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SPECIALTY DRUGS IN WORKERS' COMPENSATION
A POPULATION BASED ASSESSMENT

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Executive Summary

...many specialty drugs require a high level of clinical monitoring...

Specialty drugs represent the fastest growing category of drugs in the United States and projections indicate that they will account for half of all drug costs in less than five years. In general terms specialty drugs are defined as very expensive drugs that are designed to treat relatively rare conditions. Although prevailing opinion has indicated that many of these conditions, such as multiple sclerosis and hemophilia, will have little impact on drug spending in workers' compensation, myMatrixx identifies seven significant patient populations in this white paper in which specialty drugs are the treatment of choice and will most likely be deemed compensable. These include:

- Patients with restricted mobility such as those following orthopedic surgery,
- Workers exposed to HIV through occupational needlestick injuries or other means,
- Injured workers who experience pain and are later diagnosed with rheumatoid arthritis or ankylosing spondylitis,
- Injured workers who experience pain that is exacerbated by osteoarthritis,
- Workers exposed to hepatitis C virus through exposure to blood and other potentially infectious fluids,
- Patients with migraines and cervical dystonia, and
- Certain workers who develop cancer in states with cancer presumption laws.

Insurers that will be most impacted by the costs of these drugs will insure worker populations that include:

- Emergency first responders
- Public safety personnel
- Law enforcement officers
- Correctional officers
- Healthcare workers
- Certain defined workers in states with cancer presumption laws

In addition to the high cost of these drugs, many of these treatments require a high level of clinical monitoring on the part of the pharmacy benefit manager that is responsible for the proper use of the specialty drugs. This paper demonstrates the role of the clinical pharmacist in a complex care environment.

Introduction

Pharmacy spending for specialty drugs is rapidly growing. According to a study by Prime Therapeutics, specialty drug cost is expected to rise to 50% of total drug cost by 2018.[1] This rise can partly be attributed to increased use of non-specialty generics, but price increases, increased utilization, and continued emphasis on specialty drug development appear to be major drivers.

Over the last two decades the number of specialty drugs on the market has grown from 10 to nearly 300. In 2012, the US Food and Drug Administration approved a record number of 39 new agents, 25 of which can be classified as specialty drugs.[2] Additionally, approximately 40% of current drugs in the pipeline may be considered specialty drugs when approved. These numbers should be concerning for payers, and efforts should be made to increase vigilance and management of this sector of pharmacy spending. We should begin by understanding the criteria for specialty classification, then identify some specific agents currently being used in the workers' compensation population and examine the clinical and medical necessity for therapeutic utilization.

Specialty Classification:

The definition of a specialty drug can be different depending on the source. Between health plans, the list of specialty drugs can vary quite significantly. It's important to note that it is not an FDA designation. The most general description of specialty drugs is that they are expensive drugs used to treat rare conditions, but this definition does not necessarily qualify all drugs currently considered specialty. According to the American Journal of Managed Care, the definition of specialty drugs has five key components:

- Cost >$600/month and
- Treats a rare condition or
- Requires special handling or
- Uses a limited or restricted distribution network or
- Requires ongoing clinical assessment

The first two criteria are related. Since drugs are expensive to develop and a rare condition means fewer utilizing patients, a higher cost for the drug is necessary. A few of the rare conditions commonly referenced when specialty drugs are discussed include multiple sclerosis, hemophilia, hepatitis, and human immunodeficiency virus (HIV).

The remaining three criteria can be interpreted to represent an inherent obligation that healthcare systems have in order to ensure the safe and effective use of medicine. Special handling requirements are needed to protect patients and healthcare providers from drugs that can be hazardous. Some chemotherapy agents, for example, are known to cause secondary types of cancer in caretakers exposed to the drugs.[3] The limited or restricted distribution network requirements can be created or driven by the manufacturer. The purpose of this is to ensure that the entities involved in the distribution of the particular specialty drug possess the specialized knowledge and skills required to provide safe and effective use. The monitoring of safety and effectiveness can sometimes require strict ongoing clinical assessments. One of the most strict examples is seen with a drug called Accutane® (*no longer available under this name*). Used for the treatment of a rare type of acne, this drug can cause severe birth defects. To safeguard against this risk, the requirements for dispensing go as far as to require the patient to submit pregnancy test results on a monthly basis before the drug can be dispensed.[4] In terms of assuring effectiveness, some drugs such as Xolair®, used for refractory asthma, require very individualized dosages determined by the patient's body weight and a pretreatment blood test that measures the serum concentration of a particular antibody meant to be the target of the drug.[5]

The specialty drug classification can therefore be interpreted as an additional healthcare system measure to ensure the safe and effective use of medication. For these reasons, it can be understood that the higher cost of treatment with these medications, although more commonly related to the direct cost of the drug, is indirectly related to the various mechanisms and measures needed to ensure safe and effective treatment outcomes.

Introduction *(continued)*

Exposure and Value Assessment:

To assess the exposure workers' compensation may have to specialty drugs one simply has to consider whether the rare conditions or disease states that require specialty drug use can arise from a work-related injury. For some specialty conditions, establishing the possibility that such conditions can arise from a work-injury is straightforward. Human immunodeficiency virus (HIV), for example, can be contracted by healthcare workers who are exposed to potentially infectious material. The same occupational hazard exists for hepatitis. Other conditions such as hemophilia are clearly inherited and cannot be caused by a work injury.

For the purposes of this paper, several drug classes (based on transactions) currently seen among myMatrixx's book of business are reviewed. The questions that will be answered include what these drugs are, what conditions are being treated, and whether these drugs represent the current standard of care, i.e. whether these drugs represent the most cost and clinically effective options.

Anticoagulants

If Lovenox® (*enoxaparin*), Fragmin® (*dalteparin*), or Arixtra® (*fondaparinux*) is being used in the workers' compensation population, the patient most likely has undergone some type of orthopedic surgery. Following surgery, restricted mobility will increase a patient's risk for thromboembolic complications or blood clots. In rare cases, a blood clot can travel to the lungs and cause pulmonary embolism or even a heart attack or stroke.

Known as thromboprophylaxis, the US Agency for Healthcare Research and Quality (AHRQ) considers this patient-safety strategy the most important of all safety initiatives for patients admitted to the hospital.[6] Without prophylaxis, the incidence of deep vein thrombosis (DVT) is 40% to 60% in patients undergoing major orthopedic surgery.[7] This is the group of patients with the highest risk of DVT. Although thromboprophylaxis is highly recommended by current guidelines, only 60% to 75% of surgical patients receive adequate treatment.[8]

Lovenox and Fragmin are two drugs that are part of the subclass known as Low Molecular Weight Heparins (LMWHs). Arixtra is another anticoagulant approved for DVT prophylaxis but prevents thrombosis through a slightly different mechanism.

The duration of therapy depends on the severity of the surgical intervention, but is generally one to two weeks for all three agents. Extended prophylaxis for up to four weeks is recommended for major surgeries that render patients immobile for extended periods. For recommended doses of Fragmin 5000 IU once daily, enoxaparin 30 mg twice daily, and fondaparinux 2.5 mg once daily, the daily cost is $42.54, $48.71, and $54.66 respectively based on average wholesale price (AWP).

Table 1

Drug	Usual Dose	Cost Per Day
Fragmin®	5000 IU once daily	$42.54
Lovenox® (generic available)	30 mg twice daily	$48.71
Arixtra® (generic available)	2.5 mg once daily	$54.66

Anticoagulants for Thromboprophylaxis Primary Options

At the present time, enoxaparin appears to be the most popular option among prescribers and the least expensive for payers. The use of fondaparinux may be medically necessary for patients with a history of heparin-induced thrombocytopenia (HIT).[9,10,11] This is a rare immune reaction to heparin that can increase the risk of clot formation in patients.

HIV Antiretrovirals

In the workers' compensation population, antiretroviral drugs are used by workers exposed to the HIV virus to prevent transmission. These drugs were first developed to treat HIV infection and as healthcare workers were beginning to be exposed to HIV, the practice of giving treatment medication to prevent transmission, once proven effective, became standard protocol.

Three routes of exposure may place a healthcare worker at risk of HIV infection including percutaneous injury (*e.g., a needle stick or cut with sharp object*), contact with mucous membrane, or contact with non-intact skin (*e.g., exposed skin that is chapped, abraded, or afflicted with dermatitis*).[12]

The average risk of HIV transmission is about 0.3% following percutaneous exposure and 0.09% following mucous membrane exposure.[12] In work places where workers risk exposure, the Occupational Safety & Health Administration (OSHA) requires a written policy and procedure for controlling risk of transmission, not just from HIV, but for all pathogens that are bloodborne (*e.g., hepatitis*). This is known as a PEP or post-exposure prophylaxis protocol.

The Centers for Disease Control and Prevention (CDC) provides reliable guidelines for the management of occupational exposure to HIV. The guidelines provide recommendations on when to use PEP, which drugs are appropriate, treatment duration, and the number of drugs to be used. The number of drugs used depends on the level or severity of exposure and knowledge about HIV status of the source.

At a minimum, a two-drug regimen is recommended for less severe exposure (solid needle or superficial injury), but three or more drugs may be necessary for more severe exposure such as those from sources with symptomatic or uncontrolled disease (high viral loads). The recommended duration of therapy is four weeks. However, these drugs are very toxic and for that reason a high proportion of healthcare workers (range: 17% to 47%) are not able to complete the full four week course of therapy.

The various available drugs target different stages of the viral replication cycle and, in theory, combining drugs with activity at separate stages offers an additive prevention effect. By this theory, the more drugs used means a higher potential effectiveness of prevention although data supporting this is presently lacking. So if the question is whether more than two drugs should be used if added security is desired, the CDC recommends offering a two-drug regimen as a more practical or viable option because the benefits of completing a full, four week course exceeds the benefits of adding a third or fourth drug and risking non-completion.

Antiretroviral drugs are used by workers exposed to the HIV virus to prevent transmission.

3 routes of exposure place a worker at risk:

1. **Percutaneous injury**
2. **Contact with mucous membrane**
3. **Contact with non-intact skin**

A two-drug regimen is referred to as a basic regimen and a regimen of three or more drugs is referred to as an expanded regimen. Truvada®[13] is a combination product containing tenofovir and emtricitabine. A generic formulation is not currently available for Truvada as the first patent for the drug is not set to expire until July 2017.[14] The AWP is currently $48.93 per tablet and, prescribed once daily, a 30 day course is approximately $1,467.90. Although the recommended duration is only four weeks, these medications are packaged in 30 day supplies and must be dispensed in the original containers.

The alternative to Truvada is Combivir®[15] which is also a two-drug combination product. Combivir is available in generic form as lamivudine/zidovudine with a current AWP of $14.63 per tablet. Combivir, however, has to be taken twice daily and, therefore, a 30 day course is $877.80 or only about 40% less expensive than Truvada. Many PEP protocols favor Truvada over Combivir because of the once daily dosing and reported better tolerability.

HIV Antiretrovirals *(continued)*

When an expanded regimen is necessary, the CDC recommends adding an agent from the class of drugs known, by mechanism, as protease inhibitors or PIs, and the preferred drug is Kaletra®.[16] Kaletra is not expected to be available generically until December 2016.[17] The prescribed dose of 200-50 mg, 4 capsules daily results in a four-week course (120 capsules) cost of $922.80 (AWP= $7.69/capsule). Kaletra is a combination of two protease inhibitors: lopinavir and ritonavir. The antiretroviral activity, however, is only attributed to lopinavir as ritonavir is only added to inhibit the metabolism of lopinavir, a pharmacokinetic strategy known as "boosting."

Table 2

Regimen	Drug(s)	Cost Per 30 Day Supply
preferred Basic regimen	Truvada® (once daily)	$1,467.90
alternative Basic regimen	generic Combivir® (twice daily)	$877.80
preferred Expanded regimen	Truvada® + Kaletra® (4 caps/day)	$2,390.70
alternative Expanded regimen	generic Combivir® + Kaletra® (4 caps/day)	$1,800.60

HIV Post-exposure Prophylaxis Primary Options

Most protease inhibitors require or can benefit from boosting with ritonavir. Kaletra combines a protease inhibitor with ritonavir and for this reason it is the most cost effective alternative to use when an expanded regimen is required. If any of the other alternative protease inhibitors are used in place of Kaletra, the need for boosting with ritonavir will result in an added cost of approximately $617.40 which is the cost of 60, 100 mg tablets at $10.29 per tablet (usual boosting dose is 100 mg twice daily) in addition to the cost of the primary protease inhibitor, none of which are currently available generically.

Most exposure types would require only a basic regimen and Truvada is currently the drug of choice because of its convenient dosing (once daily) and recognition that it is well tolerated. Guiding prescribers toward Combivir will result in an approximate 40% cost savings for the base price of the drug in addition to the higher generic discount. The cost savings related to the use of Combivir, however, may be negated if nausea and diarrhea are experienced and require additional medication.

The occurrence of nausea is important to consider because prescribers frequently choose ondansetron (Zofran®) as the drug of choice. This may be due to the fact that ondansetron is a powerful antiemetic that is FDA approved for prevention of cancer chemotherapy-induced nausea and vomiting. Ondansetron, although generic, has one of the highest AWP of all available antiemetic alternatives as 30, 8 mg tablets can cost as much $1,243.70 (AWP=$41.46 per tablet). A complicating factor is that there does not appear to be any predictable trend that would help payers anticipate where ondansetron would likely be used, as our transactions show patients taking Combivir or Truvada with and without the concomitant use of ondansetron.

If an expanded regimen is necessary, Kaletra should be recommended as the primary agent. Deviations from these preferred agents may be necessary in situations where:

- There is a known drug interaction between the antiretroviral agent and medication the exposed patient is currently taking,
- The HIV positive source patient is known to be resistant to the antiretroviral agent being considered for PEP, or
- The prescriber chooses to use the same antiretroviral agent for PEP as the HIV positive source patient is currently taking to the control the active disease.

In addition to the choice of drugs that should be recommended and used for PEP, perhaps the more difficult question is when PEP should and should not be used. If a healthcare worker is exposed to blood originating from an HIV positive patient, the decision to use PEP should be straightforward. If the HIV status of the source is unknown or if the source altogether is unknown, such as in the case of a found needle, the decision to start PEP would be more difficult. It should be noted that PEP must be started within hours following exposure as delays can result in reduced or lost efficacy and a delay of 72 hours is considered the outer limit of opportunity to initiate PEP. The key to timely management of exposure risk lies in a comprehensive policy with clearly outlined standard operating procedures. Organizations are encouraged to consult the CDC guidelines to draft such policies and can also seek up-to-the-minute advice on PEP from the National Clinicians' Post-Exposure Prophylaxis Hotline (PEPline).[18] myMatrixx has developed a PEP formulary for clients with a worker

HIV Antiretrovirals *(continued)*

population that may experience one of the above routes of exposure. This formulary is designed to ensure that PEP initiation is not delayed for an exposed worker, as well as to ensure that the client does not pay for HIV medication in a case that is not related to a workplace injury.

Biologic DMARDs

Biological DMARDs (*disease modifying antirheumatic drugs*) are approved for rheumatoid arthritis (RA). Other uses include psoriasis, ulcerative colitis, Crohn's disease, and ankylosing spondylitis (AS). Workers' compensation compensability for these medications may be more commonly related to RA and AS which are inflammatory conditions that result in pain. This is because workers who report an onset of pain on the job can later go on to be diagnosed with RA or AS. Rheumatoid arthritis causes pain in the small joints of hands and feet, and less often in larger joints such as the shoulders and knees. Pain is the hallmark clinical feature of AS.

It should be noted that neither RA nor AS should be considered work-related conditions. A person is genetically predetermined to have RA or AS whether the onset of pain is experienced at home or on the job. However, experience dictates that RA and AS claims are sometimes accepted as compensable. First line biological DMARDs include drugs from the TNF-alpha inhibitor class and the T-cell modulator class:

Table 3

TNF-alpha inhibitor	Annual Cost	T-cell modulator	Annual Cost
Enbrel® (etanercept)	$39,413	Orencia® (abatacept)	$30,124
Remicade® (infliximab)	$19,740		
Humira® (adalimumab)	$39,041		
Cimzia® (certolizumab pegol)	$86,398		

Primary Biological DMARD Options; TNF-alpha inhibitors and Orencia® (9t-cell modulator) have the same level of recommendation.
The corresponding cost represents the approximate annual wholesale cost based on a typical or median maintenance dose.

Orencia® has the same level of recommendation as the TNF-alpha inhibitor. In 2013, Orencia was compared to Humira® in a head-to-head trial and was shown to have similar efficacy, safety, and time to respond.[19] Other biological DMARD options include a B-cell modulator, Rituxan® (rituximab), and an IL-6 inhibitor, Actemra® (tocilizumab).

Table 4

B-cell modulator	Annual Cost	IL-6 inhibitor	Annual Cost
Rituxan® (rituximab)	$16,466	Actemra® (tocilizumab)	$44,814

Secondary Biological DMARD Options;
The corresponding cost represents the approximate annual wholesale cost based on a typical or median maintenance dose.

Rituxan and Actemra are recommended as secondary options mainly because the side effect profile is worse than the primary options. Actemra can cause elevated liver enzymes, hematologic abnormalities, GI perforation, and an increase in LDL cholesterol.[20] Rituxan can cause severe and fatal infusion reactions, 80% of which occur during the first infusion.[21]

Before any biological DMARD is considered, the guidelines from the American College of Rheumatology recommend the use of a non-biological DMARD including methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine.

All non-biological DMARDs are available in generic formulations. Therapy typically begins as monotherapy with methotrexate as the first-line option.[22] Combination therapy with either double or triple therapy is recommended for inadequate responses. Combination therapy may be more effective than monotherapy.[23] Therefore, if a patient does not respond adequately to methotrexate alone, one or two

Biologic DMARDs *(continued)*

of the other non-biological DMARD can be added. The usual trial period is three months and if patients don't respond, i.e. disease activity is not improved, a biological DMARD is recommended, usually a TNF-alpha inhibitor.

Table 5

Drug	Maximum Maintenance Dose	Average Annual Cost	Comments
methotrexate	25mg once weekly	$1,853	-Effective -Slows disease progression -Low toxicity -Inexpensive
leflunomide	20 mg per day	$5,993	-As effective as methotrexate -Side effects include diarrhea, alopecia, rash, headache, and hepatotoxicity
hydroxychloroquine	400 mg daily	$751	-Requires several weeks to exert therapeutic effect -Maximum effect may not be obtained for several months -Discontinue if objective improvement does not occur within 6 months
sulfasalazine	1000 mg 3 times daily	$401	-3g/day dose is used if no response from 2g/day after 12 weeks

Non-biological DMARD Alternatives

If a patient does not respond to the first TNF-alpha inhibitor, a second may be tried. If a patient fails with two TNF-alpha inhibitors, a non-TNF agent should be tried. Combining biological DMARDs is not recommended because of the risk of adverse events.[24]

Certain criteria, however, can preclude the trial of a non-biological DMARD. The American College of Rheumatology recommends TNF-alpha inhibitors as first line for patients with early disease of high activity and poor prognosis with or without methotrexate. Remicade, however, should always be used with methotrexate and not as monotherapy.[25]

Early disease is defined as disease duration of less than six months. Patients with a poor prognosis show signs of functional limitation, extra-articular disease, are positive for rheumatoid factor or anticyclic citrullinated peptide antibodies, or bony erosions.[26] Disease activity is measured using tools such as the Simplified Disease Activity Index or Clinical Disease Activity Index.

A newer specialty drug that is not considered a biological is Xeljanz® (*tofacitinib*). Unlike the biological DMARDs, it is taken orally and not injected. This drug should be used in patients who have not responded to non-biological DMARD therapy. It can be added to drugs such as methotrexate or used alone. However, because of additional adverse events including an increase in cholesterol, liver injury, and lower blood cell count, Xeljanz should be used after failure of a TNF-alpha inhibitors agent. The usual dose is 5 mg twice daily, which projects the annual cost to be $32,075.

Neither RA nor AS should be considered work-related conditions.

Viscosupplementation: Hyaluronic Acid Derivatives

Viscosupplementation is a treatment alternative for osteoarthritis (OA), which is a degenerative joint disease that can affect the joints of the knee, hip, hands, and lumbar and cervical spine. When patients are first diagnosed with OA, the initial approach to treatment is to manage or control the pain and stiffness of the affected joint to improve function. First-line therapy includes local analgesics such as capsaicin, methylsalicylate creams, or topical NSAIDs (*Voltaren gel*). Additionally, nonpharmacological approaches such as exercise programs, physical and occupational therapy, manual mobilization, use of braces and corrective footwear, and canes may be prescribed. For flare-ups or exacerbation of symptoms, intra-articular corticosteroid injections may be used. This option is especially effective for knee pain. Effects are temporary and only last for a few weeks. If local analgesics do not control symptoms, acetaminophen is recommended to be added. Acetaminophen is anticipated to provide only a modest effect on pain. Therefore, if pain is still not adequately controlled with local analgesics and acetaminophen, NSAID therapy should be added.

The remaining pharmacological options include opioids and viscosupplementation. It is important to note that the remainder of this discussion is related only to OA of the knee since It is the only condition for which vicosupplementation is approved.

The decision to proceed with opioid therapy or viscosupplementation is controversial. Viscosupplementation is not very effective and quite expensive while opioids may be more effective, but can be addictive.

Viscosupplementation involves injecting hyaluronic acid into the intra-articular space. Hyaluronic acid is a major component of the synovial fluid, which acts to reduce the friction within the joint during movement. The viscosity of the synovial fluid is increased by hyaluronic acid. The mechanism by which this acts to reduce pain is not known and is complicated by the fact that these compounds are broken down very quickly once injected.[27] This perhaps explains why studies have been relatively contradictory. Newly-updated guidelines from the American Academy of Orthopaedic Surgeons (AAOS) provide more specific recommendations. After analyzing 14 studies that assessed the efficacy of intra-articular hyaluronic injections, the Academy provided a strong recommendation against the use of viscosupplementation with hyaluronic acid, noting that the evidence did not show that minimum clinically-important improvement outcomes were met.

Whether these new guidelines will result in reduced utilization remains to be seen. It's important to note, however, that agreement with guidelines is rarely unanimous and prescribers will likely consider hyaluronic acid as a preventive alternative against opioids, as they can be viewed as more problematic in the long run.

There are currently six options available for viscosupplementation, as seen in **Table 6**.

Table 6

HA-derivative (drug)	Recommended dose	# of injections per course	Cost per injection (AWP)	Cost of Course
Euflexxa®	Inject 20 mg (2 mL) once weekly	3	$369.98	$1,109.94
Hyalgan®	Inject 20 mg (2 mL) once weekly	5	$198.00	$990.00
Orthovisc®	Inject 30 mg (2 mL) once weekly	3-4	$383.96	$1,151.88 - $1,535.84
Supartz®	Inject 25 mg (2.5 mL) once weekly	5	$241.80	$1,209.00
Synvisc®	Inject 16 mg (2 mL) once weekly	3	$398.38	$1,195.15
Synvisc-One®	Inject 48 mg (6 mL) into one knee only	1	$1,195.15	$1,195.15

Hyaluronic Acid Derivatives Options

Hepatitis C Antivirals

An estimated 3.2 million persons in the United States are chronically infected with hepatitis C virus (HCV). In 2007 (the most recent available data), the incidence of HCV was 849 cases but the CDC estimates that approximately 17,000 new HCV infections occurred that year, adjusting for asymptomatic patients and underreporting.[28]

The occupational risk of HCV exposure is likely most prevalent for healthcare workers, however, exposure to blood and other potentially infectious fluids can occur across a wide variety of occupations. Other occupations may include emergency responders, public safety personnel, law enforcement officers (LEOs), and correctional officers, etc.

HCV is primarily transmitted through exposure to large amounts of blood or repeated direct percutaneous exposures to blood. HCV is not transmitted efficiently through occupational exposures to blood, with one study indicating that transmission occurred only from hollow-bore needles.[29] Transmission rarely occurs through mucous membrane exposure to blood and only in one instance was there transmission in a healthcare provider attributed to exposure of non-intact skin to blood.[30] The average risk of HCV infection after a single HCV-positive needle stick is 1.8% (range 0-7%).[31]

The CDC recommends that workers exposed to HCV-contaminated blood be tested for antibodies right away and again six months later. The CDC has recommended the following protocol for occupational HCV exposures:

- Testing the source for anti-HCV.
- Baseline testing for anti-HCV and ALT activity, with follow-up testing at 4-6 months for anti-HCV and ALT activity.
- Confirming all anti-HCV results reported positive by enzyme immunoassay using supplemental anti-HCV testing.[32]
- Measuring HCV viral load should be performed if positive for HCV antibody.[33]
- If found to have positive results for anti-HCV test and negative results for HCV RNA, persons should be informed that they do not have evidence of current (active) HCV infection.[34]

Persons exposed to HCV-infected blood do not need to take special precautions to prevent secondary transmission during the follow-up period. They should, however, refrain from donating blood, plasma, organs, tissue, or semen.

Once it has been determined that a person has contracted HCV, testing for genotype is recommended. This is because the HCV genotype will determine the appropriate therapy used for treatment. There are six genotypes of HCV currently described, with genotype 1 being the most prevalent in the United States and accounting for 70%[35] of all HCV patients. For this reason, genotype 1 treatment is what will be the focus of this summary.

Figure 1:
Peg interferon-Alpha-2a

The average risk of HCV infection after a single HCV-positive needle stick is 1.8% (range 0-7%).

Interferon

Treatment gained traction in the 1990s with interferon monotherapy for 48 weeks, producing a sustained virologic response (SVR) rate of 16%. Interferon research dates back to 1957 when a substance was found that interfered with the growth of influenza virus. As a result, Interferon is often considered the first specialty drug and, as indicated by the cartoon below, it was considered a miracle drug at the time.

Interferon is often considered the first specialty drug

In fact, additional measures must be taken to potentiate the effect of interferon. By adding ribavirin, SVR rates rose to approximately 42%. Pegylating the interferon (adding a long polymer chain to prolong the half-life) increased the SVR rate to 46%.[36]

For these reasons, early standard care for HCV combined Pegasys® (*peginterferon alfa-2a*) with ribavirin.

Table 7

Drug	Duration	Cost per Unit	Units per Week	Cost per Drug per Cycle	Total Cost of Regimen	SVR
Pegasys®	48 weeks	$925.52	1	$44,424.96	$46,642.56	46%
ribavirin	48 weeks	$1.32	35*	$2,217.60		

Early Standard Care for Treatment-Naive Patients; costs represent the shortest possible treatment duration for each regimen. Therapies can be as long as 48 weeks.

Pegasys® =peginterferon alfa-2a. *ribavirin is dosed based on weight, 1000 mg daily for patients weighing less than 165 lbs (35, 200 mg tablets weekly) or 1200 mg daily for patients weighing more than 165 lbs (42, 200 mg tablets weekly)

Interferon *(continued)*

Pegasys works by inducing the innate antiviral immune response of our bodies. Unlike the HIV medications which specifically inhibit the function of proteins and structures within the virus, Pegasys' antiviral activity is achieved by its ability to alter interactions between the host and virus in a complex manner.[37]

Ribavirin's mechanism is much less understood. It is a synthetic nucleoside analog, specifically a purine analog. It can increase the mutation frequency of the genomes of RNA viruses, causing lethal mutagenesis of the virus' genome. In addition, ribavirin inhibits HCV RNA polymerase, thus preventing viral replication.[38, 39]

As knowledge about the structure, pathogenesis, and functions of HCV increased, new therapy development intensified due to lingering subpar response rates from HCV genotype 1 patients. Protease inhibitors were the first direct-acting antivirals (DAAs) to show promise. The ones that emerged from clinical trials were Victrelis® (boceprevir) and Incivek® (*telaprevir*), both approved in 2011.

Table 8

Drug	Duration	Cost per Unit	Units per Week	Cost per Drug per Cycle	Total Cost of Regimen	SVR
Victrelis®	24 weeks	$23.88	84	$48,142.08	$75,350.24	63%
Pegasys®	28 weeks	$925.52	1	$25,914.56		
ribavirin	28 weeks	$1.32	35*	$1,293.60		
Incivek®	12 weeks	$157.51	42	$79,385.04	$102,706.32	72%
Pegasys®	24 weeks	$925.52	1	$22,212.48		
ribavirin	24 weeks	$1.32	35*	$1,108.80		

Protease Inhibitor Based Triple Therapy for Treatment-Naive Patients; costs represent the shortest possible treatment duration for each regimen. Therapies can be as long as 48 weeks. Pegasys®=peginterferon alfa-2a. *ribavirin is dosed based on weight, 1000 mg daily for patients weighing less than 165 lbs (35, 200 mg tablets weekly) or 1200 mg daily for patients weighing more than 165 lbs (42, 200 mg tablets weekly)

These two protease inhibitors work by blocking the NS3/4A protease of HCV genotype 1. This enzyme is necessary for the cleavage of the HCV polyprotein into mature forms of the NS4A, NS4B, NS5A, and NS5B proteins. It is also essential for viral replication.

Originally planned to be used as monotherapy, resistance to these drugs developed rapidly within the virus. By combining the protease inhibitors with Pegasys and ribavirin, resistance dramatically declined. The SVR rates improved to 63% for Victrelis and 72% for Incivek-based therapy, respectively, for 24-48 weeks of response-guided therapy as compared to a regimen of Pegasys and ribavirin dual therapy.[40]

Adverse effects to these therapies were a significant limiting factor when evaluating patients' response during clinical trials. For Pegasys and ribavirin dual therapy, fatigue/asthenia occurred in 65% of patients, fever in 41%, muscle pain in 40%, headache in 43%, irritability in 33%, insomnia in 30%, and nausea/vomiting in 25%. Overall, 11% of patients receiving 48 weeks of Pegasys with or without ribavirin discontinued therapy.[41]

For the Incivek-based triple therapy, rash and fatigue occurred in 56%, pruritus in 47%, nausea in 39%, and anemia in 36% of patients. Overall, 14% of patients on triple therapy had to discontinue it due to adverse drug reactions.[42]

Interferon *(continued)*

The Victrelis-based triple therapy caused anemia in 50%, nausea in 46%, fatigue in 58%, taste abnormality in 35%, irritability in 22%, and insomnia in 34% of patients. Thirteen percent of patients discontinued treatment with Victrelis-based triple therapy due to intolerable adverse effects.[43]

Because of the high incidence of side effects, prolonged treatment duration, high pill burden, and lower than desirable SVR rates, further research and development went into novel HCV therapies. This resulted in the approval of two new antivirals in late 2013: Olysio® (*simeprevir*) and Sovaldi® (*sofosbuvir*).

Table 9

Drug	Duration	Cost per Unit	Units per Week	Cost per Drug per Cycle	Total Cost of Regimen	SVR
Olysio®	12 weeks	$948.00	7	$79,632.00	$102,953.28	88%
Pegasys®	24 weeks	$925.52	1	$22,212.48		
ribavirin	24 weeks	$1.32	35*	$1,108.80		
Sovaldi®	12 weeks	$1,200.00	7	$100,800.00	$112,460.64	89%
Pegasys®	12 weeks	$925.52	1	$11,106.24		
ribavirin	12 weeks	$1.32	35*	$554.40		

Newest Triple-Therapy Regimens for Treatment-Naive Patients; costs represent the shortest possible treatment duration for each regimen. Pegasys®=peginterferon alfa-2a. Olysio*=simeprevir; Sovaldi*=sofosbuvir. *ribavirin is dosed based on weight, 1000 mg daily for patients weighing less than 165 lbs (35, 200 mg tablets weekly) or 1200 mg daily for patients weighing more than 165 lbs (42, 200 mg tablets weekly)

Olysio works by the same mechanism as the previous protease inhibitors, by blocking the NS3/4A protease. Sovaldi represents a novel mechanism of action against HCV. It is a prodrug that, when metabolized intracellularly, inhibits the NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Also, it acts as a chain terminator to prevent the addition of any more nucleotides to the RNA strand.

In clinical trials, Olysio achieved SVR of 88%[44] in patients with genotype 1 who were treatment-naïve. It is important to note that in patients with genotype 1a with the Q80K mutation, the SVR was only 53%. This is a common polymorphism for patients with genotype 1a within the United States. As a result, the manufacturer recommends testing for this mutation in patients with genotype 1a who will receive Olysio.

The most common adverse effects associated with Olysio-based triple therapy include rash in 28% and pruritus and nausea in 22% of patients. The discontinuation rate due to adverse effects, which is much lower compared to previous protease inhibitor therapies, was only 2%.[47]

In trials, Sovaldi achieved an SVR rate of 89% in treatment-naïve patients with genotype 1. Unlike Olysio, there is no issue between genotypes 1a and 1b in regards to SVR with rates of 92% and 82%, respectively.[46] Resistance to Sovaldi has not been detected in any clinical trials to date.

Adverse effects commonly experienced with Sovaldi triple therapy include fatigue in 59%, headache in 36%, nausea in 34%, insomnia in 25%, and anemia in 21% of patients. However, the discontinuation rate due to adverse effects was only 2%. This could be attributed to the short duration of treatment required for genotype 1 patients (12 weeks).[47]

Interferon *(continued)*

Although Pegasys/ribavirin with Incivek or Victrelis for 24-48 weeks using response guided therapy is FDA-approved, these therapies are markedly inferior to the preferred and alternative regimens listed below. They have higher rates of serious adverse events such as rash and anemia, longer treatment durations, higher pill burdens, numerous drug interactions, more frequent dosing, a higher intensity of monitoring for continuation and stopping of therapy, and are required to be taken with food or high-fat meals.

For these reasons the 2014 updated guidelines from the American Association for the Study of Liver Diseases and Infectious Disease Society of America (AASLD/IDSA), recommend Olysio or Sovaldi-based triple therapy as first-line options.[48] For those who are interferon-ineligible, Sovaldi + Olysio with or without ribavirin for 12 weeks is recommended (recomm. class I, level B). Clinical trials determined that the SVR rate after 12 weeks was 96% with ribavirin and 93% without ribavirin using this regimen.[49]

The criteria for interferon-ineligibility include: a) intolerance to interferon; b) autoimmune hepatitis and other autoimmune disorders; c) hypersensitivity to pegylated interferon or any of its components; d) decompensated hepatic disease; e) history of depression or clinical features of depression; f) baseline neutrophil count <1500/microliter or a baseline platelet count <90,000/microliter or baseline hemoglobin <10 g/dL; g) history of preexisting cardiac disease.

Because of the high incidence of side effects, prolonged treatment duration, high pill burden, and lower than desirable SVR rates, further research and development went into novel HCV therapies. This resulted in the approval of two new antivirals in late 2013: Olysio® (*simeprevir*) and Sovaldi® (*sofosbuvir*).

Table 10

Drug	Duration	Cost per Unit	Units per Week	Cost per Drug per Cycle	Total Cost of Regimen	SVR
Olysio®	12 weeks	$948.00	7	$79,632.00		
Sovaldi®	12 weeks	$1,200.00	7	$100,800.00	$180,986.40	96%
ribavirin	12 weeks	$1.32	35*	$554.40		

Regimens for Interferon-Ineligible, Treatment-Naive Patients; costs represent the shortest possible treatment duration for each regimen. Olysio*=simeprevir; Sovaldi*=sofosbuvir. *ribavirin is dosed based on weight, 35 tablets (1000 mg daily) or 42 tablets weekly (1200 mg daily)† option to use with or without ribavirin.

Botulinum toxins: Botox®

OnabotulinumtoxinA *(brand name Botox)*, also known simply as botulinum toxin A, is a purified neurotoxin complex consisting of the neurotoxin botulinum toxin A and several accessory peptides.[50] The complex includes limited quantities of the bacteria associated with the development of botulism poisoning.

Botulinum toxin works by binding to nerve terminals and decreasing the release of the neurotransmitter acetylcholine causing a neuromuscular blockade effect. Recovery from this blockade often occurs via the muscle re-growing and forming new neurons to allow for new neuronal connections.[51]

Beginning in 1949, it was discovered that botulinum toxin could reduce muscle spasms by blocking neuromuscular transmission.[52] In the following decades, studies began to explore the use of botulinum toxin as a treatment for strabismus. In 1989, Botox® was approved by the FDA to treat blepharospasms (*eyelid spasms*) and strabismus.

One decade later, in 2000, cervical dystonia (*spasmodic torticollis*) was added to Botox's indications to reduce the severity of abnormal head position and neck pain. In 2002 the FDA approved Botox Cosmetic for treating moderate to severe frown lines between the eyebrows. Two years later, in 2004, Botox was approved for severe underarm sweating when topical medications weren't working well enough.

Then, in 2010, two more indications were added by the FDA: increased muscle stiffness of the elbow, wrist, and finger muscles with upper limb spasticity, and chronic migraine prophylaxis. Finally, in 2011, treatment for overactive bladder was added to the list of indications for those with neurologic conditions or spinal cord injury with inadequate response to anticholinergic medications.[53]

Despite the many indications approved for Botox, only a few can be potentially related to workers' compensation injuries. These include chronic migraine headaches, upper limb spasticity associated with traumatic brain injury or spinal cord injury (SCI), cervical dystonia associated with trauma, and overactive (*neurogenic*) bladder associated with SCI.

Migraine headache is a debilitating neurologic disorder characterized by an intense pulsing or throbbing pain in one area of the head. These headaches are often accompanied by symptoms of nausea, vomiting, and sensitivity to light and sound. Chronic migraine sufferers experience increased headache-related disability, reduced quality of life, and greater comorbidity.

In the US, the one-year population prevalence of migraine in adults, using strict diagnostic criteria, is 18% in women and 7% in men, and is stable. Prevalence varies by income, age, sex, and race, being highest in those of lower income, between the ages of 25 and 55 years, in women, and in Caucasians (with intermediate prevalence in African-Americans and lowest prevalence in Asian-Americans).[54]

Furthermore, chronic migraine imposes a significant socioeconomic burden on individuals and society.[55] In the United States alone, migraine headaches are responsible for $1 billion in medical costs and $16 billion in lost productivity per year.[56]

Though not fully understood, the pharmacological actions of Botox in treating chronic migraines include a direct analgesic effect. It is thought that the mechanism of action underlying its prophylactic effect in chronic migraine involves the inhibition of peripheral and central sensitization in trigeminovascular neurons.[57]

The disorder presents itself in both chronic and episodic forms, and migraine sufferers can be characterized based on the frequency of their headaches. Chronic migraine is characterized by 15 or more headache days per month, with headache lasting four hours a day or more, and with at least half of the headaches being migraines.[58]

Botox is the only FDA-approved medication for the treatment of chronic migraines. The safety and effectiveness of Botox for episodic migraines was not established despite seven placebo-controlled trials. Botox

Botulinum toxins: Botox® *(continued)*

for chronic migraines is given at recommended intervals of 12 weeks as 5-unit injections across 31 sites around the head/neck muscle areas.

Currently Botox is usually reserved for those patients who have attempted and inadequately responded to conventional medication therapies. This includes failing other first-line medications for episodic prophylaxis, which can include beta-blockers (*such as propranolol or timolol*), antiepileptic drugs *(such as divalproex sodium or topiramate*), triptans *(such as sumatriptan or zolmitriptan)*, antidepressants *(such as amitriptyline or venlafaxine)*, or ACE inhibitors/ARBs *(such as lisinopril or candesartan)*.

Adverse effects associated with Botox for the prophylaxis of chronic migraines include neck pain, headache, worsening migraine, and muscular weakness. These were also the most common causes for discontinuation of Botox due to adverse effects in clinical trials, which occurred in 4% of the treatment group compared to 1% in the placebo group.

Upper limb spasticity often occurs as a result of traumatic brain injury (TBI) involving the brain stem or cerebellum, which leads to interruption of the reflex signals going to muscles. This can cause changes in muscle tone, movement, sensation, and reflex. Since reflex centers of the brain are more complex than that of the spinal cord, it is more difficult to treat spasticity due to TBIs compared to spinal cord injuries or other neurological disorders.[59]

Every year, at least 1.7 million TBIs occur either as an isolated injury or along with other injuries.[60] About 20% of patients have injuries that require hospitalization, 6% suffer permanent disability, and about 3% die. The direct medical costs and indirect costs, such as lost productivity, of TBI totaled an estimated $76.5 billion in the United States in 2000.[61]

Despite the many indications approved for Botox, only a few can be potentially related to workers' compensation injuries.

Upper limb spasticity, while not life-threatening, can greatly diminish a person's quality of life. This is due to the inability to do simple tasks such as dressing or grooming oneself without great struggle or effort.

The Official Disability Guidelines currently recommend the use of Botox for upper limb spasticity associated with traumatic brain injuries.[62] It is indicated for use in muscles of the elbows, wrists, and fingers as a result of increased muscle tone.

Safety and effectiveness for spasticity of the lower limbs has not been established. It is also important to note that Botox has not been shown to improve upper extremity functional abilities or range of motion at a joint affected by increased muscle tone.[63]

Dosing for Botox in upper limb spasticity varies depending on the site of injection. Usually 100 to 200 units divided among four sites are injected for elbow spasticity associated with the biceps. It is recommended that 12.5 to 50 units are injected into each of the two wrist muscles as a single injection. For finger spasticity, the recommended dose is 30 to 50 units per site.[64]

The effects of Botox injections into the muscle generally appear within a few days and last anywhere from 12-16 weeks.

Adverse effects associated with treatment of upper limb spasticity include an increased risk of bronchitis and upper respiratory tract infections. Low incidences of nausea, fatigue, and pain in the extremities were also noted.

Cervical dystonia, also known as spasmodic torticollis, is characterized as a movement disorder of the muscles of the neck causing tremors or posturing of the head in a rotated, twisted, or abnormally flexed or extended position (or any combination of these).

Data is lacking on the prevalence and incidence of cervical dystonia due to trauma or other non-congenital causes. The prevalence has been estimated at 1 in 10,000 to 1 in 20,000 people in the general population.[65] According to the ODG, cervical dystonia is not commonly associated with workers' compensation injuries. The ODG does

Botulinum toxins: Botox® *(continued)*

recommend Botox for use in cervical dystonia if it is compensable, but it is not recommended for mechanical neck disorders such as whiplash.[66]

Botox has become first-line therapy for cervical dystonia in recent years and is preferred over other formulations of botulinum toxin (*particularly botulinum toxin B, brand name Myobloc®*). This is due to botulinum toxin B having a high antigenicity that limits long-term efficacy.[67] Botox also provides more objective and subjective benefit than trihexyphenidyl or other anticholinergic drugs.

Criteria for use of Botox in cervical dystonia, according to the ODG are: 1) moderate or greater severity; 2) clonic and/or tonic involuntary contractions of multiple neck muscles; 3) duration of condition is longer than six months; 4) and alternative causes of symptoms have been considered and ruled out, including chronic neuroleptic treatment, contractures, or other neuromuscular disorders.[68]

Dosing for cervical dystonia is dependent on whether the patient is botulinum toxin-experienced or not, but the maximum dose should not exceed 50 units per site. For toxin-naïve patients, it is recommended to start with a lower dose. An example would be 100 units or less total dose injected into the sternocleidomastoid muscle. This is to reduce the risk of dysphagia (*see adverse effects below*). For toxin-experienced patients, the range of dose studied was 200 to 300 units divided among the affected muscles.

Clinical improvement can be expected within the first two weeks of injection with a maximum clinical benefit approximately six weeks after injection. Most patients returned to pre-injection status by 12 weeks post-treatment.[69]

Dysphagia was the most common adverse reaction in clinical trials and may be attributed to the spread of the toxin outside the injected muscle. Many of these cases also report dyspnea or trouble breathing. Other events include upper respiratory injection, neck pain, and headache.[70]

There are more than 200,000 patients with traumatic spinal cord injury in the United States, with an incidence of approximately 12,000 new cases estimated annually.[71] It is estimated that 70 to 84% of patients with spinal cord injuries have at least some degree of bladder dysfunction.[72,73] Botox is indicated to treat bladder over-activity associated with a neurologic condition for those who have an inadequate response to or are intolerant of an anticholinergic. In the setting of workers' compensation, that is usually due to spinal cord injury.

The ODG recommends Botox for use in neurogenic bladder conditions including overactive bladder causing urinary incontinence. There are multiple high-powered studies that confirm Botox's efficacy for this condition. Improvements in maximum bladder capacity, maximum pressure during first involuntary detrusor contraction, and incontinence quality of life were significant versus placebo.[74,75]

The recommended dose for neurogenic bladder is 200 units per treatment and should not be exceeded. The 200 units are divided into 30 injections throughout the detrusor muscle of the bladder.[76] Patients should be considered for reinjection when the clinical effect of the previous injection diminishes, but not sooner than 12 weeks from the previous injection.[77]

Patients must not have a urinary tract infection at the time of treatment and prophylactic antibiotics should be administered 1-3 days pretreatment, on the treatment day, and 1-3 days post-treatment to reduce the likelihood of urinary tract infection.[78]

Table 11

Condition Treated	Units Injected	AWP per Unit	Cost per injection
Chronic Migraine	155 units	$6.30	$976.50
Upper Limb Spasticity	50 units per muscle site	$6.30	$315.00 per site
Cervical Dystonia	50 units per muscle site	$6.30	$315.00 per site
Neurogenic Bladder	200 units	$6.30	$1,260.00

Cost of treating conditions with Botox; the AWP of Botox is $630.00 for the 100 unit vial and $1,260.00 for the 200 unit vial. Frequency of injection for each condition is no sooner than 12 weeks.

Chemotherapeutic Agents

An examination of specialty medications requires the inclusion of cancer treatment. Cancer medications meet all five criteria for specialty classification identified by the American Journal of Managed Care. Cost is typically more than $600 per month, prescriptions are for rare conditions, and most require special handling, restricted distribution, and ongoing clinical monitoring. While a comprehensive evaluation of standard treatments and medications for cancer (**as seen in Table 13 and 14**) can exceed the scope of this paper, it is believed that the reader may benefit from a brief discussion regarding the controversy related to assignment of compensability of cancer afflictions under workers' compensation. This controversy involves the growing trend of cancer presumption laws adopted at the state level for firefighters and emergency medical service (EMS) providers.

Cancer presumption laws essentially remove the traditionally required burden of proof prescribed upon the employee that an injury, illness, or disease is caused by occupational exposure. Work-relatedness of the affliction is automatically presumed. This is because it is believed that firefighters are at higher risk for certain cancers compared to the general population. According to a 2009 report by the National League of Cities (NLC), there were 71 studies that addressed firefighters and cancer between 1995 and 2008. Seventeen of these studies, conducted with accepted scientific methods, identified the firefighting occupation as a possible risk factor for cancer.[79] Definitive causation, however, could not be made from the evaluation of this body of literature because of numerous cited study limitations. The ultimate conclusion of the NLC report was that more research is needed and at the present time there is insufficient evidence to support or refute occupational cause of cancer for firefighters.

Work-relatedness of the affliction [cancer] is automatically presumed.

This presents a difficult situation for employers because in the absence of supporting evidence, the financial burden is placed upon them by default. The law does allow the employer to refute the claim, but considering the social prestige of the firefighting occupation, any attempt to do this is anticipated to be viewed with disdain. However, equity is a fundamental element of law and considering the many different causes of cancer, it may be considered an inherent responsibility for payers to examine and refute all claims when findings dictate.

According to a recent article by the National Association of Workers' Compensation Judiciary (NAWCJ), 33 states have enacted firefighter cancer presumption laws.[80]

Table 12

State	Year + (major amendment)	State	Year + (major amendment)
California	1982 (2010)	Arizona	2001
Rhode Island	1986	Washington	2002 (2007)
Nevada	1987 (2003), (2009)	Kansas	2003
Oklahoma	1987	Texas	2005
New Hampshire	1988	Indiana	2006
Minnesota	1988	Colorado	2007
Alabama	1990	Illinois	2007
Massachusetts	1990	Missouri	2007
Maryland	1991 (2012)	Vermont	2007
South Dakota	1991	Alaska	2008
Tennessee	1991	Iowa	2009
Virginia	1994 (2000)	Maine	2009
Louisiana	1995 (2004)	Oregon	2009
Nebraska	1996	Connecticut	2010
New York	1997 (2002)	New Mexico	2010
North Dakota	1997	Pennsylvania	2011
Wisconsin	1997		

States with Enacted and Expanded Firefighter Cancer Presumption Laws

Chemotherapeutic Agents *(continued)*

It's important to note that the statutes vary greatly from state to state, with differences related to the criteria for coverage under presumption. The general criteria are as follows:

- Type of cancer— some states provide a finite list of cancer types while others have no restrictions at all.
- Type of occupation— some states extend the presumption privilege beyond firefighters to certain other emergency medical service providers. Whether a firefighter is part-time, full-time, or a volunteer may also confer different coverage.
- Pre-claim or pre-employment physical exam— some state statutes require that the pre-existence of cancer has been ruled out.
- Employee's current work status— most states specify the current work status of the claimant as a condition of coverage.
- Time frame of employment or emergence of disease— the amount of time the employee has worked may also be addressed in addition to the amount of time between the emergence of the disease and the time the employee has ceased employment.
- Retroactivity— as presumption laws are enacted or expanded, the question of retroactivity is important to consider. Some statutes specifically address this question.
- Disability— some laws specify that presumption can only be claimed if cancer results in disability.

For example, in the state of Pennsylvania, which is the most recent state to enact cancer presumption laws for firefighters, there are no restrictions to the type of cancer inflicted. The law applies to career and voluntary firefighters who have served at least four years of continuous service. It is also specified that the employee must "...have successfully passed a physical examination prior to asserting a claim under this subsection or prior to engaging in firefighting duties, and the examination failed to reveal any evidence of the condition of cancer." For those not currently working as a firefighter, presumption is applicable within

300 weeks of last exposure and not applicable beyond 600 weeks after the last date of employment. Retirees are also permitted to apply for presumption. Lastly, based on specific language regarding lung disease, *(silicosis, anthraco-silicosis, coal worker's pneumoconiosis, or asbestosis)* it appears that compensation shall only be payable for "for total disability or death."[81]

The second topic of discussion for cancer presumption laws pertains to employer rebuttals. When presenting evidence that the cancer is not work-related states may specify that evidence either be competent, substantive, or preponderance.

According to NAWCJ guidance, in all states medical opinions are not sufficient to rebut a presumption claim because "no one can render opinions with regard to the cause of cancer in this patient or in other firefighters," or that "it is impossible scientifically to render opinions as to the cause of cancer in this case."[82]

Also, there are two theories of assumption: the "Wigmore-Thayer" and the "Morgan approach." The Wigmore-Thayer, which applies to Pennsylvania and Minnesota statutes, shifts the burden of proof back to the employee when the employer submits a rebuttal. Essentially, the presumption "drops out" of the case. In the Morgan approach, the presumption is preserved as the burden of proof remains with the employer. It appears that at this point, most states have adopted the Morgan approach.

As the spending for specialty medications is expected to increase for numerous reasons, it is anticipated that more state adoption of cancer presumption laws will have an added effect.

Chemotherapeutic Agents *(continued)*

Table 13

Therapy	Drug	Common Dosing	AWP	Price per Cycle	Cycle Length	Total Price Per Cycle
Combination therapy for advanced non-small cell lung cancer	carboplatin 50 mg/5mL Taxotere® (docetaxel) 20 mg/2 mL	Target AUC X (GFR + 25) on day 1 75 mg/m² IV on day 1	$2.40 $71.82	$156 $1,023.44	Every 21 days, max 6 cycles	$1,179.44
Combination therapy for non-small cell lung cancer	carboplatin 50 mg/5 mL Alimta® (pemetrexed) 100 mg inj	Target AUC X (GFR + 25) on day 1 500 mg/m² on day 1	$2.40 $707.24	$156 $7,072.40	Every 21 days, max 4 cycles	$7,183.40
Triple therapy for advanced non-small cell lung cancer	Erbitux® (cetuximab) 2 mg/mL Erbitux® (cetuximab) 2 mg/mL Navelbine® (vinorelbine) 10 mg/mL cisplatin 1 mg/mL	400 mg/m² on day 1 of first cycle only 250 mg/m² weekly, beginning on day 8 of first cycle 25 mg/m² on days 1 and 8 80 mg/m² on day 1	$12.35 $12.35 $21.60 $0.41	$4,693.00 First Cycle: $5,866.25 Subsequent: $8,799.38 $205.20 $62.32	Every 21 days, max 6 cycles; followed by maintenance cetuximab.	First Cycle: $10,826.77 Subsequent Cycles: $13,759.90
Combination therapy for chemotherapy-naive patients with advanced non-squamous, non-small cell lung cancer	Alimta® (pemetrexed) 100 mg inj cisplatin 1 mg/mL	500 mg/m² on day 1 75 mg/m² on day 1	$707.24 $0.41	$7,072.40 $58.43	Every 21 days, max 6 cycles	$7,130.83
Combination therapy for non-small cell lung cancer	carboplatin 50 mg/5mL Gemzar® (gemcitabine) 1000 mg/26.3 mL	Target AUC X (GFR + 25) on day 1 1000 mg/m² on days 1 and 8	$2.40 $2.04	$156.00 $203.87	Every 21 days, max 4 cycles.	$359.87
Combination therapy for non-small cell lung cancer	Gemzar® (gemcitabine) 1000 mg/26.3 mL cisplatin 1 mg/mL	1200 mg/m² on days 1 and 8 75 mg/m² on day 1	$2.04 $0.41	$244.62 $58.43	Every 21 days, max 6 cycles	$303.05
Combination therapy for non-small cell lung cancer	Taxol® (paclitaxel) 30 mg/5 mL carboplatin 50 mg/5 mL	200 mg/m² on day 1 Target AUC X (GFR + 25) on day 1	$4.08 $2.40	$258.40 $156.00	Every 21 days, max 6 cycles	$414.40
Triple therapy for advanced non-small cell lung cancer	Taxol® (paclitaxel) 30 mg/5 mL carboplatin 50 mg/5 mL bevacizumab (Avastin®) 100 mg/4 mL	200 mg/m² on day 1 Target AUC X (GFR + 25) on day 1 15 mg/kg on day 1	$4.08 $2.40 $194.74	$258.40 $156.00 $9,429.31	Every 21 days, max 6 cycles, followed by maintenance therapy with bevacizumab every 3 weeks	$9,843.71
Adjuvant therapy for resected early stage non-small cell lung cancer	Navelbine® (vinorelbine) 10 mg/mL cisplatin 1 mg/mL	25 mg/m² on days 1, 8, 15, and 22 50 mg/m² on days 1 and 8	$21.60 $0.41	$410.40 $77.90	Every 28 days, for 4 cycles	$488.30

Common Therapies for Non-Small Cell Lung Cancer *Assume dosing for an average male with a weight of 80.7 kg, BSA of 1.9 m², and a GFR of 125 mL/min. Carboplatin target AUC is assumed to be 5.

Chemotherapeutic Agents *(continued)*

Table 14

Therapy	Drug(s)	Common Dosing*	AWP	Price per Cycle	Cycle Length	Total Price Per Cycle
Combination	Alimta® (pemetrexed) 100 mg inj cisplatin 1 mg/mL	500 mg/m² on day 1 75 mg/m² on day 1	$707.24 $0.41	$7,072.40 $58.43	21 days	$7,130.83
Combination	Alimta® (pemetrexed) 100 mg inj carboplatin 50 mg/5mL	500 mg/m² on day 1 Target AUC X (GFR + 25) on day 1	$707.24 $2.40	$7,072.40 $156.00	21 days	$7,183.34
Combination	Gemzar® (gemcitabine) 1000 mg/26.3 mL cisplatin 1 mg/mL	1000 mg/m² on days 1, 8, and 15 100 mg/m² on day 1	$2.04 $0.41	$305.82 $77.90	28 days	$383.72
Other agents that may be used as single agents or in combination (typically off label)	methotrexate 1 gram	High dose therapy 3 g total dose in a phase II trial	$76.32	$228.96	4-8 cycles total	$228.96
	Navelbine® (vinorelbine) 10 mg/mL	30 mg/m² (max dose: 60 mg) every 7 days	$21.60	$738.72	6 weeks	$738.72
	Mutamycin® (mitomycin) 5 mg inj	10 mg/m2 on day 1	$67.20	$255.36	4 weeks for 3 cycles	$255.36
	Adriamycin® (doxorubicin) 10 mg/5 mL	60-75 mg/m² on day 1	$2.40	$171.00	21 days	$171.00
	Ellence® (epirubicin) 2 mg/mL	110 mg/m² on day 1 based on a phase II trial	$2.80	$292.60	3 weeks	$292.60
	Cytoxan® (cyclophosphamide) 500 mg inj	40-50 mg/kg in divided doses over 2-5 days OR 10-15 mg/kg every 7-10 days OR 3-5 mg/kg twice weekly	$439.50	$3,546.77	Variable	$3,546.77

Systemic Treatment for Unresectable Malignant Pleural Mesothelioma *Assume dosing for an average male with a weight of 80.7 kg, BSA of 1.9 m², and a GFR of 125 mL/min. Carboplatin target AUC is assumed to be 5.

Risk of Noncompliance

Many complications could arise due to inadequate treatment or noncompliance. These complications could lead to costs that insurers must pay and which could potentially be much more than if adequate treatment was provided.

Anticoagulants

Inadequate thromboprophylaxis post-orthopedic surgery can result in venous thromboembolism (VTE) and subsequently lead to a deep vein thrombosis (DVT) or a pulmonary embolism (PE) event. Once a patient experiences a VTE event, the risk of experiencing a second event increases substantially. In a case-control study, patients with a history of VTE were ≈8 times more likely to develop a new episode during a subsequent high-risk period compared with patients without a history of DVT or PE.[83] This ultimately leads to an increased cost of care. In another study, it was concluded that cost of treatment for a VTE-related event and succeeding events incurred an average health plan cost of $14,957 per event.[84] Further complications could arise after development of a VTE, such as stroke, atrial fibrillation, and ultimately death, all which have further associated costs.

HIV Antiretrovirals

Complications that arise from the inability to access antiretroviral medications could potentially be deadly. Without drug therapy, the risk of the virus spreading, and thus the significant decrease in a patient's CD4, will result in the patient being classified as having acquired immune deficiency syndrome (AIDS). This, in turn, puts the patient at an increased risk of opportunistic infections due to an improperly functioning immune system. Opportunistic infections develop depending on the level of CD4 cells available and can include, but are not limited to: Kaposi's Sarcoma, Pneumocystis Jirovecii Pneumonia, Cytomegalovirus, etc.[85] The costs associated with these include extensive inpatient treatment as well as outpatient follow-up and additional medications prescribed for prophylaxis on a long term basis. According to the CDC, the most recent published estimate of lifetime HIV treatment costs was $379,668.[86] This is a major factor if the virus is not eradicated after continuous/rigorous use of a 4 week antiretroviral therapy (ART) regimen due to occupational exposure.

Biologic DMARDs

Without optimal treatment with biological DMARDs when needed, further damage to bones, cartilage, and other structures of the joints can occur. Joint damage typically worsens over time and is irreversible.[87]

Further potential complications include: osteoporosis, carpal tunnel syndrome, lung problems leading to shortness of breath, and heart problems leading to hardened and blocked arteries that could result in stroke and heart attack.[88] According to the National Bureau of Economic research, the average cost to traditional health insurers for the first 90 days following a heart attack is $38,501.[89]

Hepatitis C Antivirals

The risk of not having proper treatment for Hepatitis C is further damage to the liver. Although the liver is able to repair itself, the damage occurs over many years. In some people, scar tissue can form and accumulate in the liver and can eventually become extensive, leading to cirrhosis and improper functioning. People with cirrhosis have a severely scarred liver and are at increased risk for serious complications, including liver cancer.[90]

Once the liver is scarred beyond self-repair, a liver transplant is warranted. The costs of a transplant, including preliminary testing, the surgery itself, and post-operative recovery costs vary across the country and depend on the hospital and organ type. The estimated cost per transplant in 2011 (U.S.) was $577,100.[91]

Risk of Noncompliance *(continued)*

Complex Care

myMatrixx recognizes that the needs of patients receiving specialty drugs are complex and, as a result, has created complex care management programs designed to monitor the therapy and care of patients taking specialty medications as well as critically-injured patients. By combining pharmacy and nursing services under one program, myMatrixx has created an agile system that will:

- Monitor FDA approval of new specialty drugs and expansion of indications for existing drugs.
- Inform our clients of new specialty medications and the potential impact on their injured worker population.
- Provide medication therapy management programs that encourage the patient to be part of his/her recovery by:
  - Monitoring and facilitating adherence to complex drug regimens
  - Reporting adverse drug events or side effects
  - Informing treating physicians of non-adherence or other medication-related concerns
  - Ensuring client dollars are not wasted as a result of treatment failure or inappropriate drug selection.

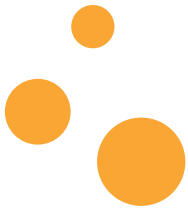
Conclusion

Specialty drugs are the fastest growing segment of the pharmaceutical market and will definitely have an impact on certain populations of injured workers. The degree of that impact will depend largely on the worker demographics of the insured entity as well as future policy decisions with regard to presumption. Currently the most likely injured workers to receive specialty drugs include emergency first responders, public safety personnel, law enforcement officers, correctional officers, and healthcare workers, etc.; in addition to certain defined workers in states with cancer presumption laws.

Specialty drugs are the fastest growing segment of the pharmaceutical market.

About myMatrixx

myMatrixx is a full-service pharmacy and ancillary benefit management company focused on the workers' compensation market. By combining advanced technology, clinical expertise, and comprehensive reporting, myMatrixx simplifies the management of claims. Our results-driven solutions deliver reduced costs for our clients and improve outcomes for their injured workers. For more information, visit www.mymatrixx.com.



Appendices

Appendix A: Select Specialty Medications

Drug Class	Medications	Route of Administration
Anticoagulants		
	Fragmin (dalteaparin)	Injection
	Lovenox (enoxaparin)	Injection
	Arixtra (fondaparinux)	Injection
HIV Antiretrovirals		
	Truvada (tenofovir/emtricitabine)	Oral
	Combivir (lamivudine/zidovudine)	Oral
	Kaletra (lopinavir/ritonavir)	Oral
Disease modifying antirheumatic drugs (DMARDs)		
TNF-alpha inhibitor		
	Enbrel (etanercept)	Injection
	Remicade (infliximab)	Infusion
	Humira (adalimumab)	Injection
	Cimzia (certolizumab pegol)	Injection
T-cell modulator		
	Orencia (abatacept)	Infusion
B-cell modulator		
	Rituxan (rituximab)	Infusion
IL-6 inhibitor		
	Actemra (tocilizumab)	Infusion
Janus-associated kinase (JAK) inhibitor		
	Xeljanz (tofacitinib)	Oral
Viscosupplementation: Hyaluronic acid derivatives		
	Euflexxa (1% sodium hyaluronate)	Injection
	Hyalgan (sodium hyaluronate)	Injection
	Orthovisc (high molecular weight hyaluronan)	Injection
	Supartz (sodium hyaluronate)	Injection
	Synvisc (hylan G-F 20)	Injection
	Synvisc-One (hylan G-F 20)	Injection
Hepatitis C antivirals		
	Pegasys (peginterferon alfa-2a)	Injection
	Rebetol (ribavirin)	Oral
	Victrelis (boceprevir)	Oral
	Incivek (telaprevir)	Oral
	Olysio (simeprevir)	Oral
	Sovaldi (sofosbuvir)	Oral
Botulinum toxins		
	Botox (onabotulinumtoxinA)	Injection
	Myobloc (botulinum toxin B)	Injection

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