# CPAG Summary Report for Clinical Panel – 1713
# Anakinra for periodic fever and auto inflammatory diseases

| **1.0 The Benefits of the Proposition - Anakinra to treat cr-FMF compared to placebo** | | | |
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| *No* | *Metric* | *Grade of evidence* | *Summary from evidence review* |
| 1. | Survival | not measured | |
| 2. | Progression free survival | not measured | |
| 3. | Mobility | not measured | |
| 4. | Self-care | not measured | |
| 5. | Usual activities | not measured | |
| 6. | Pain | not measured | |
| 7. | Anxiety / Depression | not measured | |
| 8. | Replacement of more toxic treatment | not measured | |
| 9. | Dependency on care giver / supporting independence | not measured | |
| 10. | Safety / adverse events | Adverse events identified [B] | The outcome measure is defined as any side effect reported in patients receiving anakinra compared with patients receiving placebo (a dummy treatment).<br><br>The results of a study in which people are allocated to treatment at random (randomised control trial) with 25 patients: 12 treated with anakinra and 13 with placebo (Ben Zvi et al 2017) suggest that patients receiving anakinra experienced similar side effects (adverse events) compared to patients receiving placebo during a 4 month follow up period.<br><br>Overall the study was well conducted; however it included a small sample size and short follow up. Therefore these factors need to be taken into account when interpreting its results. This is the case for all aspects of this proposition. |
| 11. | Delivery of intervention | not measured | . |

| **1.1 Other health metrics determined by the evidence review -- Anakinra to treat cr-FMF compared to placebo** |
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| No | Metric | Grade of evidence | Summary from evidence review |
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| 1 | Total number of FMF attacks per month | Grade A | The outcome measure is defined as the total number of Familial Mediterranean Fever (FMF) attacks per month recorded in patients receiving anakinra compared with patients receiving placebo.<br><br>The results of a randomised control trial with 25 patients ( 12 treated with anakinra and 13 with placebo) with a follow up of 4 months suggest that patients receiving anakinra experience almost 50% fewer attacks compared to patients receiving placebo during a 4 month follow up period. The result is statistically significant, i.e. the probability that the result is due to chance is small. |
| 2 | Number of patients with <1 attack per month | Grade A | The outcome measure is defined as the number of patients receiving anakinra compared with patients receiving placebo, who experienced less than one attack per month.<br><br>The results of a randomised control trial suggest that 50% patients receiving anakinra experienced less than 1 attack per month compared to 0% patients receiving placebo during a 4 month follow up period. The result is statistically significant i.e. the probability that the result is due to chance is small. |
| 3 | Number of attacks per FMF site | Grade A | The outcome measure is defined as the number of site specific attacks in patients receiving anakinra compared with patients receiving placebo.<br><br>The results of a randomised control trial suggest that 50% of patients receiving anakinra experience between 25%-50% fewer site specific attacks per month compared to 0% patients receiving placebo during a 4 month follow up period. The result is statistically significant for all sites except skin, i.e. the probability that the result is due to chance is small. |
| 4 | Biomarkers values | Grade A | The outcome measure is defined as the difference in biomarker values in patients receiving anakinra compared with patients receiving placebo at the time of last measurement (the lower the value the better).<br><br>A randomised control trial suggested that indicators of severity of the condition (biomarker values) in patients receiving anakinra experience were lower (C-reactive protein was 20% lower and serum amyloid A (SAA) was 10% lower) compared to patients receiving placebo during a 4 month follow up period. The result is statistically significant for both biomarkers, i.e. the probability that the result is due to chance |

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| | | | is small. |
| 5 | Quality of Life (QOL) score | Grade A | The outcome measure is defined as the visual analogue score (VAS) in patients receiving anakinra compared with patients receiving placebo. This is a scale used to measure characteristics or attitudes.<br><br>A randomised control trial suggests that patients receiving anakinra experienced a 50% improvement in QOL compared to patients receiving placebo during a 4 month follow up period. The result is statistically significant, i.e. the probability that the result is due to chance is small. |

| **2.0 The Benefits of the Proposition - Anakinra to treat cr-FMF (no comparator)** | | | |
|---|---|---|---|
| *No* | *Metric* | *Grade of evidence* | *Summary from evidence review* |
| 1. | Survival | not measured | |
| 2. | Progression free survival | not measured | |
| 3. | Mobility | not measured | |
| 4. | Self-care | not measured | |
| 5. | Usual activities | not measured | |
| 6. | Pain | not measured | |
| 7. | Anxiety / Depression | not measured | |
| 8. | Replacement of more toxic treatment | not measured | |
| 9. | Dependency on care giver / supporting independence | not measured | |
| 10. | Safety | Advserse events identified [A] | The outcome measure is defined as any side effect reported in patients receiving anakinra.<br><br>A systematic review which included 64 patients treated with anakinra from 22 publications with a cumulative follow up of 885 months reported serious side-effects warranting the discontinuation of anakinra in five patients. This included four patients with injection site reactions and one patient who developed interstitial pneumonia (a lung condition) possibly related to anakinra use (Van der Hilst et al 2016).<br><br>The results suggest a small proportion of patients receiving anakinra experience severe side effects. |

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| | | | These results should be interpreted with caution as they are based on a systematic review of small case reports. It means that it did not randomise patients or compare the treatment with any other standard treatment. Therefore it does not reduce the risk of other factors influencing the results and it does not provide evidence that anakinra is any better or worse than other treatments for this outcome. |
| 11. | Delivery of intervention | not measured | . |

| **2.1 Other health metrics determined by the evidence review - Anakinra to treat cr-FMF** | | | |
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| No | Metric | Grade of evidence | Summary from evidence review |
| 1 | Response to treatment | Grade A | The outcome measure is defined as clinical response to anakinra in patients. Response is categorised as complete (not a single attack while on treatment), partial (decrease in attack frequency and inflammation) and no response.<br><br>A systematic review which included 64 patients treated with anakinra from 22 publications with a cumulative follow up of 885 months reported the following response to treatment (Van der Hilst et al 2016):<br>• Complete response (not a single attack while on treatment) during treatment was reported in 76.5% of patients.<br>• Partial response (decrease in attack frequency and inflammation) was reported in 18.8% patients.<br>• There was no clinical response to anakinra in 3 patients<br><br>The results suggest majority of patients receiving anakinra had complete or partial response.<br><br>These results should be interpreted with caution as they are based on a systematic review of small case reports. It means that it did not randomise patients or compare the treatment with any other standard treatment. Therefore it does not reduce the risk of other factors influencing the results and it does not provide evidence that anakinra is any better or worse than other treatments for this outcome. This is the same for the measurement of all health outcomes in this section. |
| 2 | AA amyloidosis | Grade A | The outcome measure is defined as clinical response to anakinra in patients with AA amyloidosis. AA amyloidosis is characterised by the abnormal deposition of fibres of insoluble protein in the extracellular space of various tissues and organs. This can lead to renal disease.<br><br>A systematic review was conducted of 22 publications which included patients with AA amyloidosis who were treated with anakinra (Van der Hilst et al 2016). Of the 19 patients who had AA amyloidosis, 4 had nephrotic syndrome (a condition that causes kidneys to leak large amounts of protein into the |

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| | | | urine). After anakinra was commenced in these patients, their levels of protein in urine (proteinuria) decreased. Eight patients had end-stage renal disease when anakinra was started. Three of these patients underwent kidney transplantation while on anakinra. No recurrence of amyloidosis was reported in these patients with a kidney transplant while receiving anakinra treatment.<br>The results suggest patients with AA amyloidosis may benefit from anakinra. |
| 3 | Reduction in other treatments | Grade A | The outcome measure is defined in the reduction of use in accompanying treatments (such as steroids) following initiation of treatment with anakinra in patients.<br><br>In a retrospective analysis which included 9 patients treated with anakinra and concomitant treatments (Rossi Semerano et al 2015), reduction in other treatment was reported in 6 out of 9 patients (66.7%).<br><br>The results suggest that anakinra could potentially help reduce use of accompanying treatments in two-thirds of patients receiving it. |

| **3.0 The Benefits of the Proposition - Anakinra to treat TRAPS** | | | |
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| *No* | *Metric* | *Grade of evidence* | *Summary from evidence review* |
| 1. | Survival | not measured | |
| 2. | Progression free survival | not measured | |
| 3. | Mobility | not measured | |
| 4. | Self-care | not measured | |
| 5. | Usual activities | not measured | |
| 6. | Pain | not measured | |
| 7. | Anxiety / Depression | not measured | |
| 8. | Replacement of more toxic treatment | not measured | |
| 9. | Dependency on care giver / supporting independence | not measured | |

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| 10. | Safety / adverse events | Advserse events identified [A] | The outcome measure is defined as any side effect reported in patients receiving anakinra.<br><br>In a prospective cohort study of five patients with poorly controlled TRAPS requiring high dose steroids during a mean follow up of 11.4 months, apart from variable skin reactions (pain, rash, itching) at the site of the injections, which were observed in all patients during the first weeks of treatment, no serious adverse events were observed (Gattorno M, et al 2008).<br><br>These results should be interpreted with caution as they are based on a small case series study. It means that it did not randomise patients or compare the treatment with any other standard treatment. Therefore it does not reduce the risk of other factors influencing the results and it does not provide evidence that anakinra is any better or worse than other treatments for this outcome. |
| 11. | Delivery of intervention | not measured | |

| **3.i Other health metrics determined by the evidence review - Anakinra to treat TRAPS** | | | |
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| No | Metric | Grade of evidence | Summary from evidence review |
| 1 | Response to treatment | Grade A | The outcome measure is defined as the clinical response to anakinra in patients.<br><br>In a prospective cohort study of five patients with poorly controlled TRAPS requiring high dose steroids, all 5 patients were reported to have a response to anakinra, with disappearance of the fever and other clinical manifestations of TRAPS during a mean follow up of 11.4 months (Gattorno M, et al 2008).<br><br>The results suggest all patients treated with anakinra respond to treatment leading to disappearance of clinical symptoms.<br><br>These results should be interpreted with caution as they are based on a small case series study. It means that it did not randomise patients or compare the treatment with any other standard treatment. Therefore it does not reduce the risk of other factors influencing the results and it does not provide evidence that anakinra is any better or worse than other treatments for this outcome. This is the same for all aspects of the evidence considered for the treatment of TRAPS. |
| 2 | Biomarker values | Grade A | The outcome measure is defined as the difference in biomarker values in patients receiving anakinra at the time of last measurement (with the nearer to normal levels the better).<br><br>In a prospective cohort study of five patients with poorly controlled TRAPS requiring high dose steroids, a decrease in levels of acute-phase reactants was observed, with |

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| | | | normalisation after 15 days of treatment. The results suggest biomarkers are normalised in patients treated with anakinra. |
| 3 | Reduction other treatments | Grade A | The outcome measure is defined in the reduction of use in concomitant treatments (such as steroids) following initiation of treatment with anakinra in patients.<br><br>In a prospective cohort study of five patients with poorly controlled TRAPS requiring high dose steroids, reduction in other treatment was achieved in 2 of the 4 patients receiving concomitant treatment during a mean follow up of 11.4 months. (Gattorno M, et al 2008). One patient with a chronic disease course was able to discontinue steroid treatment. In one patient who also had allergic asthma, the prednisone dosage was progressively tapered and maintained at a dosage of 5 mg/day in order to control his respiratory symptoms. |

| **4.0 The Benefits of the Proposition - Anakinra to treat HIDS / MKD** | | | |
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| *No* | *Metric* | *Grade of evidence* | *Summary from evidence review* |
| 1. | Survival | not measured | |
| 2. | Progression free survival | not measured | |
| 3. | Mobility | not measured | |
| 4. | Self-care | not measured | |
| 5. | Usual activities | not measured | |
| 6. | Pain | not measured | |
| 7. | Anxiety / Depression | not measured | |
| 8. | Replacement of more toxic treatment | not measured | |
| 9. | Dependency on care giver / supporting independence | not measured | |
| 10. | Safety Adverse events | Adverse events identified [B] | The outcome measure is defined as any side effect reported in patients receiving anakinra.<br><br>In a systematic review which included 21 patients, adverse events reported included pain at injection site, neutropenia, bacterial pneumonia, Herpes zoster infection.(Kostjukovits etc al 2015)<br><br>The results suggest there are some adverse events in patients receiving anakinra. However, the proportion of patients affected is not reported.<br><br>These results should be interpreted with caution as they are based on a systematic review of small case reports. It means that it did not randomise patients or compare the treatment with any other |

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| | | | standard treatment. Therefore it does not reduce the risk of other factors influencing the results and it does not provide evidence that anakinra is any better or worse than other treatments for this outcome. This is the same for all aspects of the evidence review for HIDS/MKD. |
| 11. | Delivery of intervention | not measured | . |

| **4.1 Other health metrics determined by the evidence review - Anakinra to treat HIDS / MKD** | | | |
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| No | Metric | Grade of evidence | Summary from evidence review |
| 1 | Response to treatment | Grade B | The outcome measure is defined as clinical response to anakinra in patients. Response is categorised as complete, partial and no response.<br><br>In a systematic review which included 21 patients, the following response to treatment with anakinra was reported (Kostjukovits et al 2015):<br>• Complete response was reported in 4 out of 21 patients (19%).<br>• Partial or positive response was reported in 15 of 21 patients (71%).<br>• No response was reported in 1 of 21 patients (5%).<br><br>The results suggest majority of patients receiving anakinra had complete or partial response. A small proportion of patients did not respond to treatment. |

| **5.0 The Benefits of the Proposition Use of anakinra to treat Schnitzler's syndrome** | | | |
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| *No* | *Metric* | *Grade of evidence* | *Summary from evidence review* |
| 1. | Survival | not measured | |
| 2. | Progression free survival | not measured | |
| 3. | Mobility | not measured | |
| 4. | Self-care | not measured | |
| 5. | Usual activities | not measured | |
| 6. | Pain | not measured | |
| 7. | Anxiety / Depression | not measured | |
| 8. | Replacement of more toxic treatment | not measured | |
| 9. | Dependency on care giver / supporting independence | not measured | |

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| 10. | Safety Adverse events | Adverse events identified [B] | The outcome measure is defined as the any side effect reported in patients receiving anakinra.<br><br>In a study reporting a retrospective analysis of 42 patients, the following results were reported:<br><br>• Six patients experienced severe infections, including one case of a severe sore throat and five cases of pneumonia.<br>• Injection site reactions were reported in five patients (17%)<br><br>The results suggest some patients treated with anakinra have experience adverse events.<br><br>These results should be interpreted with caution as they are based on a small retrospective case reports. It means that it did not randomise patients or compare the treatment with any other standard treatment. Therefore it does not reduce the risk of other factors influencing the results and it does not provide evidence that anakinra is any better or worse than other treatments for this outcome. This is the same for all aspects for the evidence review of Schnitzler's syndrome. |
| 11. | Delivery of intervention | not measured | . |

**5.1 Other health metrics determined by the evidence review - Anakinra to treat Schnitzler's syndrome**

| No | Metric | Grade of evidence | Summary from evidence review |
|---|---|---|---|
| 1 | Response to treatment | Grade B | In a study reporting a retrospective analysis of 42 patients, the following results were reported:<br><br>• Complete response (signs of active disease were absent and reported inflammatory markers had normalised) was reported in 24 out of 29 patients (83%).<br>• Partial response was reported in 5 (3 had mild residual bone pain) of 29 patients (17%).<br>• No response was reported in 0 of 29 patients (0%).<br><br>The results suggest majority of patients treated with anakinra have a complete or partial clinical response to it. |
| 2 | Reduction in other treatments | Grade B | The outcome measure is defined in the reduction of use in concomitant treatments (such as steroids) following initiation of treatment with anakinra in patients. |

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| | | | In a retrospective analysis of which included 7 patients treated with anakinra and concomitant treatments (Rossi Semerano et al 2015), reduction in other treatment was reported in 5 out of 7 patients (71%%)<br><br>The results suggest that anakinra could potentially help reduce use of concomitant treatments in two-third patients receiving it. |

Financial summary

**SECTION 2 – IMPACT REPORT (Not included in CPAG Papers, section 2 only)**

| No | Item | N/Cost £K | Level of uncertainty |
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| 1. | Number of patients affected in England | 47 | These patients have been identified as potentially benefitting from using anakinra rather than following existing pathways. |
| 2. | Total cost per patient over 5 years | £31,853 | The total cost over the first 5 years divided by the total patients treated in the same period |
| 3. | Budget impact year 1 | (£227k) | The benefit delivered in year 1 by switching patients from existing treatments onto Anakinra pathway |
| 4. | Budget impact year 2 | (£250k) | The benefit delivered in year 2 by switching patients from existing treatments onto Anakinra pathway |
| 5. | Budget impact year 3 | (£293k) | The benefit delivered in year 3 by switching patients from existing treatments onto Anakinra pathway |
| 6. | Budget impact year 4 | (£301k) | The benefit delivered in year 4 by switching patients from existing treatments onto Anakinra pathway |
| 7. | Budget impact year 5 | (£284k) | The benefit delivered in year 5 by switching patients from existing treatments onto Anakinra pathway |
| 8. | Total number of patients treated over 5 years | 238 | Patients benefitting over 5 years including the recognition of growth in line with ONS statistical analysis and a backlog of patients currently being |

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| | | | recognised |
| 9. | Net cost per patient treated over 5 years | (£5,699) | The policy will deliver a cost saving over the 5 years analysed |
| 10. | Estimated proportion of patients benefitting (%) | N/A | N/A |
| 11. | Total cost per patient benefitting over 5 years | N/A | N/A |
| Key additional information | | | |