

CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
3Q17 July – August

BRAND NAME

Renflexis[™]

GENERIC NAME

Infliximab-abda

MANUFACTURER

Samsung Bioepis (for Merck & Co., Inc.)

DATE OF APPROVAL

April 21, 2017

PRODUCT LAUNCH DATE

Q4 2017 (anticipated)

REVIEW TYPE

Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastics, antipsychotics, antiretrovirals, and immunosuppressants)

Review type 5 (RT5): Abbreviated Review for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATIONS

New Indications¹

- **Crohn's Disease:**

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- Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease.
- **Pediatric Crohn's Disease:**
 - Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- **Ulcerative Colitis:**
 - Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- **Rheumatoid Arthritis in combination with methotrexate:**
 - Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active disease.
- **Ankylosing Spondylitis:**
 - Reducing signs and symptoms in patients with active disease.
- **Psoriatic Arthritis:**
 - Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function.
- **Plaque Psoriasis:**
 - Treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

Unlike Remicade[®] (infliximab), Renflexis is not approved for the treatment of Pediatric Ulcerative Colitis. Remicade possesses orphan drug exclusivity for this indication expiring on September 23, 2018.

OFF-LABEL USES

Uveitis associated with Behcet's Disease/Syndrome

CLINICAL EFFICACY

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The biosimilarity and efficacy comparison of Renflexis to Remicade was established in two clinical trials (SB2-G11-NHV and SB2-G31-RA, respectively).

Pharmacokinetic Comparison/Bridging in Healthy Subjects (SB2-G11-NHV)²: The first trial was a Phase I, pharmacokinetic (PK) bridging comparison conducted as a single-blind, three-arm, parallel group study in 159 healthy subjects. All subjects received a single 5 mg/kg intravenous infusion of study drug (i.e., Renflexis [SB2], European Remicade [EU-INF], US Remicade [US-INF]) and then were observed for 10 weeks to study PK, safety and immunogenicity. The primary PK parameters were area under the concentration-time curve (AUC) from time zero to infinity (AUC_{inf}), AUC from time zero to the last quantifiable concentration (AUC_{last}) and maximum concentration (C_{max}). Bioequivalence for the primary PK parameters was to be concluded using an analysis of variance (ANOVA) if the 90% confidence intervals (CIs) for the ratio of geometric least squares means (LS Means) of the treatments compared were completely contained within the pre-defined equivalence margin, 0.8–1.25.

Comparisons between SB2 and both EU-INF and US-INF showed high similarity in mean serum concentration time profiles. The mean values for PK parameters (AUC , C_{max} , T_{max} , V_d , $T_{1/2}$, CL) were similar between treatment groups. The 90% CIs of the ratios of AUC_{inf} , AUC_{last} , and C_{max} were all within the established 0.8-1.25 equivalence margin. Similarity in immunogenicity was established by conducting sub-analyses based on post-dose ADA (anti-drug antibody) results. There was no statistically significant difference in post-dose ADA incidence across the three treatment groups ($p = 0.432$ between SB2 and EU-INF, $p = 0.432$ between SB2 and US-INF and $p = 1.000$ between EU-INF and US-INF). Treatment-emergent adverse effects (TEAE) were similar between all three arms of the study. Nasopharyngitis and headache were the most frequently reported TEAEs. There were no deaths or discontinuations due to AEs during the study.

Clinical Efficacy Comparison Trial in RA Patients (SB2-G31-RA)³: This was a Phase III, randomized, double-blind, multinational, multicenter, parallel group study conducted to compare the efficacy, safety, PK, and immunogenicity of SB2 compared with Remicade in 584 subjects with moderate to severe RA despite methotrexate (MTX) therapy. The study consisted of a 6 week screening period followed by 54 weeks of active treatment. At randomization, eligible subjects with moderate to severe RA (who were diagnosed at least 6 months prior to study entry), who had an inadequate response to MTX and who had been on a stable dose of MTX 10–25 mg/week given orally or parenterally for at least 4 weeks prior to screening, were randomized at Week 0. Subjects were randomized in a 1:1 ratio to receive either SB2 3 mg/kg or Remicade 3 mg/kg via a 2 hour IV infusion, at Weeks 0, 2 and 6 and then every 8 weeks through Week 46. From Week 30 the dose level could be increased step-wise by 1.5 mg/kg, up to a maximum of 7.5 mg/kg, every 8 weeks if the subject's RA symptoms were not well controlled by the existing dose. From week 54 through week 78, a transition-extension period was conducted and consisted of 24 weeks of active treatment where patients receiving Remicade from the initial randomized,

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double-blind period were randomized again, 1:1, to either continue on Remicade or be transitioned to SB2, up to week 70. Subjects who were receiving SB2 from the initial double-blinded randomization continued to receive SB2 through week 70.

The primary efficacy endpoint was the American College of Rheumatology 20% response rate (ACR20) at week 30 in the per-protocol set. Secondary efficacy endpoints included the ACR50/70, 28 joints-erythrocyte sedimentation rate (DAS28-ESR), and European League Against Rheumatism (EULAR) response rate. Secondary endpoints for safety, immunogenicity, and PK were also conducted during this study; however, the main clinical data for these secondary measures was derived from the original, Phase I study (SB2-G11-NHV).

A total of 584 subjects were randomized: 291 subjects were randomized to the SB2 treatment group and 293 subjects were randomized to the Remicade treatment group. At Week 54, 201 subjects from the SB2 treatment group and 195 subjects from the Remicade treatment group were re-randomized to the transition-extension period. Of 195 subjects who received Remicade during the randomized, double-blind period, 94 subjects were transitioned to SB2 (Remicade/SB2) and 101 subjects continued on Remicade (Remicade/Remicade). The 201 subjects who received SB2 during the randomized, double-blind period continued to receive SB2 (SB2/SB2).

At Week 30, the proportion of subjects achieving ACR20 response was similar between the SB2 (64.1% (148/231)) and Remicade (66.0% (163/247)) treatment groups. The time-response curves of SB2 and Remicade up to Week 30 showing the ACR20 response over time were also estimated to be similar. The 95% CI for the rate difference was -10.26% to 6.51%, which was within the pre-specified equivalence margin of $\pm 15\%$. During the study period 499 treatment-emergent AEs (TEAEs) occurred in 167 patients (57.6%) in the SB2 treatment group and 529 TEAEs occurred in 170 patients (58.0%) in the Remicade treatment group. The most common TEAEs that occurred were latent TB, increased alanine aminotransferase (ALT) levels, and headache. Overall, the safety profile between SB2 and Remicade was similar. Patients who developed anti-drug antibodies (ADA) up to week 30 were 55.1% (158/287) in the SB2 treatment group and 49.7% (145/292) in the Remicade treatment group, the difference was not statistically significant ($p=0.212$). Overall, the C_{trough} of infliximab was similar between SB2 and Remicade over time and was also similar within each ADA subgroup (ADA-positive and ADA-negative) between SB2 and Remicade.

CONTRAINDICATIONS

Renflexis is contraindicated in doses >5 mg/kg in moderate to severe heart failure and in patients with a previous severe hypersensitivity reaction to infliximab products or known hypersensitivity to inactive components of Renflexis or to any murine proteins.

BLACK BOX WARNINGS

- Serious Infections:

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- Active tuberculosis (reactivation of latent tuberculosis);
- Invasive fungal infections;
- Bacterial, viral, or other infections due to opportunistic pathogens including legionella and listeria.
- Malignancies:
 - Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including infliximab products.
 - Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including infliximab products. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of reported cases have occurred in patients with Crohn's disease or ulcerative colitis and most were in adolescent and young adult males.

DRUG INTERACTIONS

- Anakinra or Abatacept: use has resulted an increased risk of serious infections with no added clinical benefit. The combination of Renflexis and anakinra or abatacept is not recommended.
- Tocilizumab: may result in increased risk for immunosuppression and infection. Combined use is not recommended.
- Biological Therapeutics: use of Renflexis with other biologic products used to treat the same conditions as Renflexis is not recommended.
- Methotrexate and other concomitant medications: Specific drug interaction studies, including interactions with MTX, have not been conducted. The majority of patients in rheumatoid arthritis or Crohn's disease clinical studies received one or more concomitant medications. In rheumatoid arthritis, concomitant medications besides MTX were nonsteroidal anti-inflammatory agents (NSAIDs), folic acid, corticosteroids and/or narcotics. Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids, 6-MP/AZA and aminosalicylates. In psoriatic arthritis clinical trials, concomitant medications included MTX in approximately half of the patients as well as NSAIDs, folic acid and corticosteroids. Concomitant MTX use may decrease the incidence of anti-drug antibody production and increase infliximab product concentrations.
- Immunosuppressants: Patients with Crohn's disease who received immunosuppressants tended to experience fewer infusion reactions compared to patients on no immunosuppressants. Serum infliximab concentrations appeared to be unaffected by baseline use of medications for the treatment of Crohn's disease including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and aminosalicylates.
- CYP enzyme substrates: Monitoring of the effect or drug concentration of CYP substrates with a narrow therapeutic index is recommended upon initiation or discontinuation of Renflexis. Adjustment of the individual dose of the drug product may be necessary.

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- Live Vaccines/Therapeutic Infectious Agents: Live vaccines should not be given concurrently with Renflexis. Infants who experienced infliximab exposure in utero should not receive live vaccines for at least 6 months following birth. Use of other therapeutic infectious agents such as live attenuated bacteria (e.g., BCG bladder instillation for the treatment of cancer) may result in clinical infections and is not recommended.

ADVERSE REACTIONS

The most common (>10%) adverse reactions reported were infections (e.g., upper respiratory, sinusitis, and pharyngitis), infusion-related reactions, headache, and abdominal pain.

DOSAGE AND ADMINISTRATION

- Crohn’s Disease
 - o 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response.
- Pediatric Crohn’s Disease
 - o 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.
- Ulcerative Colitis
 - o 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.
- Rheumatoid Arthritis
 - o In conjunction with methotrexate, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks.
- Ankylosing Spondylitis
 - o 5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks.
- Psoriatic Arthritis and Plaque Psoriasis
 - o 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

PRODUCT AVAILABILITY

Not available on the market as of yet. When it becomes available it will be packaged as 100 mg of lyophilized infliximab-abda in a 20 mL vial for intravenous injection.

THERAPEUTIC ALTERNATIVES

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)
acitretin (Soriatane [®])	Plaque Psoriasis 25 or 50 mg PO daily
azathioprine (Imuran [®])	Rheumatoid Arthritis 1 mg/kg/day PO given as a QD or BID Crohn’s Disease and Ulcerative Colitis 100 - 250 mg PO daily

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corticosteroids	<p>Crohn's Disease Prednisone 40 mg PO QD for 2 weeks or IV 50-100 mg Q6H for 1 week</p> <p>budesonide (Entocort EC[®]) 6-9 mg PO QD</p>
cyclosporine (Sandimmune[®], Neoral[®])	<p>Rheumatoid Arthritis, Plaque Psoriasis 2.5 – 4 mg/kg/day PO divided BID</p>
hydroxychloroquine (Plaquenil[®])	<p>Rheumatoid Arthritis Initial dose: 400-600 mg PO QD Maintenance dose: 200-400 mg PO QD</p>
mercaptopurine (Purinethol[®])	<p>Crohn's Disease, Ulcerative Colitis 75 – 125 mg PO daily</p>
methotrexate (Rheumatrex[®])	<p>Rheumatoid Arthritis 7.5 mg/week PO or 2.5 mg PO Q12hr for 3 doses/week</p> <p>Polyarticular Juvenile Arthritis 10mg/m² PO weekly</p> <p>Plaque Psoriasis 10 to 25 mg/week, IM, IV or PO</p>
Pentasa [®] (mesalamine)	<p>Crohn's Disease and Ulcerative Colitis 1000 mg PO QID</p>
sulfasalazine (Azulfidine[®])	<p>Rheumatoid Arthritis 2 gm/day PO in divided doses</p> <p>Ulcerative Colitis Initial dose is 3 to 4 gm/day PO; maintenance is 2 grams/day PO. Administer in evenly divided doses (not exceeding 8-hour intervals)</p>

Utilization Management Recommendation
<ul style="list-style-type: none"> • There is not significant potential for inappropriate use relative to Remicade. • The UM strategy for Renflexis should mirror that of Remicade and Inflectra, the first biosimilar to Remicade.
Product Comparison
<ul style="list-style-type: none"> • Equal therapeutic outcomes are anticipated for Renflexis and Remicade therefore it would be appropriate to provide equal access to both or to require a trial of one before the other.

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- An FDA approval of Renflexis for pediatric ulcerative colitis cannot be granted until Remicade's patent exclusivity on that indication expires, which will be in September 2018. Until then, a prior trial of Renflexis should not be required before coverage of Remicade for pediatric ulcerative colitis.

REFERENCES

¹ Renflexis [Prescribing Information]. Kenilworth, NJ. Merck & Co; April 2017.

² Shin D, et al. A randomized, Phase I pharmacokinetic study comparing SB2 and infliximab reference product (Remicade) in healthy subjects. *BioDrugs* 2015;29:381-388.

³ Choe JY, et al. A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2017;76:58-64.

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