Conitec

Recomendation report

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Ixekizumab for the treatment of adult patients with moderate to severe psoriasis with treatment failure, contraindication or intolerance to adalimumab

Brasília – DF
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Technology: Ixekizumab.

Indication: Adult patients with moderate to severe plaque psoriasis with treatment failure, contraindication or intolerance to adalimumab, and who are therefore candidates for the second stage of treatment.

Applicant: Eli Lilly do Brasil LTDA.

Background: Psoriasis is a chronic systemic inflammatory disease with predominantly skin, nail and joint manifestations, that typically follows a relapsing and remitting course. With a similar distribution between the sexes, it is more frequent between the third and fourth decades of life, and its prevalence in Brazil isranges from 1.31% toto 2.5%. In the Brazilian Public Health System (SUS), patients have the guarantee should be provided withof access to the treatments recommended in the therapeutic guidelines, starting with topical medications and progressing to other options such as phototherapy, oral and injectable medications according to severity. The recommended systemic drugs as first-line treatment are methotrexate, acitretin and ciclosporin. In case they fail, there are four biological therapies available: two anti-TNF drugs (adalimumab and etanercept), and two anti-interleukin drugs (anti-IL12/23 [ustekinumab], and anti-IL17 [secukinumab]).

Question: Is ixekizumab effective, safe and cost-effective compared with the biological systemic therapies approved by CONITEC (ustekinumab and secukinumab) for the second biological treatment of adult patients with moderate to severe plaque psoriasis?

Scientific evidence: A Cochrane systematic review with a network meta-analysis aimed to compare and provide a ranking of conventional and biological systemic agents, according to their efficacy and safety, for patients with moderate to severe psoriasis according to their efficacy and safety. Through extensive searches, the review included 140 studies evaluating 19 treatments, with a total of 51,749 randomized participants with mean age of 45 years. All results (except for two studies) were limited to the induction phase (8 to 24 weeks after randomisation). Problems with blinding of patients and personnel (performance) and assessors were the most frequently identified risk of bias. Among other risks, most studies declared pharmaceutical-company funding, and 22 studies did not report the source of funding. In relation to the outcome of PASI 90, the result of the network meta-analysis indicated that two anti-IL17 drugs (ixekizumab and secukinumab) were significantly more effective than ustekinumab and adalimumab. For the outcome of PASI 75, the class of anti-IL17 drugs was also associated with a higher probability of reaching it compared to other classes. For the outcome of serious adverse events (SAE), infliximab, ixekizumab and secukinumab had a higher risk of SAE compared with methotrexate. Statistically significant associations were found demonstrating that, in general, anti-IL17 drugs had a higher risk of adverse events compared with anti-IL23 and anti-IL12/23 drugs. The certainty of the evidence of effectiveness of ixekizumab was assessed as moderate (downgraded for inconsistency), as well as for the outcome of SAE (downgraded for imprecision).

Economic evaluation: The applicant submitted a 'cost per response analysis' that suffered from a lack of methodological rigour of the full economic evaluations. Therefore, it was developed a cost-effectiveness model was developed to evaluate all the options available in SUS, and which is being analysed by CONITEC for the treatment of moderate to severe psoriasis. Based on a well-known model designed by researchers at York University, a decision tree model (induction phase) combined with a Markov model (maintenance phase) was used to assess costs and consequences in terms of quality adjusted life years (QALY) for the following treatment strategies: ixekizumab; secukinumab; ustekinumab; risankizumab; adalimumab and infliximab. According to the results obtained, using the efficiency-frontier approach, infliximab (simple dominance) and secukinumab (extended dominance) were found to be dominated (less effective and more costly) by adalimumab, ustekinumab and ixekizumab. Treatment with risankizumab was found to

have an effectiveness similar to that of ixekizumab, but at a higher cost. A threshold analysis using the efficiency-frontier approach showed that it would be necessary to reduce the price of secukinumab, ixekizumab and risankizumab by at least 10.74%, 9.08% and 55.09%, respectively, in order to be considered cost-effective. The acceptability curve showed that as the willingness to pay increased, adalimumab, followed by ustekinumab and ixekizumab, had a higher probability of being the most cost-effective treatment.

Budget impact analysis: CONITEC's critical analysis of the budget impact analysis submitted by the applicant considered it adequate and consistent with previous discussions. Nevertheless, some data were revised and updated resulting in new impact estimates. The applicant's original analysis indicated savings of BRL 14,322,953.00, but based on the updated cost data and failure rate for adalimumab, the incremental impact was then estimated to be BRL 4,052,249.89 in five years.

International recommendations: The National Institute for Health and Care Excellence - NICE (England) and the Canadian Agency for Drugs and Technologies in Health – CADTH (Canada) recommend ixekizumab for plaque psoriasis.

Technology horizon scanning: Seven potential drugs were identified for adult patients with moderate to severe psoriasis, after failure in the first stage of the second-line treatment: apremilast, bimekizumab, BMS-986165, brodalumab, guselkumab, mirikizumab, and piclidenoson.

Considerations: According to the comparative effectiveness estimates from the network meta-analysis, ixekizumab and secukinumab were significantly more effective than ustekinumab and adalimumab. Regarding safety, statistically significant associations were found demonstrating that, in general, anti-IL17 drugs had a higher risk of adverse events compared with anti-IL23 and anti-IL12/23 drugs. The certainty of the evidence of effectiveness was assessed as moderate for the outcomes of effectiveness and safety for ixekizumab. In the acceptability curve according to the willingness to pay, adalimumab, followed by ustekinumab and ixekizumab, had a higher probability of being the most cost-effective treatment. Through a reasonable price reduction, ixekizumab would be likely to have a cost-effectiveness profile similar to the most effective treatments available in SUS. In the updated budget impact model, the incremental impact of incorporating ixekizumab, in the scope of SUS, was estimated to be BRL 4,052,249.89 in five years.

Initial Recommendation: CONITEC, at its 85th Ordinary Meeting, on February 4th, 2020, decided not to recommend the incorporation of ixekizumab in the scope of SUS, for the treatment of adult patients with moderate to severe psoriasis with treatment failure, contraindication or intolerance to adalimumab. It was considered that, despite ixekizumab is associated with incremental benefits in terms of effectiveness, its efficiency (cost-effectiveness) is lower than the treatments available in SUS at the price proposed by the manufacturer. The subject matter was made available in a public consultation.

Public consultation: There were 142 technical-scientific contributions, and 280 experience or opinion contributions, and the majority disagreed with CONITEC's preliminary recommendation. The main points raised were the need for more therapeutic alternatives or mechanisms of action, and superiority among the treatments available. Moreover, there were new price proposals were submitted, and limitations of the previous analysis were addressed. The manufacturer indicated a reduction of 2.7% in the price initially proposed. In the updated model, ixekizumab was shown to be more cost-effective than secukinumab, but less cost-effective than risankizumab, which was also being under consideration. In the updated budget impact model, savings were estimated to be up to BRL 37,955,681.00 in five years, considering incorporation of ixekizumab in the same line and same indication of secukinumab. After analysing the contributions received in the Public Consultation, and taking into consideration the superiority of ixekizumab versus adalimumab and ustekinumab, limitations in the models used, professional and

personal experiences with the treatment, and the new price proposals, CONITEC's plenary session decided that there was no sufficient reason to change the preliminary recommendation against the incorporation of ixekizumab, based on the cost-effectiveness analysis, in the scope of SUS.

Final Recommendation: The CONITEC's members present at its 89th Ordinary Meeting, on August 6th, 2020, unanimously decided not to recommend the incorporation of ixekizumab in the scope of SUS, for the treatment of adult patients with moderate to severe psoriasis with treatment failure, contraindication or intolerance to adalimumab.

Decision: Not to incorporate ixekizumab for the treatment of adult patients with moderate to severe psoriasis with treatment failure, contraindication or intolerance to adalimumab, in the scope of SUS, according to Ordinance No. 27, published in the Official Gazette of the Federal Executive No. 160, Section 1, page 117, on August 20th, 2020.