2012 - PFE's Xeljanz (tofacitinib)

XELJANZ® (tofacitinib) tablets, for oral use
XELJANZ® XR (tofacitinib) extended-release tablets, for oral use
Initial U.S. Approval: 2012

WARNING: SERIOUS INFECTIONS AND MALIGNANCY
See full prescribing information for complete boxed warning.

- **Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving XELJANZ. (5.1)**
- **If a serious infection develops, interrupt XELJANZ/XELJANZ XR until the infection is controlled. (5.1)**
- **Prior to starting XELJANZ/XELJANZ XR, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting XELJANZ/XELJANZ XR. (5.1)**
- **Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative. (5.1)**
- **Lymphoma and other malignancies have been observed in patients treated with XELJANZ. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications. (5.2)**

- PFE's tofacitinib was approved in 2012 for the treatment of RA along with a black box warning for serious infections (tuberculosis and other opportunistic infections) and malignancy (lymphoma).

2018 - LLY's Olumiant (baricitinib)

OLUMIANT (baricitinib) tablets, for oral use
Initial U.S. Approval: 2018

WARNING: SERIOUS INFECTIONS, MALIGNANCY, AND THROMBOSIS

See full prescribing information for complete boxed warning.

- **Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving OLUMIANT. (5.1)**
- **If a serious infection develops, interrupt OLUMIANT until the infection is controlled. (5.1)**
- **Prior to starting OLUMIANT, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting OLUMIANT. (5.1)**
- **Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative. (5.1)**
- **Lymphoma and other malignancies have been observed in patients treated with OLUMIANT. (5.2)**
- **Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, some fatal, have occurred in patients treated with OLUMIANT. Patients with symptoms of thrombosis should be evaluated promptly. (5.3)**

- LLY/INCY's baracitinib was only approved at the lower 2mg dose after an FDA advisory panel voted against the safety profile of the 4mg dose due to serious venous thromboembolic events, which made it on to its label.

2019 - ABBV's Rinvoq (upadacitinib)

RINVOQ™ (upadacitinib) extended-release tablets, for oral use
Initial U.S. Approval: 2019

WARNING: SERIOUS INFECTIONS, MALIGNANCY, AND THROMBOSIS

See full prescribing information for complete boxed warning.

- **Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving RINVOQ. (5.1)**
- **If a serious infection develops, interrupt RINVOQ until the infection is controlled. (5.1)**
- **Prior to starting RINVOQ, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting RINVOQ. (5.1)**
- **Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative. (5.1)**
- **Lymphoma and other malignancies have been observed in patients treated with RINVOQ. (5.2)**
- **Thrombosis, including deep vein thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated with Janus kinase inhibitors used to treat inflammatory conditions. (5.3)**

- ABBV's upadacitinib – approved for RA – received a black box warning for infections, malignancies, and thromboembolic events despite rates in both the placebo-controlled and OLE remaining consistent with the background rate in the RA population. We note the language to include "Janus kinase inhibitors" instead of Rinvoq specifically, highly suggests the FDA views this as a class effect.

DARWIN3 Long Term Safety Data In Comparison To Peers

Event per 100 PYE	filgotinib	baricitinib	tofacitinib	upadacitinib	tocilizumab	adalimumab
	50-200 mg	2 and 4 mg QD	5 mg BID	6 and 12 mg BID	4 and 8 mg/kg	
Patient year exp.	2,203	6,637	5,278	725	14,994	23,943
Serious infection	1.2	2.9	2.4	2.3	4.5	4.6
herpes zoster	1.5	3.2	3.8	3.7	ND	ND
DVT/PE	2/2,203 0.1	31/6,754 0.5	3/1,849 0.2	5/725 0.7	ND	ND
Deaths	0.2	0.3	0.6	0.3	0.6	0.8
Malignancy excluding NMSC	0.5	-	-	-	-	-
MACE	0.1	-	-	-	-	-
Source	DARWIN3 wk156	Genovese *et al* ACR2017	Wollenhaupt ACR 2017	Genovese ACR2017	Genovese ACR 2012	Burmester 2011

FINCH Safety Data Up To Week 24

N (%)	PBO/MTX	ADA 40 mg EOW	FIL 100 mg + MTX/cDMARDs	FIL 200 mg + MTX/cDMARDs	FIL 200 mg monotherapy	FIL total
	N=1039	N=325	N=840	N=1038	N=210	N=2088
serious infection	10 (1.0)	8 (2.5)	13 (1.5)	13 (1.3)	3 (1.4)	29 (1.4)
herpes zoster	4 (0.4)	2 (0.6)	5 (0.6)	6 (0.6)	1 (0.5)	12 (0.6)
DVT/PE	3 (0.3)	0 (0)	0 (0)	1 (0.2)*	0 (0)	1 (<0.1)
deaths	2 (0.2)	0 (0)	1 (0.1)	3 (0.3)	0 (0)	4 (0.2)
malignancy excl. NMSC	4 (0.4)	1 (0.3)	1 (0.1)	0 (0)	0 (0)	1 (<0.1)
MACE	5 (0.5)	1 (0.3)	2 (0.2)	2 (0.2)	1 (0.5)	5 (0.2)

Note: FINCH 1, 2, and 3 events up to week 24
**Excludes retinal vein occlusion observed in FINCH 2*
FIL: filgotinib; ADA: adalimumab; MTX: methotrexate; PBO: placebo; csDMARD: conventional synthetic disease-modifying antirheumatic drug; DVT: deep vein thrombosis; PE: pulmonary embolism; NMSC: nonmelanoma skin carcinoma; MACE: major cardiovascular event