Rheumatology Subcommittee of PTAC
Meeting held 7 October 2014

(minutes for web publishing)

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Note:

- that this document is not necessarily a complete record of the Rheumatology Subcommittee meeting; only the relevant portions of the minutes relating to Rheumatology Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

The Respiratory Subcommittee may:

(a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
(c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes were reviewed by PTAC at its meeting on 7 & 8 February 2015, the record of which is available on our website.

Record of the Rheumatology Subcommittee of PTAC meeting held at PHARMAC on 7 October 2014

1 Benzbromarone and febuxostat

1.1 The Subcommittee noted that benzbromarone has been funded since 1 April 2013 as a last-line treatment for gout subject to the Special Authority criteria. The funded brand (Benzbromaron AL 100) is supplied by Link Pharmaceuticals under section 29 of the Medicines Act 1981 and must be prescribed in accordance with section 25 of the Medicines Act.

1.2 The Subcommittee noted that febuxostat (Adenuric) 80 mg and 120 mg tablets, supplied by TeArai BioFarma, was funded on 1 June 2014 as an alternative last-line option for gout, subject to Special Authority criteria.

1.3 The Subcommittee noted that PHARMAC staff had received requests for changes and clarifications in the Special Authority criteria for febuxostat and/or benzbromarone from clinicians and Te Arai BioFarma and was seeking the Subcommittee's advice on these requests.

1.4 The Subcommittee considered that it was reasonable to specify more information about the use of probenecid in the Special Authority criteria for clarity and to ensure that it was used at appropriate doses most likely to achieve clinical benefit.

1.5 The Subcommittee considered that there was no compelling reason to specify a lower creatinine clearance rate in the febuxostat Special Authority given that information about the use of febuxostat in renal impairment is included on the Medsafe datasheet, including advice that no dose adjustment is necessary in mild to moderate renal impairment. However, the Subcommittee considered that it was reasonable to maintain the lower rate in the benzbromarone Special Authority as there was limited evidence of efficacy of benzbromarone in patients with CrCl <20 ml/min.

1.6 The Subcommittee considered that, at present, there was no need to add a requirement for liver function testing (LFT) to the febuxostat Special Authority, noting that clinicians could refer to the Medsafe datasheet for guidance on this. The Medsafe datasheet for febuxostat currently states "liver function test is recommended prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgement." The Subcommittee considered that the LFT requirements on the benzbromarone Special Authority were possibly excessive but given the lack of a Medsafe datasheet it would be prudent to retain them at this stage. The Subcommittee noted that both treatments have the potential to cause liver toxicity, albeit by different mechanisms.

1.7 The Subcommittee noted that Te Arai BioFarma had requested that the target serum urate level specified in the Special Authority for febuxostat be lowered from 0.36 mmol/l to 0.30 mmol/l. The Subcommittee noted that the current European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) guidelines recommend a target of 0.36 mmol/l, although members noted that this may change in the new EULAR guidelines due for publication next year.

1.8 The Subcommittee noted that the goals of gout treatment are to prevent gout attacks and dissolve tophi. The Subcommittee noted that a serum urate level below 0.36 mmol/l is adequate to achieve the treatment goals in many patients, while in others a lower serum urate is required to meet these goals. The Subcommittee considered that

the evidence for increased benefit of aiming for a serum urate level below 0.36 mmol/l in asymptomatic patients without tophi was weak.

1.9 The Subcommittee considered that the majority of patients with gout would be unlikely to achieve a serum urate level of 0.30 mmol/l in the 'real world' setting (i.e. normal clinical practice outside a clinical trial), given the finding from a recent ACR conference abstract that only 45% of patients achieved 0.36 mmol/l from allopurinol in a real world setting (Baumgartner et al. Allopurinol dose titration and efficacy: a large-scale, international 6-month multicentre prospective study. ACR/ARHP Annual Meeting; October 25-30; 2013; San Diego).

1.10 The Subcommittee considered that the target serum urate level of 0.36 mmol/l specified in the Special Authority criteria for benzbromarone and febuxostat was reasonable and economically appropriate as a funding requirement, noting that there was nothing in the criteria that would prevent clinicians from attempting to achieve a lower serum urate level with allopurinol and/or probenecid if clinically appropriate prior to using febuxostat or benzbromarone.

1.11 The Subcommittee noted that, given the large cost differential between the funded last-line treatments and allopurinol, if the target serum urate level in the entry criteria were to change in future then consideration could be given to requiring the same target level to be met on the last-line treatments in order to obtain a renewal.

1.12 The Subcommittee noted that the Rider and Jordan (Rheumatology 2010;49:5-14) reference provided by Te Arai BioFarma in relation to National Institute for Health and Care Excellence (NICE) guidance for gout treatments was not the correct reference for NICE guidance as it was an independent publication and the algorithms in the paper were developed by the authors, not by NICE. The Subcommittee noted that there appeared to be no current NICE guidance for the use of probenecid.

1.13 The Subcommittee noted that both the NICE guidance for febuxostat and the Rider and Jordan (2010) publication recommend febuxostat as a possible treatment for chronic hyperuricaemia in people with gout only if patients have contraindications to, or are intolerant of, allopurinol, which is more restrictive than PHARMAC's funding criteria.

1.14 The Subcommittee noted that the algorithm referred to by Te Arai BioFarma (Figure 2 of the Rider and Jordan (2010) publication) recommends benzbromarone, but not febuxostat, in patients who have not achieved target serum urate on allopurinol, and also recommends allopurinol at up to doses of 900 mg/day.

1.15 The Subcommittee noted a recent publication by Kydd et al (J Rheumatol Suppl 2014;41 Suppl 92:33-41), summarising two Cochrane reviews, that concluded there is moderate quality evidence supporting the efficacy and safety of allopurinol, febuxostat, benzbromarone and probenecid in gout, and that there is insufficient evidence for the most optimal sequencing of the available treatments.

1.16 The Subcommittee noted Te Arai BioFarma's request to remove the requirement for a trial of probenecid prior to accessing febuxostat. The Subcommittee considered that there was no compelling clinical reason either to retain or to remove this requirement, so the choice of whether or not to remove the requirement would need to be assessed only from a cost perspective. The Subcommittee considered that PHARMAC staff should review the average daily cost of the two treatments at such time as a year of febuxostat funding data was available and if the costs were the same, or febuxostat was cheaper, then it would be reasonable to remove the requirement for a trial of probenecid from the febuxostat Special Authority.

1.17 The Subcommittee noted Te Arai BioFarma's request that benzbromarone be delisted from the Pharmaceutical Schedule, and that funding for benzbromarone be restricted only to consideration under NPPA under strict criteria for transplant patients only. The Subcommittee did not support the delisting of benzbromarone from the Pharmaceutical Schedule. The Subcommittee considered that benzbromarone provided a useful treatment option in treatment-resistant patients, particularly for Māori and Pacific Islanders, and that the current Special Authority criteria were appropriate (noting the recommended amendments in paragraph 6.19, below).

1.18 After reviewing the various requests and submissions, the Subcommittee **recommended** that the Special Authority criteria for febuxostat be amended as follows (additions in bold, deletions in strikethrough):

Special Authority for Subsidy
Initial application from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
Both:
1 Patient has been diagnosed with gout; and
2 Any of the following:
2.1 The patient has a serum urate level greater than 0.36 mmol/l despite treatment with allopurinol at doses of at least 600 mg/day and ~~appropriate doses of~~ **addition of** probenecid **at doses of up to 2 g per day or maximum tolerated dose**; or
2.2 The patient has experienced intolerable side effects from allopurinol such that treatment discontinuation is required and serum urate remains greater than 0.36 mmol/l despite ~~appropriate doses of~~ **use of** probenecid **at doses of up to 2 g per day or maximum tolerated dose**; or
2.3 ~~Both:~~
~~3.1~~ The patient has renal impairment **such that probenecid is contraindicated or likely to be ineffective** and serum urate remains greater than 0.36 mmol/l despite optimal treatment with allopurinol (see Note)~~; and~~
~~3.2 The patient has a rate of creatinine clearance greater than or equal to 30 ml/min~~.

Renewal from any relevant practitioner. Approvals valid for 2 years where the treatment remains appropriate and the patient is benefitting from the treatment.

Note: Optimal treatment with allopurinol in patients with renal impairment is defined as treatment to the creatinine clearance-adjusted dose of allopurinol then, if serum urate remains greater than 0.36 mmol/l, a gradual increase of the dose of allopurinol to 600 mg or the maximum tolerated dose.

1.19 The Subcommittee **recommended** that criteria 1, 2 and 3.1 be similarly amended on the benzbromarone Special Authority but 3.2 should not be removed from the benzbromarone Special Authority.

1.20 The Subcommittee noted the "Corrigendum to the Rheumatology Subcommittee Meeting October 2013 Minutes" provided by Te Arai BioFarma. The Subcommittee considered that no amendments should be made to the minutes, noting that the minutes were an accurate reflection of the discussion at the time.

1.21 The Subcommittee noted PTAC's concern that the patient information leaflet for benzbromarone produced by Canterbury DHB, and available on the New Zealand Rheumatology Association (NZRA) website, did not contain information about the fact that benzbromarone is not registered in New Zealand. Members advised that the leaflet would be updated to reflect this. The Subcommittee considered that the information about the potential side effects that would require patients to contact their doctor was sufficient.

2 Undifferentiated Spondyloarthropathies

2.1 The Subcommittee noted that in February 2014 PTAC reviewed an application from a clinician to fund TNF-alpha inhibitors for undifferentiated spondyloarthritis (u-SpA) and that the Committee had recommended that the application be declined and also recommended that the application be referred to the Rheumatology Subcommittee for further advice.

2.2 The Subcommittee noted that while the majority of patients with u-SPA eventually differentiate into definite ankylosing spondylitis (AS) or psoriatic arthritis (PsA), there is a subset of patients whose disease remains undifferentiated in the long term (e.g. Collantes et al. Joint Bone Spine 2000;67:516-20). The Subcommittee estimated that approximately 10%-30% of patients diagnosed with u-SPA would remain undifferentiated in the long term.

2.3 The Subcommittee considered that patients with long-term u-SPA experienced worsening of disease activity over time in much the same way as patients with AS and PsA. The Subcommittee considered that PTAC's particular question about the value of early initiation of TNF-alpha inhibitor treatment in patients with u-SPA to possibly prevent progression, was not relevant to the funding application, because the funding application was for patients with established u-SPA, as a particular diagnosis, with severe and intractable disease, not for patients with early disease.

2.4 Similarly, the Subcommittee considered that PTAC's question relating to prediction of progression to AS or PsA was not relevant to the application, because funding was not being sought for early intervention in u-SPA with the intent of preventing differentiation to AS or PsA. The Subcommittee considered that there was no reliable way to predict which patients with early disease would subsequently differentiate to AS or PsA, although results of one long-term cohort study suggested that HLA-B27 and buttock pain predicted evolution into AS (Sampaio et al. J Rheumatol 2010;37:1195-9).

2.5 The Subcommittee noted that earlier intervention with a TNF-alpha inhibitor would potentially be useful in any of the funded arthropathies, as treatment before joint damage occurs is likely to provide greater benefit than treatment after damage occurs. The Subcommittee noted that the best evidence for early initiation of TNF-alpha inhibitors preventing future joint destruction and disability was in PsA. However, as noted in the previous paragraph, this was not relevant to the funding application.

2.6 The Subcommittee considered that the severity of pain and disability experience by patients with severe and intractable u-SPA would be the same or similar to that of patients with AS or PsA. A recent real-life prospective cohort study that compared clinic patients with u-SpA, PsA and AS showed that symptoms were similar or worse in u-SpA, compared to PsA or AS as measured by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (median 5.3, 3.2, 5.0) and patient global assessment of disease activity (median 63, 38, 50) (Paramarta et al. Rheumatology 2013;52:1873-8). The Subcommittee considered that patients with u-SpA and similar or worse disease activity than AS or PsA on a disease activity instrument measurement would have similar disability to patients with AS or PsA.

2.7 The Subcommittee noted that most of the data in support of the use of TNF-alpha inhibitors in u-SpA were for adalimumab, but considered that it was likely that all TNF-alpha inhibitors would have similar efficacy for u-SpA. The Subcommittee noted that there are no head-to-head randomised controlled trials (RCTs) in u-Sp (or in AS or

PsA), but the experience with TNF-alpha inhibitors in other SpAs would suggest that the agents are roughly similar in all SpAs.

2.8 The Subcommittee considered that, in determining appropriate targeting criteria for u-SPA, a general principle should be to ensure equivalence with other similar disorders for which TNF-alpha inhibitors are funded, in terms of disease severity and non-response to conventional treatments. The Subcommittee noted the characteristics of u-SpA patients included in RCTs that showed benefits of TNF-alpha inhibitor treatment (Paramarta et al. Ann Rheum Dis 2013;72:1793-1799; Sieper et al. Ann Rheum Dis 2013;72:815-822; Haibel et al. Arthritis Rheum 2008;1981-91; Dougados et al Ann Rheum Dis 2010;69:1430-1435).

2.9 The Subcommittee considered that including severe and intractable single joint disease as an access criterion for u-SpA would create inconsistencies with the access criteria for other SpAs. The Subcommittee noted that the design of studies to test efficacy of treatments for single joint disease is challenging. The Subcommittee noted that there is no RCT evidence for the efficacy of TNF-alpha inhibitors for isolated knee synovitis in SpA, although there is some non-experimental evidence that is supportive of intra-articular TNF-alpha inhibitors in this setting (e.g. Haroon et al. Joint Bone Spine 2010;77:232-4; Conti et al. Arthritis Rheum 2005;52:1224-6).

2.10 The Subcommittee noted that the applicant had included several additional joints (subtalar, tarsus, forefoot) that do not appear in the PsA or RA criteria, which would potentially enable patients to access treatment more readily. The Subcommittee considered that this was reasonable because u-SpA has a greater propensity to affect lower limb joints. The Subcommittee also proposed that the sternoclavicular joint be added to the list because this is a joint commonly affected in u-SpA. Members noted that the distribution of joints involved in peripheral SpA is different from RA which was the model used for the PsA access criteria. PsA has varying phenotypes including an RA lookalike as well as the more typical lower limb SpA presentation. In peripheral u-SpA the pattern is one of asymmetry and lower limb predominance. The Subcommittee considered that if these joints were accepted in the final criteria for u-SPA then it would be preferable for access to be similarly widened under the PsA criteria.

2.11 The Subcommittee noted that the initial Special Authority criteria in the RA and PsA applications relating to C-reactive protein (CRP) levels were problematic in that that it was not uncommon, where patients had a CRP measurement lower than 15 mg/L, for clinicians to then start patients on prednisone in order to avoid the requirement for CRP to be measured in order to fulfil the funding requirements. Members noted that this was less than ideal as long-term prednisone is a treatment with predictable and cumulative side effects. Members noted that patients with higher CRP tended to respond better to TNF-alpha inhibitor treatment.

2.12 The Subcommittee considered that the renewal criteria for u-SpA should be the same as for PsA.

2.13 The Subcommittee **recommended** that access to adalimumab and etanercept be widened on the Pharmaceutical Schedule to include use in u-SpA, subject to the Special Authority criteria below. In the context of the rheumatology therapeutic area the Subcommittee considered that this would be a high priority.

Initial application — (undifferentiated peripheral spondyloarthritis) only from a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1 Patient has undifferentiated peripheral spondyloarthritis with active peripheral joint arthritis in at least four joints from the following: hip, knee, ankle, subtalar, tarsus, forefoot, wrist, elbow, shoulder, sternoclavicular; and
2 All of the following:
    2.1 Patient has tried and not responded to at least three months of oral or parenteral methotrexate at a dose of at least 20 mg weekly or a maximum tolerated dose; and
    2.2 Patient has tried and not responded to at least three months of sulphasalazine at a dose of at least 2 g per day (or maximum tolerated dose); and
    2.3 Patient has tried and not responded to at least three months of leflunomide at a dose of up to 20 mg daily (or maximum tolerated dose); and
4 Any of the following:
    4.1 Patient has a C-reactive protein level greater than 15 mg/L measured no more than one month prior to the date of this application; or
    4.2 Patient has an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour; or
    4.3 ESR and CRP not measured as patient is currently receiving prednisone therapy at a dose of greater than 5 mg per day and has done so for more than three months.

Renewal — (undifferentiated peripheral spondyloarthritis) only from a rheumatologist or Practitioner on the recommendation of a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1 Either:
    1.1 Applicant is a rheumatologist; or
    1.2 Applicant is a Practitioner and confirms that a rheumatologist has provided a letter, email or fax recommending that the patient continues with TNF-alpha inhibitor treatment; and
2 Either:
    2.1 Following 3 to 4 months' initial treatment, the patient has at least a 50% decrease in active joint count from baseline and a clinically significant response to treatment in the opinion of the physician; or
    2.2 The patient demonstrates at least a continuing 30% improvement in active joint count from baseline and a clinically significant response to prior TNF-alpha inhibitor treatment in the opinion of the treating physician; and
3 TNF-alpha inhibitor to be administered at doses no greater than x dose every x days. [40 mg per 14 days for adalimumab and 50 mg every 7 days for etanercept]

2.14 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals.*

2.15 The Subcommittee noted that there was another similar group of patients with chronic reactive arthritis (which is another form of SpA) which could potentially benefit from treatment and which does not meet the current access criteria for biologic treatment. PHARMAC staff noted that PHARMAC would be pleased to assess a funding application for this patient group should an application be submitted.

3 Inflammatory bowel disease-associated arthritis

3.1 The Subcommittee noted that in February 2014 PTAC reviewed an application from a clinician to fund TNF-alpha inhibitors for inflammatory bowel disease-associated arthritis (IBD-A) and that the Committee had recommended that the funding of TNF-alpha inhibitors (at least one of adalimumab and infliximab) should be widened to include IBD-A with a low priority. The Committee recommended seeking advice from the Rheumatology Subcommittee on appropriate Special Authority criteria.

3.2 The Subcommittee considered that the overall severity of pain and disability in patients with IBD-A is likely to be worse than patients with IBD alone and worse than patients with AS alone since patients with IBD-A have both gut and joint symptoms that can be problematic.

3.3 The Subcommittee noted that patients with IBD-A are usually unable to take NSAIDs as these cause colitis flare, which disadvantages IBD-A patients compared with AS and PsA patients.

3.4 The Subcommittee considered that the available evidence suggests that SpA disease severity or symptoms are similar between IBD-A and other SpA (AS and PsA). For example, in one publication BASDAI, ASQoL and BASFI were all similar across AS, PsA and IBD-A but BASRI-spine was 7 (AS) compared to 4.8 (IBD-A) (Perez Alamino et al. J Rheumatol 2011;38:1656-60).

3.5 In considering appropriate Special Authority criteria, the Subcommittee noted that leflunomide is often associated with diarrhoea which could be problematic in the setting of IBD; further, leflunomide has not shown to be effective in axial disease.

3.6 The Subcommittee considered that the risk of slippage would be low as long as the criteria included the measures of disease severity and non-response to prior treatments as outlined in the proposed criteria, below.

3.7 The Subcommittee **recommended** that, if funded, the following funding criteria should apply to the use of adalimumab or infliximab in IBD-A. The Subcommittee considered that any alterations from the criteria initially proposed by the applicant would be unlikely to have any impact on patient numbers.

Initial application — (inflammatory bowel arthritis – axial) only from a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
Both
1 Patient has a confirmed diagnosis of ulcerative colitis or Crohn's disease made by a gastroenterologist; and
2 All of the following:
    2.1 Patient has severe axial inflammatory pain for six months or more; and
    2.2 Patient is unable to take non-steroidal anti-inflammatory drugs (NSAIDs); and
    2.3 Patient has bilateral sacroiliitis demonstrated by plain radiographs, CT or MRI scan; and
    2.4 Patient's inflammatory bowel arthritis has not responded adequately to prior treatment consisting of at least 3 months of an exercise regime supervised by a physiotherapist and concomitant sulphasalazine (unless contraindicated); and
    2.5 A Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of at least 6 on a 0-10 scale (see Note).

Notes: The BASDAI must have been determined at the completion of the 3 month exercise trial, but prior to ceasing any previous pharmacological treatment. The BASDAI measure must be no more than 1 month old at the time of initial application.

Initial application — (inflammatory bowel arthritis – peripheral) only from a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
Both
1 Patient has a confirmed diagnosis of ulcerative colitis or Crohn's disease made by a gastroenterologist; and
2 All of the following:
    2.1 Patient has active peripheral joint arthritis in at least four joints from the following: hip, knee, ankle, subtalar, tarsus, forefoot, wrist, elbow, shoulder, sternoclavicular; and

2.2 Patient has tried and not responded to at least three months of oral or parenteral methotrexate (unless patient is on azathioprine) at a dose of at least 20 mg weekly or a maximum tolerated dose; and
2.3 Patient has tried and not responded to at least three months of sulphasalazine (or sulphasalazine is contraindicated); and
2.4 Any of the following:
2.4.1 Patient has a C-reactive protein level greater than 15 mg/L measured no more than one month prior to the date of this application; or
2.4.2 Patient has an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour; or
2.4.3 ESR and CRP not measured as patient is currently receiving prednisone therapy at a dose of greater than 5 mg per day and has done so for more than three months.

Renewal — (inflammatory bowel arthritis – axial) only from a rheumatologist or Practitioner on the recommendation of a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1 Either:
1.1 Applicant is a rheumatologist; or
1.2 Applicant is a Practitioner and confirms that a rheumatologist has provided a letter, email or fax recommending that the patient continues with TNF-alpha inhibitor treatment; and
2 Following 12 weeks of TNF-alpha inhibitor treatment, BASDAI has improved by 4 or more points from pre-adalimumab baseline on a 10 point scale, or by 50%, whichever is less; and
3 Physician considers that the patient has benefited from treatment and that continued treatment is appropriate; and
3 TNF-alpha inhibitor to be administered at doses no greater than x dose every x days. [40 mg per 14 days for adalimumab and 5 mg/kg every 8 weeks for infliximab]

Renewal — (inflammatory bowel arthritis – peripheral) only from a rheumatologist or Practitioner on the recommendation of a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1 Either:
1.1 Applicant is a rheumatologist; or
1.2 Applicant is a Practitioner and confirms that a rheumatologist has provided a letter, email or fax recommending that the patient continues with TNF-alpha inhibitor treatment; and
2 Either:
2.1 Following 3 to 4 months' initial treatment, the patient has at least a 50% decrease in active joint count from baseline and a clinically significant response to treatment in the opinion of the physician; or
2.2 The patient demonstrates at least a continuing 30% improvement in active joint count from baseline and a clinically significant response to prior TNF-alpha inhibitor treatment in the opinion of the treating physician; and
3 TNF-alpha inhibitor to be administered at doses no greater than x dose every x days. [40 mg per 14 days for adalimumab and 5 mg/kg every 8 weeks for infliximab]

3.8 The Subcommittee considered that, in the context of the rheumatology therapeutic area, the priority rating for the funding proposal should be high (not low, as per the PTAC recommendation).

3.9 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals.*