Apremilast

Instructions for use

Table 1: Instructions for use (Apremilast)

Pre-treatment

- Physicians are encouraged to enrol their patients in a registry (if available)
- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/Skindex-29 or -17)
- Medical history and physical examination including:
    - Check for skin cancer
    - Check for evidence of active and chronic infection
    - Check for contraception and breastfeeding
    - Check for need for vaccines (see “vaccination”)
    - Check for hypersensitivity, metabolic, gastrointestinal and renal disorders/dysfunction and underweight
    - Check for depression, anxiety
    - Check for co-medication: CYP3A4 enzyme inducers
    - Laboratory parameters including pregnancy test (see **Table 2**)

During treatment

- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/ Skindex-29 or -17)
- Medical history and physical examination focusing on malignancies, infections, contraception, depression and anxiety
- Laboratory parameters only when indicated on medical history or physical examination
- Reliable Contraception

Post-treatment

- For information regarding the ongoing need for contraception immediately following treatment cessation, please see chapter "wish for child / pregnancy"

[1] due to personal-financial conflict of interest 4 abstentions

Recommendations for lab controls

Table 2: Recommended laboratory controls (Apremilast)

Parameter	Pre-treatment	Only when indicated on medical history or physical examination
Blood count	x	(x)
ALT, AST	x	(x)
Serum creatinine/eGFR	x	(x)
Pregnancy test (urine or blood)	x	(x)
Hepatitis B and C	Optional	(x)
HIV	Optional	(x)
Not all tests may be necessary for all patients. Medical history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risks and exposure.		

The recommendations are based on clinical experience. No evidence is available.

Adverse drug reactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Diarrhoea and nausea

"The most commonly reported adverse reactions in Phase III clinical studies have been gastrointestinal (GI) disorders including diarrhoea (15.7%) and nausea (13.9%). These GI adverse reactions were mostly mild to moderate in severity, with 0.3% of diarrhoea and 0.3% of nausea reported as being severe. These adverse reactions generally occurred within the first 2 weeks of treatment and usually resolved within 4 weeks." [1]

Body weight loss

"Patient weight was measured routinely in clinical studies. The mean observed weight loss in patients treated for up to 52 weeks with apremilast was 1.99 kg. A total of 14.3% of patients receiving apremilast had observed weight loss between 5-10% while 5.7% of the patients receiving apremilast had observed weight loss greater than 10%. None of these patients had overt clinical consequences resulting from weight loss. A total of 0.1% of patients treated with apremilast discontinued due to adverse reaction of weight decreased." [1] The weight of underweight patients should be monitored from start of treatment. In case of inexplicable and significant weight loss discontinuation of treatment should be considered.

Risk of infection

Phase II/III studies reported more upper respiratory infections with apremilast compared to placebo [2-4]. There are no reactivations of tuberculosis or opportunistic infections reported [2-5]. Screening for latent tuberculosis was not required before enrolment in the randomized clinical trials; however, a history of incompletely treated tuberculosis was an exclusion criterion [2-5].

Depression and suicidal behaviour

Some patients may experience psychiatric symptoms with apremilast, including depression and suicidal thoughts. Stop treatment if patients have new psychiatric symptoms or if existing symptoms worsen. (see chapter: "Depression" for further details.)

Special consideration during treatment

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Surgery:

There is no evidence to date that continuous treatment with apremilast will lead to perioperative complications. Patients who need minor surgical treatments including dental treatments and skin surgery, may continue apremilast treatment. In the case of major surgery, the decision of apremilast withdrawal should be taken case-by-case considering patient characteristics, the risk of infection, the risk of psoriasis worsening after counselling with the surgeon.

Important contraindications

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Absolute contraindications

- Pregnancy or breast-feeding
- Severe acute infections

Relative contraindications

- Galactose intolerance, lactase deficiency or glucose-galactose malabsorption
- Malignancies or lymphoproliferative disorders
- Severe impairment of renal function (eGFR less than < 30 mL/min)
- Major depression and suicidal ideation
- Anorexia

Drug interactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Co-administration of strong cytochrome P450 3A4 (CYP3A4) enzyme inducer including rifampicin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of apremilast. [6] Therefore, the use of strong CYP3A4 enzyme inducers including rifampicin, phenobarbital, carbamazepine, phenytoin with apremilast is not recommended. There was no clinically meaningful drug-drug interaction with ketoconazole, methotrexate and oral contraceptives [6].

Overdose/ measures in case of overdose

"In case of an overdose, it is recommended that the patient is monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment is instituted." [1]

References

1. European Medicines Agency. Otezla - Summary of product characteristics (Annex I). 08/07/2016 Otezla -EMEA/H/C/003746 -PSUSA/10338/201506. In. 2016.
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3. Papp K, Reich K, Leonardi CL *et al.* Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). *J Am Acad Dermatol* 2015; **73**: 37-49.
4. Paul C, Cather J, Gooderham M *et al.* Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). *The British journal of dermatology* 2015; **173**: 1387-99.
5. Papp KA, Kaufmann R, Thaci D, Hu C, Sutherland D, Rohane P. Efficacy and safety of apremilast in subjects with moderate to severe plaque psoriasis: results from a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison study. *Journal of the European Academy of Dermatology & Venereology* 2013; **27**: e376-83.
6. Liu Y, Zhou S, Wan Y, Wu A, Palmisano M. The impact of co-administration of ketoconazole and rifampicin on the pharmacokinetics of apremilast in healthy volunteers. *British journal of clinical pharmacology* 2014; **78**: 1050-7.