Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

APHTHEAL 5% w/w Oromucosal Paste

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1g oromucosal paste contains 50 mg amlexanox.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oromucosal Paste.
The product is a granular beige-coloured paste.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Aphtheal 5% oromucosal paste, is indicated for the treatment of minor aphthous ulcers in adults.

4.2 Posology and method of administration

Adults
The paste should be applied as soon as possible and within 48 hours of the start of symptoms once the patient is aware of the symptoms of minor aphthous ulcers. The paste should be applied four times daily, after meals and oral hygiene.

Approximately 0.5cm of paste, equivalent to 3mg amlexanox, should be squeezed onto a finger tip and then the paste should be gently applied onto the ulcer. Repeat this procedure with a further 0.5 cm of paste for each ulcer in the mouth. In the clinical studies up to three ulcers were treated, equating to a maximum daily dose of 36 mg. Use of the medicinal product should be continued up to a maximum of seven days treatment.

Children and adolescents (<18 years) and the elderly
Aphtheal 5% oromucosal is not recommended for use in children below 18 years or in the elderly due to a lack of data on safety and efficacy (see sections 5.1 and 5.2). i.e. no specific studies have been conducted in these patient groups.

4.3 Contraindications

Hypersensitivity to the active substances (amlexanox), or to any of the excipients.

4.4 Special warnings and precautions for use

Caution should be taken when using Aphtheal 5% oromucosal paste in patients with renal or hepatic impairment as no specific studies have been conducted in these patient groups.

The hands should be washed immediately after applying the paste. In case of contact with the eye, the eye should be promptly irrigated with water.

4.5 Interaction with other medicinal products and other forms of interactions

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
Reproduction studies in rats and rabbits with doses, on a mg/kg body weight basis, up to fifteen hundred times the projected human daily dose have revealed no evidence of impaired fertility or foetal harm related to amlexanox. There are no adequate controlled studies in pregnant women. Therefore, Aphtheal 5% oromucosal paste should not be used in pregnancy.

Lactation
Amlexanox was found to be transferred to the foetus and mother's milk in rats. Aphtheal 5% oromucosal paste should not be used during lactation.

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. Aphtheal 5% oromucosal paste is unlikely to effect the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions considered to be related or possibly related to Aphtheal 5% oromucosal paste, have not been reported by more than 5% of patients.

Transient pain, stinging and/or burning at the site of application has been reported by 1-2% of patients. Infrequent adverse reactions in clinical studies were contact mucositis, nausea and diarrhoea.

Adverse reactions with a suspected relationship to treatment, are listed below by system organ class and frequency (very common ≥ 1/10; common ≥ 1/100 to < 1/10; uncommon ≥ 1/1000 to < 1/100).

System Organ Class	**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)**
Immune System Disorders					Hypersensitivity (including angioedema)
Gastro intestinal disorders			Oral mucositis, dry lips, bumps on lip, nausea, diarrhoea		
Skin and subcutaneous tissue disorders			Contact Dermatitis 0		
General disorders and administration site conditions		Application site pain			

During the development of a tablet formulation in Japan, oral amlexanox was administered within the range of 75 mg to 150 mg per day. Gastrointestinal and skin adverse events were observed, as well as elevated serum transaminases. The frequency of these adverse events was very rare (<1/10,000), including isolated reports.

4.9 Overdose

No case of overdose has been reported.

The ingestion of a full tube of 3 g or 5 g of Aphtheal 5% oromucosal paste is unlikely to lead to signs of systemic toxicity. Gastrointestinal symptoms such as nausea, vomiting and diarrhoea could result from an overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other agents for local oral treatment

ATC code: A01 AD 07

Amlexanox is an antiallergic, anti-inflammatory agent, however, the mechanism of action for accelerating the healing of aphthous ulcers is unknown. *In vitro* studies have demonstrated amlexanox to be a potent inhibitor of the formation and/or release of inflammatory mediators (histamines, leukotrienes) from mast cells, neutrophils and mononuclear cells.

Meta analysis of data from the three pivotal studies in Table 1 illustrates time to healing and pain resolution for amlexanox 5% oromucosal paste compared to paste (vehicle) alone. Time to healing and pain resolution for amlexanox 5% oromucosal paste compared to no treatment is illustrated in Table 2 for a pivotal study in which "no treatment" was included.

Table 1: Amlexanox 5% oromucosal paste vs. vehicle.

All patients analysis: three pivotal studies, combined database.

	Time to healing		Time to resolution of pain	
	Amlexanox 5% (N=464)	Vehicle (N=465)	Amlexanox 5% (N=464)	Vehicle (N=465)
MEDIAN DAYS	4.9	5.6	3.4	4.1
Log-rank Statistic	p<0.001		p<0.001	

Table 2: Amlexanox 5% oral paste vs. no treatment.

All patients analysis: single pivotal study.

	Time to healing	Time to resolution of pain

	Amlexanox 5% (N=197)	No treatment (N=133)	Amlexanox 5% (N=197)	No treatment (N=133)
MEDIAN DAYS	5.0	6.6	3.6	5.0
Log-rank Statistic	p<0.001		p<0.001	

5.2 Pharmacokinetic properties

Absorption
Amlexanox is rapidly absorbed from the gastro-intestinal tract.

After a single oromucosal application of 100 mg of amlexanox paste (5 mg amlexanox) maximal serum levels of 116.7 ± 70.4 ng/ml were observed at 2.4 hours. Approximately 33% of the total dose is absorbed following oromucosal application. Following oral administration of amlexanox tablets 12.5mg in the fasting state, maximum serum levels of amlexanox were achieved in approximately 1.16 hours. The mean C_{max} was 490ng/ml. Both maximum and minimum serum concentrations under the plasma concentration curve (AUC) were generally dose dependant

Distribution
Radiolabelled tissue distribution studies in rats show that amlexanox is widely distributed in the tissues.

Metabolism
Metabolites formed by the hydroxylation and oxidation of the isopropyl moiety were found with the hydroxylated metabolite (M-1) being the major component. No evidence of hepatic microsomal enzyme induction was found in rats given daily doses of amlexanox orally for 7 days at up to 100 mg amlexanox/kg/day.

Excretion
Faeces are the main route of amlexanox excretion largely as unchanged active substance. Approximately 17% of the dose is eliminated in the urine as unchanged amlexanox, a hydroxylated metabolite (M-1) and their conjugates.

With multiple applications of the oromucosal paste four times daily, steady state levels were reached within one week and no accumulation was observed with up to 4 weeks of usage.

There are no pharmacokinetic data available for amlexanox in elderly patients or in patients with renal or hepatic impairment.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential and toxicity to

reproduction. Repeat-dose toxicity studies showed hepatotoxicity but only at large multiples of the maximum clinical dose.

Amlexanox has tested positive for sensitisation potential in the guinea pig maximisation test but not in a guinea pig contact sensitisation study.

Local tolerance of Aphtheal 5% oromucosal paste at the site of administration (oral mucosa) has not been tested. However, topical application of a different formulation of 5% amlexanox to the hamster cheek pouch, at doses up to 200 mg/kg/day for seven days did not result in any signs of local intolerance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liquid paraffin
Gelatin
Pectin
Carmellose sodium
Glyceryl monostearate 40-55
Soft white paraffin
Benzyl alcohol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

3g or 5g in laminated plastic tube with high density polyethylene nozzle with polypropylene screw cap. Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
Unit 35/36 Grange Parade
Baldoyle Industrial Estate
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2010/054/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 June 2006
Date of last renewal: 18 July 2007

10 DATE OF REVISION OF THE TEXT

February 2019