SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Loramyc 50 mg, muco-adhesive buccal tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of miconazole.

Excipients: lactose monohydrate, milk protein concentrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Muco-adhesive buccal tablet.

White to slightly yellow tablets with a rounded side and a flat side debossed with “L”.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of oropharyngeal candidiasis (OPC) in immunocompromised patients (See Section 5.1)

4.2 Posology and method of administration

Gingival use.

For adults only.

Application of one muco-adhesive buccal tablet once a day for 7 to 14 days depending on the patient’s clinical response. It is preferable to apply the tablet in the morning, after brushing of the teeth, as during the night the salivary flow is less important. Loramyc can be administered with food and drinks.

In the event of clinical cure (defined as complete resolution of disease signs and symptoms) after 7 days of treatment, the use of LORAMYC can be stopped.

In the case of the confluent/extensive (severe) OPC lesions, treatment should be continued until clinical cure or up to 14 days.

Method of administration:
LORAMYC should be applied to the upper gum just above the incisor tooth:

- Once the tablet is removed from the bottle, it should be used immediately. It should be noted that the tablet has a rounded side and a flat side.
- The rounded side of the tablet should be applied on the upper gum above an incisor tooth. Hold the tablet in place for 30 seconds with a slight pressure of the finger over the upper lip.
- If the tablet does not adhere properly, it should be repositioned.
- If the tablet falls off within the first 6 hours but is not swallowed, it should be replaced immediately.
- If Loramyc is accidentally swallowed it is recommended to drink a glass of water. If swallowed within the first 6 hours after application, the tablet should be replaced only once.
- With each application of LORAMYC, the tablet should be applied to alternate sides of the upper-gum.

Elderly population: LORAMYC can be used by the elderly.

There is no experience in children.

4.3 Contraindications

- Hypersensitivity to the active substance(s), **other imidazole derivatives** or to any of the excipients listed in section 6.1.
- Allergy to milk or milk derivatives.
- In patients with liver dysfunction.
- Concomitant administration of oral anticoagulants, hypoglycaemic sulfonamides, cisapride, pimozide, ergot alkaloids: ergotamine, dihydroergotamine (See Section 4.5).

4.4 Special warnings and precautions for use

Co-administration with halofantrine is not recommended (see section 4.5).

LORAMYC should not be given to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Local irritation after the application of LORAMYC has rarely been observed. As with all drugs, hypersensitivity reactions may occur.

Severe hypersensitivity reactions, including anaphylaxis and angioedema, have been reported during treatment with miconazole formulations. If a reaction suggesting hypersensitivity or irritation should occur, the treatment should be discontinued.

As LORAMYC should be applied to the upper gum just above the incisor tooth:

- All situations that could interfere with adhesion of the tablet should be avoided including touching or pressing the tablet already placed. Chewing gum should also be avoided.
- The tablet should not be sucked, chewed or swallowed.
- If teeth brushing occur during the day, the tablet should not be touched, and the mouth should be rinsed with caution.
- If the mouth is dry, it is recommended to moisten the gum before applying the mucoadhesive buccal tablet.
- Accidental ingestion of LORAMYC may occur. If LORAMYC is accidentally swallowed it is recommended to drink a glass of water.

LORAMYC has shown a lower rate of clinical cure in patients with extensive or confluent OPC**.**

4.5 Interaction with other medicinal products and other forms of interaction

Miconazole is an inhibitor of CYP2C9 and CYP3A4. No interaction studies have been performed with Loramyc. Even if the systemic absorption observed with Loramyc has been insufficiently evaluated, administration of medicinal products with narrow therapeutic index and which are metabolised by CYP2C9 and CYP3A4 are contraindicated because of an increased exposure (see section 4.3).

Concomitant use contraindicated:

- Oral anticoagulants

Unforeseeable bleeding that could eventually be severe

- Cisapride

Increased risk of ventricular arrhythmia, e.g. torsades de pointes

- Pimozide

Increased risk of ventricular arrhythmia, e.g. torsades de pointes

- Ergot alkaloids: ergotamine, dihydroergotamine

Risk of ergotism with necrosis of extremities

- Hypoglycaemic sulfonamides

Potential occurrence of hypoglycaemic symptoms, even coma

Concomitant use not recommended:

- Halofantrine

Increased risk of ventricular arrhythmia, e.g. torsades de pointes

Concomitant use requiring precautions for use:

- Phenytoin (and fosphenytoin by extrapolation)

Increased phenytoin plasma concentrations that may reach toxic levels, due to an inhibition of the hepatic metabolism of phenytoin.
A close clinical monitoring is recommended.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of miconazole in pregnant women. Animal studies do not indicate teratogenic effects but other effects on reproduction were

recorded (see section 5.3). The risk for humans is unknown. Miconazole should be used during pregnancy only if necessary.

Lactation

There are no available data on the excretion of miconazole in human milk. Therefore, caution should be exercised when prescribing to breastfeeding mothers.

If the new-born baby or the breastfed infant takes cisapride, the administration of miconazole to the mother is contraindicated as a safety measure, due to the potential risk of drug interaction in the child (torsades de pointes).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed with Loramyc. Nevertheless miconazole is known not to affect the alertness or driving ability.

4.8 Undesirable effects

The safety of LORAMYC has been assessed in 462 patients enrolled in 3 clinical trials (462 patients including 315 HIV infected patients and 147 patients with head and neck cancer receiving radiotherapy) and from post-marketing experience. The most frequently reported serious related adverse events included gastrointestinal disorders.

Adverse reactions by system organ and frequency are listed below (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).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Gastrointestinal disorders
Common: nausea, diarrhea, abdominal pain, vomiting, dry mouth, oral discomfort, gingival pain
Uncommon: glossodynia, gingival pruritus, mouth ulceration

Nervous system disorders
Common: headache, dysgeusia, ageusia

Skin and subcutaneous tissue disorders
Common*:* pruritus, rash
Frequency unknown: Acute Generalised Exanthematous Pustulosis

General disorders and administration site conditions
Uncommon: application site irritation, fatigue, pain

Infections and infestations

Uncommon: upper respiratory tract infection

Metabolism and nutrition disorders
Uncommon: anorexia

Vascular disorders
Uncommon: hot flush
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 Yellow Card Scheme - Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms

In the event of accidental overdosage, vomiting and diarrhea may occur.

Treatment

There is no known antidote to miconazole: Overdose should be treated symptomatically.

In the event of accidental ingestion of large quantities of Loramyc an appropriate method of gastric emptying may be used, if considered necessary.

No case of overdose has been reported with Loramyc.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-infective and Antiseptics for Local Oral Treatment
ATC code: A01AB09

Mechanism of action
Miconazole exerts its antifungal activity by inhibition of ergosterol biosynthesis in the cell membrane of the pathogen. At low concentration, it interacts with fungal cytochrome P450, which results in inhibition of 14-α-demethylation, a step in ergosterol biosynthesis. The depletion of ergosterol and concomitant accumulation of lanosterol lead to some membrane-related disorders. Miconazole displays a fungistatic activity due to the inhibition of membrane sterol synthesis and a fungicidal activity by change in the barrier function of the fungal membrane.

Microbiology:
Miconazole displays broad-spectrum antifungal activity against *Candida* species, including *C. albicans,* and also *nonalbicans* species such as *C. glabrata, C. krusei, C. parapsilosis, C. tropicalis,* and *C. pseudotropicalis.*

Miconazole also displays antibacterial activities against Gram-positive bacteria (including *Streptococcus pyogenes*, *Staphylococcus aureus,* and *Erysipelothrix insidiosa*).

Candida species most often involved in buccal candidiasis (*C. albicans, C. glabrata, C. krusei* and *C. tropicalis*) are susceptible to miconazole. In most recent studies, the Minimal Inhibitory Concentration (MIC) of miconazole ranged from 0.03 to 1 µg/ml for *C. albicans* and from 0.03 to 4 µg/ml for *C.* non-*albicans*, including *C.glabrata* and *C. krusei* that are intrinsically resistant to fluconazole.

In clinical trials in HIV positive patients, *Candida albicans* was the most prevalent species (87.5%). In head and neck cancer patients, among the 321 isolates identified at baseline, *Candida albicans* represented 62.6% of isolates and *Candida* non-*albicans* 37.4% [including *C tropicalis* (30.8%), *C. Krusei* (22.5%), *and C. glabrata* (10.8%)].

The MIC_{90} of miconazole for clinical *Candida* isolates (*C. albicans*: 87.5%, *C. tropicalis* 8% and *C. parapsilosis* 2.1%) taken from a clinical trial in 577 HIV positive patients was 0.25 µg/ml before treatment. After 14 days of treatment, no resistance to miconazole was detected.

Drug Resistance

Clinically relevant resistance to systemically utilized triazoles may occur in *Candida* species. Resistance is determined by multiple mechanisms, principally changes in amino acids and/or in the regulation of the target enzyme and of a variety of efflux pump proteins. Multiple mechanisms frequently co-exist in the same isolate. Cross resistance among the azoles is not complete, even within the triazole subclass. The finding of cross-resistance is dependent upon a number of factors including the species evaluated, its clinical history, the particular azole compounds compared and the type of susceptibility test that is performed.
Resistance breakpoints, correlating in vitro potency with clinical efficacy, have not been established for miconazole.
No primary resistance of *Candida* species to miconazole, an azole drug belonging to the imidazole class, has been reported in the medical literature and acquired resistance to miconazole has been rarely described, even in patients treated repeatedly. In in vitro experiments with 150 recent clinical isolates, repeated exposure to miconazole did not induce resistance among sensitive or resistant to triazole *Candida* species. However, a significant increase of miconazole MIC was observed in 2/6 strains of *Candida spp.* even if MICs remained less than 0.5 µg/ml.

Therefore the emergence of resistant strains to miconazole should not be excluded after repeated exposure to antifungal treatments.

Clinical Experience

In a randomised, comparative, investigator blind study conducted in patients with head and neck cancer having undergone radiotherapy (all patients had mucositis, buccal inflammation, or erythema and 96% had a reduced saliva flow), the response rate at Day 14 and the relapse rate at Day 60 in patients with complete clinical response (no oral lesions) were:

	Loramyc 50 mg	**Miconazole gel**
mITT Population	**N=141**	**N=141**
Complete clinical response rate	52.48%	45.39%
Treatment difference (95% CI)	+7.09 (-19.0; 4.8)	
Relapse rate at D60	21.62%	17.19%
(95% CI)	(13.79; 32.31)	(9.92; 28.27)

PP Population	**N=107**	**N=106**
Complete clinical response rate	53.27%	51.89%
Treatment difference (95% CI)	+1.38 (-15.1 ; 12.3)	
Relapse rate at D60	24.56	14.55
(95% CI)	(15.26; 37.17)	(7.62; 26.22)

In a randomised, double-blind, double dummy, comparative study conducted in HIV-positive patients, the clinical cure rate (no signs and no symptoms of OPC) after a 14-day treatment (between Day 17 and Day 22) and the relapse rate at Day 35 were as follows:

	Loramyc 50 mg	**Clotrimazole Troches 10 mg**
ITT Population	**N=290**	**N=287**
Clinical cure rate	60.7%	65.2%
Treatment difference (95% CI)	-4.5 (-12.4;3.4)	
Relapse rate at D35	27.9%	28.1%
(95% CI)	(21.3; 35.2)	(21.8; 35.2)
PP Population	**N=240**	**N=236**
Clinical cure rate	68.3%	74.2%
Treatment difference (95% CI)	-5.9 (-14.0;2.2)	
Relapse rate at D35	26.9%	27.6%
(95% CI)	(20.2; 34.4)	(21.1; 34.9)

In an open, non comparative, study including 25 HIV-positive patients treated with LORAMYC, the response rate at Day 14 was 84% (95%CI: 63.9; 95.5) and the relapse rate at Day 45 was 38.5% (CI95: 13.8; 68.4) in patients with clinical cure (no signs, no symptoms of OPC).
HIV-positive patients included in clinical studies were markedly immunocompromised. More than 50% had a CD_4^+ count <250/mm3 and 5% had CD_4^+ count <50/mm3 and viral load was high. (117,000 copies/ml)
Overall in clinical trials, 94.3% of LORAMYC tablets adhered to the gum for more than 6 hours.

5.2 Pharmacokinetic properties

The oral bioavailability of miconazole is low (25-30%) because miconazole is poorly absorbed in the gastrointestinal tract. Most of the absorbed miconazole is metabolised by the liver. Less than 1% of the administered dose is found unchanged in urine.

In case of renal impairment the pharmacokinetics of miconazole is not significantly affected. There are no active metabolites and the terminal half-life is about 20 hours.

The single dose of LORAMYC containing 50 mg of miconazole administered to healthy volunteers provides a maximum mean salivary concentration of 15 µg/mL 7 hours after application of the tablet with an area under the curve (AUC_{0-24h}) of 55.23 µg.h/mL.

After the application of a single tablet of Loramyc 50mg, miconazole salivary concentrations above 1 μg/mL (upper limit of MIC value for *C. albicans* strains) were achieved within 1 hour and lasted a mean of 13 hours.

Plasma concentrations of miconazole were undetectable (limit of quantification: 0.4 μg/mL) in most of healthy volunteers, confirming the poor absorption of miconazole through the buccal mucosa or in the gastrointestinal tract after the saliva is swallowed.

After 7 days of treatment in patients, plasma concentrations of miconazole were undetectable (limit of quantification 0.2 ng/mL) in 21.5% of patients and negligible (below 10 ng/mL) in more than 90% of patients.

5.3 Preclinical safety data

In the toxicology studies after single-dose and repeated-dose administration, and in the pre and postnatal development studies, toxic effects have been observed in animals (mouse, rat, rabbit, dog) at doses 30 to 900-fold higher than the maximal recommended dose in humans (0.7mg/kg). Embryotoxic effects but not teratogenic effects of miconazole have been observed in the reprotoxicity studies.

Conventional studies of genotoxicity (Ames, chromosomal aberration, micronucleus) did not reveal any potential genotoxicity.

Local tolerance studies (jugal mucosa of hamster and sensitization LLNA assay in mice) did not show any toxicity.

No carcinogenicity studies have been conducted with miconazole.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose 2208

Milk protein concentrate

Maize starch

Lactose monohydrate

Sodium laurilsulfate

Magnesium stearate

Talc

6.2 Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions

Keep in the original bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

14 tablets in a bottle (HDPE) with a child-resistant cap (polypropylene) which contains a desiccant.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Onxeo
49 Boulevard du Général Martial Valin
75015 Paris
France
Phone: + 33 (0)1 45 58 76 00

8 MARKETING AUTHORISATION NUMBER(S)

PL 31030/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/10/2011

10 DATE OF REVISION OF THE TEXT

14/01/2016