Brodalumab

Instructions for use

Table 1: Instructions for use (Brodalumab)

Pre-treatment

- Physicians are encouraged to enrol their patients in a registry (if available)
- Objective assessment of disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/Skindex-29 or -17)
- Medical history and physical examination including prior exposure to treatments, malignancies, infections, inflammatory bowel disease, depression and/or suicidal ideation or behaviour
- Recommended measures include:
    - Check for skin cancer
    - Check for lymphadenopathy
    - Laboratory parameters (see **Table 2**)
    - Exclusion of tuberculosis (see chapter: “tuberculosis”)
    - Check for evidence of active infection
    - Check need for vaccines
- Reliable contraception

During treatment

- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI, Skindex-29 or 17)
- Laboratory controls (see **Table 2**)
- Medical history and physical examination focusing on infections (in particular upper respiratory tract infections, candida, tuberculosis), contraception, symptoms of depression and/or suicidal behaviour and signs or symptoms of inflammatory bowel disease

Post-treatment

- After discontinuation of brodalumab, patients should be followed up with medical history and physical examination
- For information regarding the ongoing need for contraception immediately following biologic 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 (Brodalumab)

Parameter	Pre-treatment	After 3-6 months
Full blood count	X	X
Liver enzymes	X	X
Serum creatinine	X	
Urine status	X	
Pregnancy test (urine or blood)	X	
CRP	X	
HBV/HCV	X	
HIV	X	
Interferon gamma release assay (TB exclusion)	x	
Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risk, 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:

Current evidence suggests a similar safety profile for brodalumab compared to other IL-17 antagonists ixekizumab and secukinumab. Serious infections, candidiasis, and neutropenia are considered adverse events of interest.

Common adverse events (occurring in ≥1/100 to <1/10 of patients) include influenza, tinea infections (including tinea pedis, tinea versicolor, tinea cruris), neutropenia, headache, orophageal pain, diarrhoea, nausea, arthralgia, myalgia, fatigue and injection site reactions. A 120 week follow-up of a phase III trial (AMAGINE 2) with 1790 patients receiving brodalumab or ustekinumab or placebo with subsequently brodalumab, showed a comparable safety profile as the first year of the study. Among the most frequent treatment emergent adverse events in all brodalumab treatment groups throughout the duration of the study were arthralgia, headache, diarrhoea, oropharyngeal pain, and Candida species infections. In this study 168 patients received brodalumab 210 Q2W during the entire 120 week period and in whom showed 319.7 AEs per 100 PY, and 8.8 SAEs per 100 PY [1]. Five year safety data are available from an open label extension of a Phase II trial with 181 patients and showed one or more SAEs in 29 (16%) patients. The only SAE reported by more than one patient was myocardial infarction (3 patients; 1,7%)[2].

Neutropenia

The exposure adjusted event rates of neutropenia per 100 patient-years of exposure to brodalumab 210mg Q2W through week 52 were 0.3 in the AMAGINE-2 study and 0.3 in the AMAGINE-3 study.The cases of neutropenia were not associated with serious infections, and most cases were mild (absolute neutrophil count, >1000 per cubic millimeter), transient and reversible. No cases of thrombocytopenia were reported. [1,3]

Suicidal ideation and behaviour

During the clinical development program for psoriasis, four events of suicide (one of which was later adjudicated as indeterminate) and ten attempts of suicide/suicidal behaviour were reported in phase II and III trials amongst 4464 patients with a total treatment duration of 9161.8 patient years of brodalumab exposure. [4] The follow-up time-adjusted incidence rates of SIB events were comparable between the brodalumab and ustekinumab groups throughout the 52-week controlled phases (0.20 vs 0.60 per 100 patient-years). [3]

The majority of patients with suicidal behaviour had a history of depression and/or suicidal ideation or behaviour and a causal association between treatment with brodalumab and increased risk of suicidal ideation and behaviour has not been established. [4-6]

On the other hand, of patients treated 12 weeks with brodalumab 210 mg 67% showed improvement of symptoms of depression and anxiety while approximately 20% showed a worsening of these symptoms. [4] The risk and benefit of treatment with brodalumab should be carefully weighed for

patients with a history of depression and/or suicidal ideation or behaviour, or for patients who develop such symptoms. During treatment, patients should be monitored for the emergence or worsening of depression, suicidal ideation, anxiety, or other mood changes. If a patient suffers from new or worsening symptoms of depression and/or suicidal ideation or behaviour is identified, it is recommended to discontinue treatment with brodalumab.

Inflammatory Bowel Disease

Patients with a known history of Crohn's disease were excluded from phase III clinical trials for psoriasis. One case of new onset Crohn's disease was reported in a patient who received various doses of brodalumab throughout the study. [3,7] A phase II trial of 130 patients with Crohn's disease randomized to brodalumab (210 mg, 350mg or 700 mg) or placebo was terminated early due to a disproportionate number of cases of worsening disease activity and no evidence of meaningful efficacy. [8]

Candidiasis

Related to the mechanism of action of brodalumab higher rates of fungal infections, primarily non-serious skin and mucosal candida infections are observed. Early treatment of candida infections, either with topical or systemic treatment (see Table 3) is recommended. Cases are usually described as mild-to-moderate, respond to standard treatment and do not require brodalumab treatment discontinuation. Note that clinically significant, severe infections are always a contraindication for all biologics.

Table 3: Fluconazole treatment recommendations [9-11]

Candidiasis	**Fluconazole dose (mg)**	**Duration**
Oropharyngeal	100–200 daily	7–14 days
Oesophageal		
- Acute	200–400 daily	14–21 days
- Recurrent	100–200	Three times weekly
- **Balanoposthitis**	200	14 days
Vulvovaginal		
- Acute	150	Single dose
- Severe acute	150	Every 72 hours for a total of 2–3 doses
- Recurring	150	Induction therapy by a topical agent or oral fluconazole, thereafter weekly for 6 months

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 data on the management of surgery in patients treated with brodalumab. The decision to discontinue of brodalumab prior to surgery must be based on individual factors, such as type and risk of surgical procedure, patient characteristics, severity of psoriasis in case of treatment discontinuation etc. Counselling with the surgeon is advised.

Inflammatory Bowel Disease

There is limited data in patients with IBD. Patients with a known history of Crohn's disease were excluded from phase III clinical trials. One case of Crohn's disease was reported in a patient who received various doses of brodalumab throughout the study. Caution is advised in prescribing brodalumab in patients with a history of IBD. [3,7]

Important contraindications

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

Absolute contraindications:

- Clinically important active infections

Relative contraindications:

- Depression and history of suicidal behaviour
- Pregnancy or breastfeeding
- Inflammatory bowel disease

Drug interactions

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

No drug interactions expected. Combination therapy with other immunosuppressant agents has not been studied.

Overdose/ measures in case of overdose

No cases of overdose have been reported. Doses of up to 700 mg have been administered in clinical studies. In case of overdose, the patient should be monitored and appropriate symptomatic treatment should be instituted immediately.

References

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