REPUBLIC OF BULGARIA
NATIONAL COUNCIL ON PRICES AND
REIMBURSEMENT OF MEDICINAL PRODUCTS

HEALTH TECHNOLOGY ASSESSMENT

Rinvoq

15 mg prolonged – release tablet x 28

Upadacitinib

Therapeutic indication(s)	Indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). RINVOQ may be used as monotherapy or in combination with methotrexate.
Start/end date of procedure	12.02.2020 – 30.10.2020
Final decision	Inclusion in: - Annex № 1 of the Positive Drug List (PDL) for home treatment of diseases paid by the National Health Insurance Fund (NHIF); - Annex 2 of the PDL for purchase by medical establishments with state and/or municipal participation and under Art. 5 of the Medical Establishments Act.

Summary of the report on the clinical and pharmacoeconomic assessment of the health technology of the medicinal product Rinvoq

Health problem

Rheumatoid arthritis (RA) is a chronic and progressive systemic immune-mediated inflammatory disease of the connective tissue, involving primarily the peripheral joints. Disease progresses as symmetrical erosive polyarthritis and leads to high morbidity and mortality. The development of RA is determined by the interaction of genetic, immunological and environmental factors.

Determination of disease activity is one of the main components in choosing a therapeutic approach to prevent the disability of the patients. The assessment of the quality of life is another decisive factor for a need to change the treatment plan. In order to reduce disease activity, improve clinical status, prevent complications, and improve quality of life, in recent years the use of targeted specific disease-modifying antirheumatic drugs (DMARD) has been introduced.

Upadacitinib (Rinvoq) belongs to that group, which is a reversible, selective JAK-1 inhibitor. Inhibition of JAK-1 results in disruption of the IL-6 signaling pathway, which is involved in the inflammatory process and pathogenesis of RA. It is indicated for the treatment of moderate to severe RA in adult patients with an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs. Rinvoq can be used as monotherapy or in combination with methotrexate.

With timely treatment of patients with RA, in line with the treat-to-target strategy, there is almost no loss of productivity and a significant improvement in the quality of life (QoL).

Epidemiological data

The incidence of RA in the elderly population varies widely (0.3% - 1.4%) in different regions of the world, with women suffering from 2 to 4 times more often than men. It mainly affects people between the ages of 40 and 70, with its frequency increasing with age. For Bulgaria, the number of patients suffering from rheumatoid arthritis is about 35,000.

Life expectancy in men with RA is decreased by an average of about 4 years, and in women - by 10 years. Mortality is higher in patients with early loss of motor function, in those with acute and visceral manifestations, as well as in the presence of concomitant diseases.

Efficacy data

Efficacy and safety data are based on six clinical trials, comparing the medicinal product to both placebo and active comparators.

SELECT-EARLY clinical study evaluated the efficacy and safety of upadacitinib monotherapy in patients not previously treated with methotrexate (MTX) with moderate to severe active rheumatoid arthritis (RA) versus MTX. In SELECT-EARLY, a significantly higher proportion of patients receiving upadacitinib 15 mg once daily or upadacitinib 30 mg once daily achieved remission (in all considered definitions) compared to MTX at week 12 and week 24. Higher remission rate (in all considered definitions) compared to MTX was established as early as week 4 and persisted until week 24.

SELECT-COMPARE clinical study evaluated the efficacy and safety of upadacitinib in patients with moderate to severe active RA, who had an inadequate response to MTX treatment compared to adalimumab and placebo. In SELECT-COMPARE, a significantly higher proportion of patients receiving upadacitinib 15 mg once daily + MTX or upadacitinib 30 mg once daily + MTX achieved remission (in all considered definitions) compared to adalimumab + MTX at week 12 and week 26. The proportion in patients achieving clinical remission DAS28-CRP < 2.6 was significantly higher with upadacitinib 15 mg once daily + MTX compared with adalimumab + MTX from week 8 and at all visits up to week 26 and week 48.

SELECT-NEXT clinical study evaluated the efficacy and safety of upadacitinib compared with placebo in patients with moderate to severe RA who were on background therapy with conventional synthetic disease-modifying antirheumatic drugs (csDMARD) and who had an inadequate response to csDMARD. In SELECT-NEXT, a significantly higher proportion of patients receiving upadacitinib 15 mg once daily + csDMARD or upadacitinib 30 mg once daily + csDMARD achieved clinical remission (DAS28-CRP < 2.6) at week 12 compared with placebo + csDMARD.

SELECT-MONOTHERAPY clinical study evaluated the efficacy and safety of upadacitinib monotherapy in patients with moderate to severe RA who have an inadequate response to MTX versus continued treatment with MTX. In SELECT-MONOTHERAPY, a significantly higher proportion of patients receiving upadacitinib 15 or 30 mg once daily achieved clinical remission (DAS28-CRP < 2.6) compared to MTX at week 14.

SELECT-BEYOND clinical study evaluated the efficacy and safety of upadacitinib versus placebo in patients with moderate to severe RA who were on background therapy with conventional synthetic disease-modifying antirheumatic drugs (csDMARD) and who had an inadequate response to biological disease-modifying antirheumatic drugs (bDMARD). In SELECT-BEYOND, a significantly higher proportion of patients receiving upadacitinib 15 mg once daily + csDMARD or 30 mg once daily + csDMARD achieved clinical remission (in all considered definitions) at week 12 compared with placebo + csDMARD.

SELECT-SUNRISE clinical study evaluated the efficacy and safety of upadacitinib versus placebo in Japanese patients with moderate to severe RA who were on background therapy with conventional synthetic disease-modifying antirheumatic drugs (csDMARD) and had an inadequate response to conventional disease-modifying drugs (csDMARD). In SELECT-SUNRISE at week 12, a significantly higher proportion of patients treated with upadacitinib at all doses achieved low disease activity (LDA) compared to placebo patients (53%, 69% or 72% versus 18%, respectively, $p < 0.01$).

Achieving complete clinical and biological remission is of key importance in rheumatoid arthritis in order to prevent disability, reduce mortality from complications and improve the quality of life of patients. The results obtained from SELECT clinical trials demonstrate the efficacy of upadacitinib 15 mg/day and the achievement of early clinical remission compared to the selected alternative treatments, which is a significant advantage of this target-specific disease-modifying drug.

Safety data

The safety profile of upadacitinib was analyzed based on comparisons with adalimumab, MTX and placebo. From these comparisons it has become clear that upadacitinib 15 mg once daily has an acceptable safety profile in adult patients with moderate to severe active RA.

In the phase III studies, the short-term serious adverse events rate and adverse events rate leading to discontinuation of treatment was low but higher in upadacitinib 15 mg once daily versus placebo.

The long-term rate was similar in patients receiving upadacitinib 15 mg once daily compared to adalimumab 40 mg. Deaths were reported in all groups. The rate of serious infections was higher with upadacitinib 15 mg once daily compared to placebo or MTX, but similar to adalimumab 40 mg.

The long-term major adverse cardiac events rate (MACE) was similar with upadacitinib 15 mg versus adalimumab 40 mg or MTX.

In SELECT-EARLY, the long-term serious adverse events rate with upadacitinib 15 mg once daily was comparable to that seen with MTX.
In SELECT-COMPARE, the serious adverse events rate in patients receiving upadacitinib 15 mg once daily was lower than in patients receiving adalimumab.

Serious adverse events were observed in 2% of patients on upadacitinib 15 mg once daily in the SELECT-SUNRISE clinical trial. No MACE, cases of pulmonary embolism, deep vein thrombosis and death have been reported.

Data on comparators

The following alternatives are indicated for the treatment of rheumatoid arthritis in adults with inadequate response or intolerance to one or more disease-modifying antirheumatic drugs:

- csDMARD: methotrexate, sulfasalazine
- bDMARD: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab
- tsDMARD (JAK inhibitors): baricitinib, tofacitinib

Pharmacoeconomic indicators

Published health technology assessments of governmental institutions intended for the health care systems of other countries

Positive recommendations for the medicinal product Rinvoq have been made publicly available by NICE, UK and HAS, France.

Applied analysis

A cost-benefit analysis has been applied, health benefits for patients were measured as life-year gained (LYG) and quality-adjusted life years (QALY). The perspective of the analysis is of the paying institution – the NHIF, the model has a set reimbursement level of 75%. The selected time horizon is lifelong (45 years). Costs and results are discounted with a discount rate of 3.5%. Patients with RA are divided into two subpopulations depending on the therapy:

- Patients with moderate to severe active RA, treated with csDMARD (conventional disease-modifying antirheumatic drugs)
- Patients with moderate to severe active RA, treated with bDMARD (biologically modifying antirheumatic drugs)

A model based on discrete-choice simulation (DES) was used to evaluate the value efficacy of upadacitinib. A cost-benefit analysis in the csDMARD and bDMARD populations with moderate to severe RA (rheumatoid arthritis) found that in both populations upadacitinib dominated the JAK inhibitor baricitinib, demonstrating lower treatment costs and higher values of health benefits (QALYs). Compared to other alternatives, the incremental cost-benefit ratio has positioned upadacitinib and other therapeutic alternatives outside the range of acceptable value below three times GDP per capita. Upadacitinib therapy has a higher treatment cost, but also higher values of acquired health benefits, except when compared to certolizumab pegol in the csDMARD population, where upadacitinib is a dominated therapy.

Probability sensitivity analysis (PSA) and one way sensitivity analysis (DSA) were applied. The Monte Carlo simulations and the evaluation of the cost-effectiveness acceptability curve show that the cost of medicinal products has the greatest impact on the change in ICER.

Analysis of subgroups

Two adult patient populations with moderate to severe active rheumatoid arthritis with inadequate response or intolerance to one or more disease-modifying antirheumatic drugs are included - conventional (csDMARD) or biological (bDMARD).

Costs of the assessed health technology

The costs included in the model are the direct costs of drug therapy, as well as the costs associated with the application of the treatment standard. Also included are costs for disease monitoring, for serious ADR management, tailored to the frequency of their occurrence. Palliative care costs are also taken into account, considering the increasing cost of disease progression.

Budget impact analysis

The budget impact analysis has the perspective of the paying institution – the NHIF for a period of 5 years. The target population covers adult patients, diagnosed with moderate to severe active rheumatoid arthritis with inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARD). The number of patients on Rinvoq therapy is expected to be 100 in the first year and to reach 670 in the fifth year. A tornado sensitivity analysis shows that the cost of Rinvoq and the cost of treatment with the comparators have the greatest impact on the budget.

The budget impact analysis shows that the inclusion of the new technology in the PDL will lead to cost savings mainly due to the lower cost as compared to the direct comparator from the JAK inhibitor group, without taking into account risk sharing agreements and patient access schemes.

Conclusion

Rinvoq (upadacitinib) is a JAK inhibitor that demonstrates high efficacy in a number of clinical parameters and a favorable risk-benefit profile in patients with moderate to severe rheumatoid arthritis. Therapy is dominant over the direct comparator from the group of JAK inhibitors. The inclusion of the new technology in the PDL leads to cost savings for the paying institution.