Forslag til nasjonal metodevurdering

Innsendte forslag til nasjonale metodevurderinger vil bli publisert i sin helhet. Dersom forslagsstiller mener det er nødvendig informasjon for utfylling av skjemaet som ikke kan offentliggjøres ta kontakt med sekretariatet før innsending.

Forslagsstiller er klar over at skjemaet vil bli publisert i sin helhet (kryss av): ☑

Kontaktinformasjon:

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Sted og dato:

Stockholm 13-Jan-2015

1. Tittel på bestillingen:

Proposal for evaluation of apremilast in psoriasis and psoriatic arthritis

2. Kort beskrivelse av metoden som foreslås vurdert:

Apremilast is an oral small-molecule inhibitor of phosphodiesterase-4 (PDE4) that works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. PDE4 is a cyclic (cAMP) specific PDE and the dominant PDE in inflammatory cells Apremilast is indicated for treatment of active psoriatic arthritis (PsA) and moderate to severe chronic plaque psoriasis (PsO) in adult patients. Details for the two different indications are presented below:

- ***Psoriasis***
  - Otezla is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA)
- ***Psoriatic Arthritis***
  - Otezla, alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy

The recommended dose of Otezla is 30 mg twice daily taken orally, morning and evening, approximately 12 hours apart, with no food restrictions.

Apremilast has been evaluated in two large phase III programmes, ESTEEM 1 and 2 for PsO and PALACE 1, 2, and 3 for PsA. In total, over 2700 patients have been included in these programmes.

- **ESTEEM 1 and 2**
  - Primary endpoint (PASI-75) met in both Phase III studies
  - Multiple secondary endpoints confirm the efficacy of apremilast on several manifestations of psoriasis
  - Improved signs and symptoms of psoriasis (including nail and scalp psoriasis)
  - Improved quality of life (DLQI)
  - Long term efficacy shows maintenance of response
  - Apremilast was well tolerated with an acceptable safety profile
  - Long term safety identifies no new signals
  - No increased risk for infections, MACE, malignancy, TB
- **PALACE 1, 2, and 3**
  - Primary endpoint (ACR20) met in all Phase III studies.
  - Multiple secondary endpoints confirm the efficacy of apremilast in PsA
  - Improved signs and symptoms of PsA (including enthesitis and dactylitis)
  - Improved physical function (HAQ)
  - Improved skin manifestations.
  - Long term efficacy shows maintenance of response, 104 week data available.
  - Apremilast was well tolerated with an acceptable safety profile.
  - Long term safety identifies no new signals
  - No increased risk for infections, MACE, malignancy, TB

3. **Kort beskrivelse av dagens tilbud** (Hvilken metode(r) brukes nå? Status for metoden (gir kurativ behandling, forlenget levetid etc.) Vil metoden som foreslås vurdert erstatte eller komme i tillegg til dagens tilbud?)

The majority of the patients with moderate to severe plaque psoriasis and/or active psoriatic arthritis who have failed or are intolerant to previous treatment with conventional systemic treatments such as methotrexate, leflunomide, sulfazalasine (PsA) or methotrexate, acitretin, cyclosporin (PsO) are considered for biologic systemic treatment such as adalimumab, etanercept, golimumab, certolizumab, or ustekinumab.

4. **Hva gjelder forslaget?**	**Ja**	**Nei**
En helt ny metode?	☑	☐
Et nytt bruksområde, eller en ny indikasjon for en etablert metode?	☐	☑
En sammenligning mellom flere metoder?	☐	☑
Er metoden tatt i bruk?	☐	☑
Hvis ja – metode tatt i bruk i klinisk praksis?	☐	☑
Hvis ja – metode tatt i bruk innen forskning/utprøving?	☐	☑

"Klikk her og beskriv. Inkluder også utfyllende opplysninger om eventuell bruk av metoden"

5. **Hva omfatter metoden** (flere kryss mulig)**?**

Legemiddel	☑
Medisinsk utstyr/teknologi	☐
Prosedyre	☐
Screening	☐
Høyspesialiserte tjenester/nasjonale tilbud	☐
Organisatorisk oppsett av helsetjenesten	☐
Annet (beskriv)	☐

"Klikk her og beskriv. Inkluder eventuelt hvem som er ansvarlig for utvikling av metoden"

6. **Metodens bruksområde:**

Forebygging	☐
Utredning og diagnostikk	☐
Behandling	☑
Rehabilitering	☐

Spesialisthelsetjenesten	☑
Primærhelsetjenesten	☐

Apremilast is a new oral pharmaceutical treatment that will be prescribed primarily by dermatologists and rheumatologists.

7. **Involverer metoden bruk av stråling** (ioniserende/ikke-ioniserende)**?** ☐

(Kort beskrivelse av type strålekilde, utstyr og stråleeksponering.)

"Klikk her og beskriv"

8. **Hvilke fagområde(r) gjelder metoden, og hvilke pasienter berøres?** (Får metoden evt. også konsekvenser for andre grupper (som personell, pårørende?)

Dermatology and rheumatology.

The treatment is indicated for patients with moderate to severe plaque psoriasis and/or active psoriatic arthritis. We anticipate that apremilast will be used prior to biologics after failure or contraindication to conventional systemic treatments.

9. **Hvilke aspekter er relevante for vurderingen?** (flere kryss mulig)

Klinisk effekt	☑
Sikkerhet/bivirkninger	☑
Kostnader/ressursbruk	☑
Kostnadseffektivitet	☑
Organisatoriske konsekvenser	☐
Etiske	☐
Juridiske	☐

10. **Foreslå hva som bør være hovedproblemstilling(er) for metodevurderingen, samt eventuelle underproblemstillinger** (i samsvar med pkt. 8):

We propose that apremilast should be evaluated for use in clinical practice in accordance with the approved label in comparison with current standard of care for patients with moderate to severe plaque psoriasis and active psoriatic arthritis.

11. Gi en kort begrunnelse for hvorfor det er viktig at metodevurderingen som foreslås bør gjennomføres:

There is a need for a new treatment option for patients with moderate to severe PsO and PsA that:

- **is orally administered**
- **is affordable and can delay or eliminate need for treatment with biologics for some patients**
- **has a good efficacy profile (treating skin manifestations of moderate to severe plaque psoriasis and joint manifestations in patients with PsA), enabling long-term control of the disease and improvements to patients' QoL**
- **shows effect on a broad spectrum of hard to treat manifestations that PsO and PsA patients suffer from, such as nail psoriasis, scalp psoriasis, palmoplantar psoriasis, enthesitis and dactylitis**
- **has minimal side-effects and compared with conventional systemic therapies and biologic therapies, with no drug-drug interactions, long-term organ toxicities, or safety monitoring required**
- **no specified requirements for screening and monitoring of treatment**
- **is continuously effective at its standard dose and does not require dose escalation**

As a result of these factors, there is a need to provide an alternative treatment options that has a favourable risk-benefit profile, convenient administration form, and reduced health-care resources for treatment. Such treatment option would subsequently improve patient outcomes, provide a new treatment for patients for whom current therapy is inadequate, and allow for a simple management of patients.

Expanding the treatment options for PsA and PsO is beneficial for both patients and society as these diseases are chronic, severe and debilitating if not adequately treated.

12. Kommenter metoden som forslås vurdert mht. følgende punkter:

Alvorlighetsgraden på tilstanden metoden er ment for

Moderate to severe disease

Forventet effekt

Good;

- **Psoriasis**
  - About 30% of patients respond to treatment at week 16 with increasing response rates over time measured as PASI-75 response
  - Patient responding to treatment have continued effect over time (current data cut 52 weeks)
  - Apremilast has good effect on hard to treat manifestation such as nail and scalp
  - Clinical meaningful improvements in QoL can be seen compared to placebo
- **Psoriatic arthritis**
  - About 40% of patients respond to treatment at week 16 with increasing response rates over time measured as ACR 20 response
  - Patient responding to treatment have continued effect over time and 65% reach ACR 20 response (current data cut 104 weeks)
  - Apremilast has good effect on hard to treat manifestation such as enthesitis and dactylitis
  - Clinical meaningful improvements in physical function and QoL can be seen compared to placebo

Sikkerhet (beskriv kort opplysninger om kjente risikoforhold, sikkerhetsaspekter og bivirkninger)

The tolerability profile of apremilast has been shown to be favourable with no safety warnings:

- **Short term safety characterised by mild/moderate GI events primarily nausea/diarrhoea generally early onset and resolving within 1 month. GI events rarely serious or lead to discontinuation**
- **No differences from placebo in serious adverse events such as cardiovascular events, serious infections, and malignancies**
- **No contraindications with common co-medications such as NSAIDs or methotrexate**
- **No relevant safety signals for opportunistic infection, cancer, demyelination, or lupus-like syndromes have been attributed to apremilast to date.**

Totalt antall pasienter i Norge metoden er aktuell for

Number of patients on apremilast in Norway in 2017 (two year after market introduction) is expected to be about 200-300.

Konsekvenser for ressursbruk i helsetjenesten

Same or less compared to current standard of care

Behov for revisjon av eksisterende nasjonale faglige retningslinjer, evt. utarbeidelse av nye

To be assessed by local expertise

13. Oppgi referanser til dokumentasjon om metodens effekt og sikkerhet (eks. tidligere metodevurderinger). (Inntil 10 sentrale referanser oppgis. Ikke send vedlegg på dette trinnet i prosessen.)

Gladman D et al 2013. Apremilast, an oral phosphodiesterase 4 inhibitor, is associated with long-term (52-week) improvements in enthesitis and dactylitis in patients with psoriatic arthritis: pooled results from three phase 3 randomised, controlled trials. Poster presented at ACR/ARHP Annual Meeting, October 26-30, 2013, San Diego, CA (abstract #816)

Gottlieb AB et al 2013. Efficacy, Tolerability, and Pharmacodynamics of Apremilast in Recalcitrant Plaque Psoriasis: A Phase II Open-Label Study. J Drugs Dermatol. 2013;12(8):888-897.

Kavanaugh A et al 2014a. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. Ann Rheum Dis, 2014, 0:1-7.

Kavanaugh A et al 2014b. Apremilast, an oral phosphodiesterase 4 inhibitor, is associated with long-term (104-week) improvements in patients with psoriatic arthritis: Results from a phase 3, randomised, controlled trial. Poster presented at ACR/ARHP Annual Meeting, November 15-19, 2014, Boston, MA (abstract#1590)

Mease PJ et al 2013a. Laboratory abnormalities in patients with psoriatic arthritis receiving apremilast, an oral phosphodiesterase 4 inhibitor: pooled safety analysis of three phase 3, randomised, controlled trials. Poster presented at ACR/ARHP Annual Meeting, October 26-30, 2013, San Diego, CA (abstract #348)

Mease PJ et al 2013b. Long-Term Safety and Tolerability Of Apremilast, An Oral Phosphodiesterase 4 Inhibitor, In Patients With Psoriatic Arthritis: Pooled Safety Analysis Of Three Phase 3, Randomised, Controlled Trials. Poster presented at ACR/ARHP Annual Meeting, October 26-30, 2013, San Diego, CA (oral abstract presentation#310).

Papp K et al 2012. Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial; Lancet 2012; 380: 738–46

Papp K et al 2014a. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate to severe psoriasis: Results from the randomised treatment withdrawal phase of a phase 3, randomised, controlled trial (ESTEEM 1) Poster presented at the 72th Annual meeting of the American Academy of Dermatology, March 21-25 2014 Denver, CO (8359)

Paul C et al 2014. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate to severe psoriasis: 16-week results of a phase 3, randomised, controlled trial (ESTEEM 2). Poster presented at the 72th Annual meeting of the American Academy of Dermatology, March 21-25 2014 Denver, CO (8412)

Reich K et al 2014a. Long-term Safety and Tolerability of Apremilast in Patients With Psoriasis: Pooled Safety Analysis of Two Phase 3, Randomised, Controlled Trials (ESTEEM 1 and 2). Presented at the 23rd Congress of the European Academy of Dermatology and Venerology: October 8-12 2014; Amsterdam, the Netherlands

Schafer PH et al 2010. Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psorias. British Journal of Pharmacology (2010), 159, 842–855

Schafer PH et al 2014. Apremilast is a selective PDE4 inhibitor with regulatory effects on innate immunity. Cellular Signalling 26 (2014) 2016–2029