduce the effect. When used for the treatment of chronic sialorrhea, irradiation to the head and neck including salivary glands and/or co-administration of anticholinergics may increase the effect of the toxin. The treatment of sialorrhea with Xeomin during radiotherapy is not recommended. **Undesirable effects:** Usually, undesirable effects are observed within the first week after treatment and are temporary in nature. Undesirable effects independent of indication include; application related undesirable effects (localised pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling, oedema, erythema, itching, localised infection, haematoma, bleeding and/or bruising associated with injection), class related undesirable effects (localised muscle weakness), toxin spread (very rare - excessive muscle weakness, dysphagia and aspiration pneumonia with a fatal outcome in some cases), and hypersensitivity reactions (serious and/or immediate hypersensitivity reactions including anaphylaxis, serum sickness, urticaria, soft tissue oedema and dyspnoea have rarely been reported). Needle related pain and/or anxiety may result in vasovagal responses. Management of spasmodic torticollis may cause dysphagia with varying degrees of severity. ***Blepharospasm and hemifacial spasm:*** *Very Common:* Eyelid Ptosis. *Common:* Dry eyes, blurred vision, visual impairment, dry mouth, injection site pain. *Uncommon:* Headache, facial paresis, diplopia, increased lacrimation, dysphagia, rash, fatigue, muscular weakness. ***Spasmodic torticollis:*** *Very common:* Dysphagia. *Common:* Headache, presyncope, dizziness, dry mouth, nausea, hyperhidrosis, neck pain, muscular weakness, myalgia, muscle spasms, musculoskeletal stiffness, injection site pain, asthenia, upper respiratory tract infection. *Uncommon:* Speech disorder, dysphonia, dyspnoea, rash. ***Spasticity of the upper limb:*** *Common:* Dry mouth. *Uncommon:* Headache, hypoaesthesia, dysphagia, nausea, muscular weakness, pain in extremity, myalgia, asthenia. *Unknown:* injection site pain. ***Chronic sialorrhea (adults):*** *Common:* Paraesthesia, dry mouth, dysphagia. *Uncommon:* Speech disorder, altered (thickened) saliva, dysgeusia. Cases of persistent dry mouth (> 110 days) of severe intensity have been reported, which could cause further complications as gingivitis, dysphagia and caries. ***Chronic sialorrhea (children/adolescents):*** *Uncommon:* Dysphagia. *Not known:* Altered (thickened) saliva, dry mouth, oral pain, dental caries **Post Marketing Experience:** Flu-like symptoms, hypersensitivity reactions and muscle atrophy have also been reported with unknown frequency. **Overdose:** May result in pronounced neuromuscular paralysis distant from the injection site. **Legal Category:** POM. **List Price:** 50U/vial £72.00, 100U/vial £129.90, 200U/Vial £259.80. **Product Licence Number:** PL 29978/0003, PL 29978/0001, PL 29978/0004. **Marketing Authorisation Holder** Merz Pharmaceuticals GmbH, Eckenheimer Landstraße 100, 60318 Frankfurt/Main, Germany. **Date of Preparation: September 2021. Additional Information Available in the SmPC or on request from:** Merz Pharma UK Ltd., Ground Floor Suite B Breakspear Park, Breakspear Way, Hemel Hempstead, Hertfordshire, England, HP2 4TZ.

Adverse events should be reported. Reporting forms and information for Great Britain & Northern Ireland can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Merz Pharma UK Ltd by email to UKdrugsafety@merz.com or on +44 (0) 333 200 4143.

M-XEO-UK-0263 Date of preparation: October 2021

XEOMIN®
Botulinum neurotoxin type A
HELPING PATIENTS ACHIEVE THEIR GOALS

References: 1. XEOMIN® Summary of Product Characteristics (SmPC) last accessed on EMC October 2021: https://www.medicines.org.uk/emc/product/6202/smpc. **2.** Hockstein N. et al. Am Fam Physician. 2004;69(11):2628-2635. **3.** Meningaud J. et al. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;101(1):48-57. **4.** Bavikatte G. et al. BJMP. 2012;5(1):506. **5.** Pena A. et al. J Vasc Interv Radiol. 2009; 20:368-373. **6.** Jost WH. et al. Neurology. 2019 Apr 23;92(17):e1982-e1991. doi: 10.1212/ WNL.0000000000007368. Mar 27. **7.** Merz data on file 2019 - REF 0869. **8.** MERZ data on file 2021 - REF-1387. **9.** MERZ data on file 2021 - REF 1388 **10.** Restivo D. et al. Toxins (Basel) 2018; 10(2):55.

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